PHARMACEUTICAL CARE FOR PATIENTS WITH GYNAECOLOGICAL MALIGNANCIES IN THE OUTPATIENT SETTING – A PILOT STUDY

Dissertation

zur

Erlangung des Doktorgrades (Dr. rer. nat.)

der

Mathematisch-Naturwissenschaftlichen Fakultät

der

Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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aus

Lübbecke in Westfalen

Bonn 2004

Angefertigt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Tag der Promotion	03. Dezember 2004

Diese Dissertation ist auf dem Hochschulschriftenserver der ULB Bonn
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Für Mama, Papa, Eike und Oma Eva

„Wenn Du ein Schiff bauen willst, so trommle nicht die Männer zusammen, um Holz zu beschaffen, Werkzeuge vorzubereiten und Aufgaben zu vergeben. Vermittle Ihnen zu allererst die Sehnsucht nach dem weiten Meer."

Antoine de Saint Exupéry

Content

1 Introduction 1

1.1 Gynaecological malignancies and their therapies 1

1.1.1 Breast cancer 1
1.1.1.1 Epidemiology 1
1.1.1.2 Treatment concepts 3
1.1.1.3 Public awareness 8

1.1.2 Ovarian cancer 9
1.1.2.1 Epidemiology 9
1.1.2.2 Treatment concepts 10

1.2 Specific aspects of antineoplastic drug treatment 16

1.2.1 Safety of cytotoxic drugs 16
1.2.2 Drug-related problems in systematic drug therapy 16
1.2.3 From compliance to concordance 18
1.2.4 Evidence-based drug therapy 19
1.2.5 Individualised chemotherapy 20
1.2.5.1 Dose individualisation of carboplatin 21

1.2.6 Therapeutic drug monitoring 23
1.2.7 Supportive therapy 24
1.2.7.1 ADRs associated with chemotherapy 25
1.2.7.2 Prophylaxis of nausea and emesis 26

1.2.8 Complementary medicine 30

1.3 Changes in health systems 31

1.3.1 Patient-focused approaches 31
1.3.2 Patients' needs 31
1.3.3 Current health policy trends 33
1.3.3.1 Quality management 33
1.3.3.2 Integrated care 35

1.4 Oncology pharmacy 36

1.5 Pharmaceutical care 36

1.5.1 Definition 36
1.5.2 Integration in current health policy trends 40
1.5.3 Integration in a societal context 40
1.5.4 Pharmaceutical care for the cancer patient 41
1.5.5 Pharmaceutical care research 43

2 Aim and Objectives 49

2.1 Patient satisfaction with information on cancer treatment 49

2.2 Pharmaceutical care for patients with gynaecological malignancies 49

2.3 Monitoring of carboplatin 50

2.4 Working hypotheses 50

3 Material and Methods 53

3.1 Patient satisfaction with information on cancer treatment 53

3.1.1 PS-CaTE questionnaire 53
3.1.2 Translation of the PS-CaTE questionnaire 53
3.1.3 Psychometric properties 54
3.1.4 Patient selection 55
3.1.5 Distribution among cancer centres in Germany 55

3.2 Pharmaceutical care for patients with gynaecological malignancies 56

3.2.1 Study protocol 56
3.2.1.1 Legal obligations 57
3.2.1.2 Selection of patients and drugs 57
3.2.1.3 Study design 58
3.2.1.4 Study centres 60

3.2.1.5 Patient information material 60
3.2.1.6 Outcome measurement 62
3.2.2 Therapeutic algorithm for the antiemetic prophylaxis and treatment 68
3.2.3 Evaluation of the collected data 70
3.2.4 Pharmaceutical care process 72
3.2.4.1 Patient recruitment 72
3.2.4.2 Care appointments 73
3.2.4.3 Documentation 73

3.3 Monitoring of carboplatin 74

3.3.1 Patient selection 74
3.3.2 Limited blood sampling 74
3.3.3 Drug analysis 75
3.3.3.1 Laboratory data 75
3.3.3.2 Sample collection and preparation 75
3.3.3.3 Atomic absorption spectrometry 75
3.3.3.4 Validation of the analytical method 78
3.3.3.5 Preparation of standards of calibration 78
3.3.3.6 Quality assurance during the measurement 79
3.3.3.7 From elementary platinum concentration to the carboplatin concentration 79

3.4 Statistical data analysis 79

3.4.1 Patient satisfaction with information on cancer treatment 79
3.4.2 Pharmaceutical care for patients with gynaecological malignancies. 81
3.4.2.1 Primary endpoint 81
3.4.2.2 Secondary endpoints 82
3.4.2.3 Sample size estimation for the main study 82

4 Results 87

4.1 Patient satisfaction with information on cancer treatment 87

4.1.1 The German version 87

4.1.2 Response 87
4.1.3 Psychometric assessment 89
4.1.4 Satisfaction with information 90
4.1.4.1 Predictors of satisfaction with information 92
4.1.4.2 Information sources 94
4.1.4.3 Free comments 94

4.2 Pharmaceutical care for patients with gynaecological malignancies 95

4.2.1 Quality of life 96
4.2.2 Nausea and emesis 111
4.2.3 Patient satisfaction with information on cancer treatment 113
4.2.4 Drug related problems and pharmacists' intervention 116
4.2.5 Time spent on appointments and for working off 120
4.2.6 Sample size estimation for the main study 121

4.3 Monitoring of carboplatin 122

5 Discussion 129

5.1 Patient satisfaction with information on cancer treatment 129

5.2 Pharmaceutical care for patients with gynaecological malignancies 132

5.2.1 Quality of life 132
5.2.2 Nausea and emesis 135
5.2.3 Patient satisfaction with information on cancer treatment 138
5.2.4 Drug related problems and pharmacists' inverventions 141
5.2.5 Limitations of pharmaceutical care research 142
5.2.6 Pharmacoeconomic aspects 144
5.2.7 Future prospect 145

5.3 Monitoring of carboplatin 147

6 Summary 155

References 159

Appendix

Appendix A **Patient satisfaction with information on cancer treatment**

Tab. A- 1 Alpha-if-item deleted values of the pre-test

Appendix B **Tumour classification and staging**

Tab. B-1 TNM classification of breast cancer

Tab. B-2 Stages of ovarian cancer according to TNM and FIGO

Appendix C **Levels of evidence and grades of recommendation**

Tab. C-1 Levels of evidence

Tab. C-2 Grades of recommendation

Appendix D **Standard operating procedures**

Appendix E **Patient information material**

Appendix F **Informed consent**

Appendix G **Privacy statement**

Appendix H **Coding system of drug-related problems: PI-Doc®**

Tab. H-1 Main groups of drug-related problems

Tab. H-2 Main groups of drug-related interventions

Appendix I **Care material**

Patient information on expected side effects

Appendix J **Questionnaires**

EORTC QLQ-C30 (v. 3.0)

Nausea and emesis questionnaire including patient information

Patient satisfaction questionnaire (PS-CaTE)

Appendix K **Documentation**

Patient profile I and II

Medication file

Medication profile

Care plan

Appendix L **Platinum analysis**

Tab. L-1 Instrumentation and operating conditions

Tab. L-2 Chemicals and Reagents

Tab. L-3 Validation of the FAAS method

Appendix M **Monitoring of carboplatin**

Tab. M-1 Platinum concentrations and resulting AUCs

Tab. M-2 Serum creatinine and GFR-estimation

Tab. M-3 NCI Common toxicity criteria

Publications

List of Abbreviations

ABDA	Federal Union of the German Associations of Pharmacists
ADE	Adverse drug event
ADR	Adverse drug reaction
AGO	Association for gynaecological oncology
ALL	Acute lymphoblastic leukemia
AML	Acute myelogenous leukemia
AP	Appetite loss scale of the EORTC QLQ-C30
ASCO	American Society for Clinical Oncology
ASHP	American Society for Hospital Pharmacy
AUC	Area under the concentration versus time curve [mg·min/mL]
BSA	Body surface area [m^2]
C	Cycle
CDER	Centre for drug evaluation and research
CF	Cognitive functioning scale of the EORTC QLQ-C30
CG	Control group
CI	Confidence intervall
CL	Clearance
CLL	Chronic lymphoblastic leukemia
CMF	Cyclophosphamide, methotrexate and fluorouracil combination
CML	Chronic myelogenous leukemia
CO	Constipation scale of the EORTC QLQ-C30
COPD	Chronic obstructive pulmonary disease
CT	Chemotherapy
CTC	Common toxicity criteria
CVM	Centre for veterinary medicine
DI	Diarrhea scale of the EORTC QLQ-C30
DIN EN ISO	Standardisation according to German, European and international organisations for standardisation
DMP	Disease management programme
DNA	Desoxyribonucleic acid
DRP	Drug-related problem
DY	Dyspnoea scale of the EORTC QLQ-C30
EBM	Evidence-based medicine

EC	Expert consensus or Epirubicin/Cyclophosphamide combination
ECG	Electrocardiogramm
EF	Emotional functioning scale of the EORTC QLQ-C30
EN	Enteral nutrition
EOC	Epithelial ovarian cancer
EORTC	European organisation for research and treatment of cancer
ESMO	European Society for Medical Oncology
FA	Fatigue scale of the EORTC QLQ-C30
FDA	Food and Drug Administration
FEC	Fluorouracil, Epirubicin and Cyclophosphamide combination
FI	Financial difficulties scale of the EORTC QLQ-C30
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FIP	Fédération Internationale Pharmaceutique
GCP	Good clinical practice
GF-FAAS	Graphit-tube furnace - Flameless atomic absorption spectometry
GFR	Glomerular filtration rate
GLP	Good laboratory practice
GOR	Grade of recommendations
GP	General practitioner
h	hour
HER	Human epidermal growth factor receptor
$5HT_3$	5-Hydroxytriptamine = Serotonine
ICD	International Statistical Classification of Diseases and Related Health Problems
IG	Intervention group
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LoE	Level of Evidence
LoR	Level of Recommendation
MASCC	Multinational Association of Supportive Care in Cancer
MCP	Metoclopramide
min	Minute
MPE	Mean predictive error
NCI	National Cancer Institute
n. d.	Not determined

NK	Neurokinine
n. s.	Not specified
NSCLC	Non-small cell lung cancer
OTC	Over-the-counter medication
PA	Pain scale of the EORTC QLQ-C30
PCA	Patient controlled analgesia
PCR	Pharmaceutical care research
PF2	Physical functioning scale of the EORTC QLQ-C30
PQC	Processed quality controls
PS-CaTE	Patient satisfaction with cancer treatment education questionnaire
Pt	Platinum
QL2	Global health status/ quality of life scale of the EORTC QLQ-C30
QMS	Quality management system
QoL	Quality of Life
RCT	Randomised controlled trial
RE	Relative error
RF2	Role functioning scale of the EORTC QLQ-C30
rpm	Rounds per minute
RSD	Relative standard deviation
RMSE	Root mean square error
SD	Standard deviation
SF	Social functioning scale of the EORTC QLQ-C30
SL	Insomnia scale of the EORTC QLQ-C30
SOAP	Subjective, objective, analysis, plan method
SQC	Spiked quality controls
SWB	Subjective well-being
$t_{1/2}$	Half life
TDM	Therapeutic Drug Monitoring
TNM	Staging system to categorise tumour size, nodal affection and metastases
TPN	Total parenteral nutrition
TQM	Total quality management
UF	Ultrafiltrate
UICC	International union against cancer
US	United States of America

WBC	White blood cell
WHO	World Health Organization
WMA	World Medical Association
WNL	Within normal limits

[1] Introduction

1 Introduction

Due to international concerted cancer research nowadays patients can be offered individually tailored antineoplastic therapies. Systemic therapies are part of most therapeutic strategies and for some malignancies they even seem to be the only option. More cancers are curable or can be halted in a chronic state which goes along with changing patient needs. This is why in recent years a paradigm shift occurred towards a patient-focused rather than a disease-focused approach. Patients' quality of life and patients' satisfaction during and after the antineoplastic treatment emerged to be important outcome parameters alongside the tumour response. Supportive therapy became an integral part of the antineoplastic therapy to limit the therapy-associated toxicity. Moreover the significance of complementary therapy options for cancer patients became evident. However, not only anticancer drugs have to be taken into consideration. The patient often has to take additional medication against other underlying conditions such as asthma, diabetes etc. Altogether it is crucial striving for offering the patient an appropriately indicated, effective, safe and convenient drug therapy.

1.1 Gynaecological malignancies and their therapies

1.1.1 Breast cancer

1.1.1.1 Epidemiology

Approximately 10% of all women in the western industrialised countries develop breast cancer in their lives (Engel et al., 2001). Risk factors have been determined which may account for breast cancer (Tab. 1-1). Age still seems to be the most important risk factor.

Tab. 1-1 Established risk factors for breast cancer (Armstrong et al., 2000)

Risk factor	Relative risk (data compiled from various studies)
Age (≥ 50 vs. < 50 yr)	6.5
Family history of breast cancer	
First-degree relative	1.4 - 13.6
Second-degree relative	1.5 - 1.8
Age at menarche (< 12 vs. ≥ 14 yr)	1.2 - 1.5
Age at menopause (≥ 55 vs. < 55 yr)	1.5 - 2.0
Age at first live birth (> 30 vs. < 20 yr)	1.3 - 2.2
Benign breast disease	
Breast biopsy (any histologic finding)	1.5 - 1.8
Atypical hyperplasia	4.0 - 4.4

Breast cancer is the most common type of cancer in women in the western industrialised countries. In Germany approximately 46,000 women are newly diagnosed with breast cancer every year. 19,000 are younger than 60 years old. The incidence of breast cancer increased continuously over the past 25 years (Batzler et al., 2002b). In 2001 17,504 women in Germany died of breast cancer (Statistisches Bundesamt, 2003). As a comparison in 1997 there were 18,378 cases of death.

Malignant tumours of the breast are classified according to the 'International Statistical Classification of Diseases and Related Health Problems', ICD 10, C50. Depending on the location of the carcinoma subgroups are differentiated. The WHO distinguishes between non-invasive and invasive carcinomas depending on the histological phenotype.

To ascertain the malignancy of a tumour mammography is performed in combination with ultrasound scans. Uncertain findings are ensured by vacuum stamp biopsy in order to obtain tissue which can be assessed histological. If, after these measures, a tumour is found to be malignant, the further staging can only be done after surgery.

The tumour size, nodal status and distant metastases are categorised in the TNM system (see Tab. A-2 of the appendix). The grade of differentiation is determined

according to Elston and Ellis (2002). A sum score integrating histological parameters such as architectural pattern of the cell, nuclear polymorphism and mitotic count leads to one of the following three categories:

G1 well differentiated
G2 moderately differentiated
G3 poorly differentiated

Moreover, the hormone receptor (estrogene and progesterone) and the HER2 status contribute to the staging and influence the treatment decision.

1.1.1.2 Treatment concepts

The appropriate treatment should be tailored to the individual patient. The choice of treatment depends on the staging of the tumour and the individual patient characteristics. Surgery, radiotherapy and systemic therapy (e.g. chemotherapy) are the main pillars of the therapy of breast cancer. Breast conserving surgery with mandatory subsequent radiation therapy can be an alternative to the formerly used standard modified radical mastectomy. Chemotherapy, endocrine therapy and monoclonal antibodies are options of the systemic therapy, which can be administered either alone or in combination. Curative and palliative treatment concepts are distinguished. Within the curative treatment concepts the systemic therapy can be neo-adjuvant (before the surgery) or adjuvant (to support the success of the surgical measure). The commonly applied substances are the anthracyclines epirubicin (E) and doxorubicin (A), cyclophosphamide (C), methotrexate (M), fluorouracil (F) and the taxanes paclitaxel and docetaxel. The current recommendations of the St. Gallen consensus conference for the adjuvant treatment suggest either

4 cycles EC/AC or 6 cycles CMF
or 6 cycles of an anthracycline-containing chemotherapy regimen (e.g. FEC)
or a taxane-containing chemotherapy regimen (Nitz and Mohrmann, 2003).

If patients have an increased risk for a relapse an anthracycline-containiing regimen including 3 substances is recommended. In St. Gallen the algorithm for the treatment decisions in the adjuvant situation has been updated as shown in Tab. 1-2.

Depending on the menopausal status and the hormone receptor status, the

nodal status and the individual's prognostic factors the decision is made whether chemotherapy is administered at all, alone or in combination with an endocrine therapy. Trastuzumab is not yet registered for the use in the adjuvant situation. Studies are currently being conducted which survey the value of trastuzumab in the adjuvant situation (German Adjuvant Breast Cancer Group, 2002).

Tab. 1-2 Adjuvant treatment options St. Gallen 2003 (Nitz and Mohrmann, 2003)

Nodal negative				
	Hormone-receptor positive		Hormone-receptor negative	
	Pre-menopausal	Post-menopausal	Pre-menopausal	Post-menopausal
Minimal risk T1a,b,c, N_0, G1 and ER/PR+ and ≥35 years	Tamoxifen or nothing	Tamoxifen[a] or nothing	No available data	No available data
All other constellations	Ovarian suppression + Tamoxifen / Chemotherapy[b] + Tamoxifen	Tamoxifen[a] or Chemotherapy[b] + Tamoxifen	Chemotherapy[b]	Chemotherapy[b]
[a] Anastrozole if tamoxifen is contraindicated (only for postmenopausal women) [b] Containing anthracyclines, CMF only with minimal risk				
Nodal positive				
	Hormone-receptor positive		Hormone-receptor negative	
	Pre-menopausal	Post-menopausal	Pre-menopausal	Post-menopausal
Increased risk	Ovarian suppression + Tamoxifen / Chemotherapy[b] + Tamoxifen	Tamoxifen[a] or Chemotherapy[b] + Tamoxifen	Chemotherapy[b]	Chemotherapy[b]
[a] Anastrozole if tamoxifen is contraindicated (only for postmenopausal women) [b] Containing anthracyclines				

Combination of epirubicin and cyclophosphamide

As mentioned above a variety of chemotherapy regimens are approved for the use in the adjuvant treatment of breast cancer. Since Fisher et al. showed that four cycles of an anthracycline-containing regimen have equal efficiency in terms of relapse-free and

overall survival compared to six cycles CMF, combination regimens of cyclophosphamide combined with either doxorubicine (AC) or epirubicin (EC) became a standard in the adjuvant treatment of breast cancer (Fisher et al., 1990). It is suitable for the ambulatory application and also presents with a tolerable toxicity profile.

Epirubicin

Epirubicin is a stereoisomer of doxorubicin with an inverse stereochemistry of the hydroxyl group in the C-4' position of the amino sugar. Like other anthracyclines, the precise mechanism of action of epirubicin is unknown, but it is primarily related to intercalation of the planar ring with DNA and subsequent steric inhibition of DNA and RNA synthesis. The intercalation seems to interfere with the topoisomerase-DNA-'cleavable complex'. Other discussed potential mechanisms of action are the formation of free radicals and chelate complexes with metal ions. Epirubicin acts cell cycle phase-nonspecific. Still the maximum effects appear to be in the S- and G_2-phase of the cell cycle (Roth und Fenner, 2000, Pharmacia 2003).

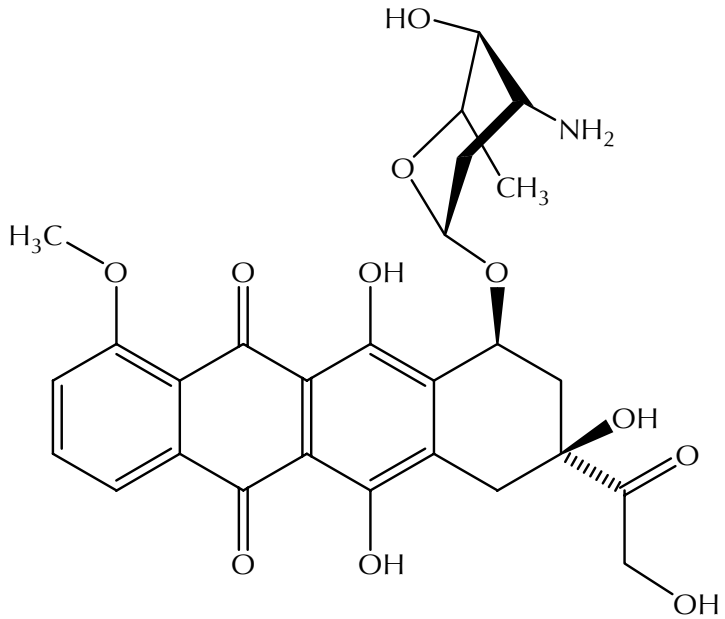


Fig. 1-1 Chemical structure of epirubicin

Epirubicin is approved for the indications breast cancer, gastric cancer, small cell lung cancer, ovarian cancer and soft tissue sarcoma. Epirubicin is mainly excreted by the biliary route (40% in 72 h). The active metaboltite is epirubicinol and as inactive metabolites two glucuronides and 4 aglycones are known.

Its pharmacokinetic properties are listed in (Tab 1-3).

Tab. 1-3 Pharmacokinetics of epirubicin

Pharmacokinetic parameter	Epirubicin
Vd	32 - 46 L/kg
CL	30 - 100 L/h
$t_{½}\alpha$	3.0 - 4.8 min
$t_{½}\beta$	1.1 - 2.6 h
$t_{½}\gamma$	18 - 45 h

The dosing depends on the protocol by which the patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. In combination with cyclophosphamide in the treatment of breast cancer it is dosed at 90 mg/m^2 BSA.

The acute dose-limiting toxicity is myelosuppression (febrile neutropenia and granulocytopenia) with a nadir between day 10 and 14 post-chemotherapy. Epirubicin is associated with cardiac toxicity. Serious, irreversible cardiomyopathy with delayed congestive heart failure often unresponsive to therapy may be encountered as the cumulative dose approaches 1000 mg/m^2. Cardiac monitoring is advised when the cumulative dose exceeds 650 mg/m^2. Observed dermatologic toxicity comprises rashes and an epirubicin flare due to histamine release. Practically all patients experience a complete alopecia which is reversible two to three months after the end of chemotherapy. In some cases mucositis (stomatitis and esophagitis) has been reported. The emetogenic potential of the substance is moderate to high (ESMO guidelines task force, 2001). Epirubicin is a vesicant and can cause tissue necrosis after extravasation. Immediate measures have to be initiated to interrupt the tissue damage. Other adverse effects are diarrhea, fever, amenorrhea, conjunctivitis and fatigue.

Cyclophosphamide

Cyclophosphamide is an oxazaphosphorine, an inactive cyclic phosphamide ester of mechlorethamine (Fig. 1-2).

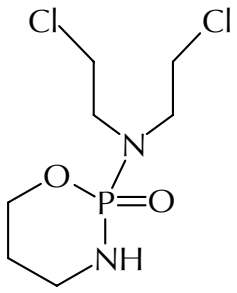


Fig. 1-2 Chemical structure of cyclophosphamide

It is converted by hepatic and intracellular enzymes to its active alkylating metabolites 4-hydroxycyclophosphamide, aldophosphamide, acrolein and phosphoramide mustard. Cyclophosphamide causes prevention of cell division primarily by cross-linking DNA strands. It is considered to be cell cycle-phase non-specific, but cell cycle specific. It has an almost complete bioavailability (ca. 70-90%) after oral administration. The maximum plasma levels are reached after approximately one hour and after six to eight hours half of the substance is eliminated. Of the unmodified cyclophosphamide 10-20% are eliminated renally (Roth and Fenner, 2000).

Toxicity caused by cyclophosphamide is dose-dependent and usually reversible. Myelosuppression presents with leukocytopenia, thrombocytopenia and anemia. The nadir is observed between day 8 and 15 following administration and is associated with immunosuppression and the risk of severe infections and fever.

Gastrointestinal adverse effects such as diarrhea, constipation, stomatitis and anorexia occur rarely. The emetogenic potential is considered moderate to high depending on the dose (ESMO guidelines task force, 2001). Dose-related hemorrhagic cystitis occurs due to direct contact of toxic metabolites accumulating in concentrated urine with the bladder mucosa. This occurs in 10% of patients and may occur during or several months after treatment. Cystitis may result in chronic inflammation leading to fibrosis, telangiectasis of the bladder epithelium and bladder cancer. Severe cases may be fatal. Prophylactic measures to reduce the incidence of cystitis include catheter bladder drainage, bladder irrigation, hyperhydration, forced diuresis and the administration of mesna.

Cyclophosphamide is approved for the use in polychemotherapy and monochemotherapy for a variety of indications such as leukemias (ALL, AML, CLL, CML), lymphomas (Hodgkin's disease, Burkitt's lymphoma, multiple myeloma,

Non-Hodgkin's lymphoma, plasmocytoma), solid tumours (breast cancer, lung cancer, ovarian cancer, neuroblastoma, Ewing sarcoma), auto-immune deficiencies and immunosuppressive treatment after organ transplantation (Seeber and Schütte, 2003).

Cyclophosphamide is dosed according to body weight in children and according to BSA in adults. The individual dosage depends on the treatment regimen. In combination with epirubicin in the adjuvant treatment of breast cancer it is dosed at 600 mg/m^2 BSA.

1.1.1.3 Public awareness

In recent years public awareness of breast cancer has clearly increased. The German government introduced disease management programmes for patients with breast cancer, new patient initiatives were founded (e.g. Mamazone e.V.) and a number of studies have been conducted which surveyed the perception of the care process by the affected women (Veronesi et al., 1999; Jänel et al., 2000; Deutsche Krebshilfe, 2003). Thirteen European countries participated in the 'Caring about women and Cancer – CAWAC' study. More than 13,000 patients completed questionnaires of which 77% had breast cancer and 10% had ovarian cancer. The study identified aspects of care which seem to offer a potential for improvement. Among others the information on side effects was judged unsatisfactory by a considerable number of patients depending on the received treatment (15-25%) (Veronesi et al., 1999). The study group concludes that although there is a raised awareness of the importance of well educated and informed patients, there are still shortcomings in the delivery of information. This has also been found by Jänel et al. (2000). They surveyed the care situation of breast cancer patients in Germany. Patients expressed their need for comprehensive information on their treatment to be able to participate in the decision process. The involved physicians criticesed the delayed information flow between the different treating institutions and supported the idea of a better interdisciplinary cooperation.

The German 'Krebshilfe' recently conducted a study to illustrate the current situation of 'women with breast cancer in the medicine system' (Deutsche Krebshilfe, 2003). Based on the results twelve goals were defined which aim at improving the provision of care to breast cancer patients. A number of these objectives are addressed by pharmaceutical care. One major proposal are guidelines for appropriate

patient-oriented information, which covers the complete treatment process. Different target groups should be considered and guidelines on how to conduct a consultation with the patient should be made available to the practitioner. Such guidelines should become a standard in the care of cancer patients just like for any other aspect of medical treatment. Another demand is the quality assurance in the treatment of breast cancer. This can be achieved by interdisciplinary cooperation, specialisation of care providers, implementation of clinical guidelines which cover the complete treatment process and certified breast centres. The information on the treatment options and the different therapy settings should be made accessible, comparable and transparent to the patient. The individual's quality of life should be a main focus for treatment decisions. The information on the planned treatment should be offered to the patient prior to the beginning of the treatment and in a sufficient amount of time to enable the patients to make informed decisions. The information process should be structured and integrate different suitable media. The results of the study undertaken by the German 'Krebshilfe' also indicate that the ambulatory sector should be integrated better in the whole treatment process.

1.1.2 Ovarian cancer

1.1.2.1 Epidemiology

In Germany approximately 7,400 new cases of ovarian cancer are diagnosed per annum. With this incidence ovarian cancer represents about 4% of malignancies in women. Ovarian cancer is the sixth most common neoplasm among women (Trope and Kristensen, 1997). The aetiology of this type of cancer has not yet been elucidated, however there are several known potential risk factors. Age, as in many other malignancies, is a discussed risk factor. The prevalence among women older than 60 years is noticeably higher than among younger women. Other risk factors include: total number of ovulations, where risk increases with increased number of ovulations, previous gynaecological malignancies and nutritional factors (Batzler et al., 2002a). A genetic predisposition underlies approximately 5-10% of the cases (Engel et al., 2001). The prevalence of ovarian cancer in Germany has been almost constant over the past 20 years. Compared to other gynaecological malignancies the prognosis is considered unfavourable. The 5-year survival rate is about 35%. Over the last

decade the mortality in Germany declined marginally (Batzler et al., 2002a). This is concordant with observations in the US. McKean-Cowdin et al. attribute this development to the increased use of oral contraceptives in the female population which has a protective effect by reducing the total number of ovulations (2000).

Ovarian cancer is referred to as a heterogeneous group of neoplasms evolved from the ovary. In the ICD 10, ovarian cancer is categorised C56 among gynaecologic malignancies. Approximately 90% of malignant ovarian neoplasms originate from the ovarian surface celomic epithelium. This type is characterised as epithelial ovarian cancer (EOC). The remaining cases are represented by germ cell tumours and stromal tumours. EOCs are differentiated according to their histological appearance. The different types are classified according to the WHO classification system (Dettmar et al., 2001; Morin and Pizer, 2001).

In addition, a histopathological grading is performed to determine the differentiation of the tumour cells. Silverberg proposed criteria in 1998 which are now commonly used (Shimizu et al., 1998). A sum score integrating histological parameters such as architectural pattern of the cell, nuclear polymorphism and mitotic count leads to one of three categories as described for breast cancer (see chapter 1.1.1.1). With complete and sound histological findings the disease staging can be performed. Usually the stage of ovarian cancer is specified according to the TNM classification and the FIGO classification (appendix B, Tab B-2).

1.1.2.2 Treatment concepts

The treatment of ovarian cancer depends foremost on its stage at diagnosis. The main treatment options applied are surgery and chemotherapy. As with most cancers the therapeutic options should be tailored to the patient's individual situation. Surgery is indicated in all malignant cases and can, depending on the stage of the disease, either be applied independently or in combination with other therapeutic options such as chemotherapy. Studies indicate a benefit of combination therapy in many situations. Radiation therapy is only performed for particular indications such as for palliative symptom relief and for inoperable tumours. In the adjuvant situation the benefit of radiation therapy is controversial (Lindner and Würschmidt, 2001).

The choice of the eligible chemotherapy depends mostly on disease stage and the type of previously administered chemotherapy regimens. To achieve an optimal treatment outcome a combination regimen using more than one chemotherapeutic agent has proved to be the most effective strategy (Advanced Ovarian Cancer Trialist Group, 1991; Trope and Kristensen, 1997; Lutz et al., 2001). The question of which antineoplastic agents are the most effective combination has been addressed in several clinical investigations. Before the introduction of the taxanes as a treatment option, the various available combination regimens did not produce convincing results in terms of survival differences or complete response rates (Advanced Ovarian Cancer Trialist Group, 1991; Trope and Kristensen, 1997). For many years a combination of cisplatin and cyclophosphamide was standard in the treatment of advanced ovarian cancer. When paclitaxel was introduced as an antineoplastic agent with a novel mechanism of action survival and response rates were improved (Ozols, 1995). Paclitaxel is now the principal component of chemotherapy regimens for advanced epithelial ovarian cancer together with either cisplatin or carboplatin (Trope and Kristensen, 1997; du Bois et al., 1999).

Combination of carboplatin with paclitaxel

Since its registration in 1992 paclitaxel has been investigated in the treatment of ovarian cancer in various combinations and doses (Calvert et al., 1995; McGuire et al., 1996; du Bois et al., 1997). At present the combination of paclitaxel (175 mg/m^2) and carboplatin (AUC 5 mg·min/mL) is the established standard regimen (du Bois et al., 1999).

When drugs are used in combination, potential drug interactions need to be considered. For the combination of paclitaxel and carboplatin neither a pharmacokinetic interaction nor a sequence-dependence of pharmacokinetic disposition could be found. Additionally a remarkable reduction of thrombocytopenia was observed when patients received carboplatin in combination with paclitaxel (Calvert et al., 1995; Obasaju et al., 1996; Calvert, 1997; Kearns and Egorin, 1997; Siddiqui et al., 1997; van Warmerdam et al., 1997). The mechanism of this protective effect still remains to be elucidated. The major dose-limiting toxicity of this combination seems to be neutropenia (Langer et al., 1995; Kearns et al., 1995). Other

non-haematologic adverse effects described are nausea and emesis, fatigue and peripheral neuropathy.

Paclitaxel

In 1992, paclitaxel, a diterpene (Fig. 1-3) isolated from the cortex of the pacific yew tree (taxus brevifolia), was registered in the United States as a new antineoplastic agent (Bartsch, 2000). Paclitaxel is obtained semi-synthetically from the natural baccatin III. Baccatin III can be found in renewable sources such as needles and saplings which guarantee sufficient amounts for industrial production. Total synthesis has proved to be a difficult task. In 1994 Nicolaou et al. were the first who succeeded in synthesising paclitaxel, however, the total synthesis does not play a role in the industrial production. To date the semi-synthetically obtained paclitaxel is being used.

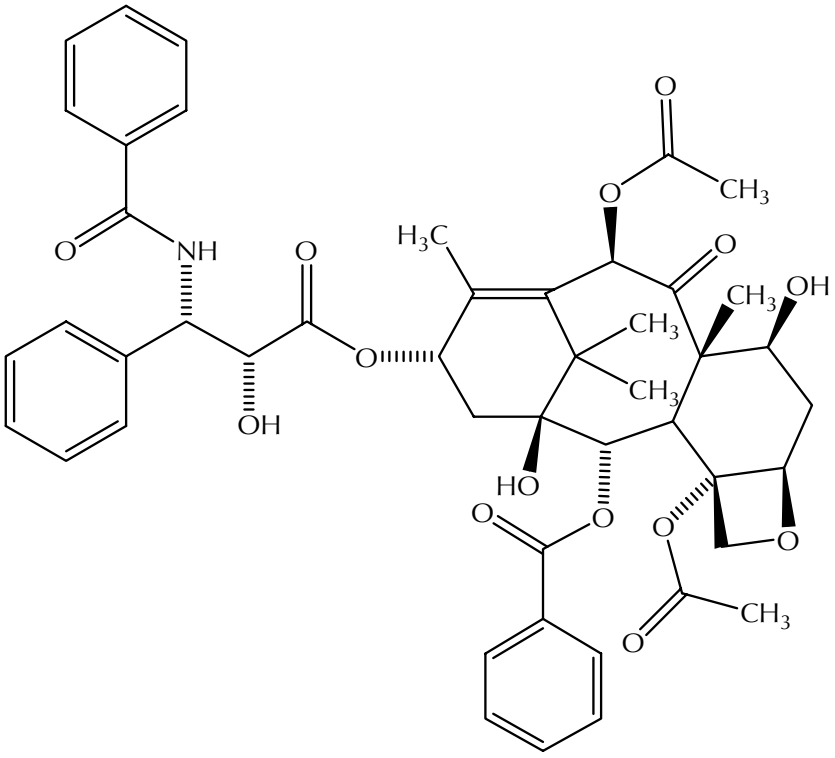


Fig. 1-3 Chemical structure of paclitaxel

Although the exact mechanism of action of paclitaxel has not been fully explained, it appears to involve the promotion and excessive stabilisation of microtubule polymer or bundle formation during the cell cycle (Bartsch, 2000).

In 1989 McGuire et al. described the effectiveness of paclitaxel against ovarian cancer even in platinum refractory types. It is now registered for the indications

NSCLC, ovarian cancer and breast cancer. Furthermore it showed in-vitro cytotoxicity against a variety of solid tumours and haematologic neoplasms such as cervical, pancreas, prostate, head and neck, colon, gastric, bladder, lung and CNS cancers, melanoma, hepatoma and leukaemia cell lines (Spencer and Faulds, 1994).

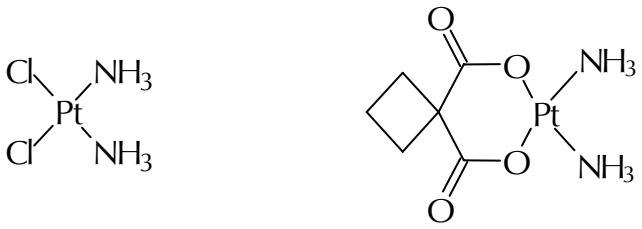
The dose-limiting toxicity of paclitaxel is myelosuppression with leukocytes affected more severely and commonly than thrombocytes or reticulocytes. Myelosuppression is related to the duration that plasma paclitaxel concentrations are greater than or equal to 0.05 µmol/L (Gianni et al., 1995; Kearns et al., 1995). Other adverse effects include myalgias, arthralgias, alopecia, diarrhea, nausea, vomiting, mucositis, and in particular peripheral neuropathy. Other undesirable effects associated with the use of the drug are hypersensitivity reactions. These reactions manifest as dyspnoea, bronchospasms, hypotension, angioedema, urticaria, flushing and/or erythematous rash and seem to be associated with the vehicle in which paclitaxel is formulated in order to increase the solubility – polyoxyethylated castor oil (Cremophor EL). Premedication with dexamethasone and H_1- and H_2-receptor antagonists reduces the incidence of severe reactions to less than 5% (Spencer and Faulds, 1994).

The pharmacokinetic of paclitaxel is nonlinear. Peak plasma paclitaxel concentrations and AUCs both change disproportionately to changes in dose. The nonlinear pharmacokinetic might be attributed to saturable processes in distribution and elimination which can be described using Michaelis-Menten kinetics (Kearns et al., 1995). Van Tellingen et al. investigated the role of Cremophor EL in the nonlinear pharmacokinetics of paclitaxel. They found that Cremophor EL is responsible for the nonlinearity which they denominate as pseudo nonlinearity as higher plasma levels do not correlate with higher tissue levels (van Tellingen et al., 1999). The drug is mainly eliminated via the biliary tract (>90%) and is highly bound to plasma proteins (88-98%) (Sonnichsen and Relling, 1994; Spencer and Faulds, 1994; Bartsch, 2000). The metabolisation is dependent on the enzymesystem CYP3A and CYP2C. The elimination half-life is between 3.8 and 16.5 hours. For paclitaxel a high interindividual variability of the pharmacokinetic parameters has been described. It would therefore be reasonable to consider TDM for this drug in order to minimise toxicity and maximise efficacy. In order to find the optimal dosage for patients it is necessary to know pharmacokinetic–pharmacodynamic relationships that relate plasma levels to

toxic effects such as neutropenia and peripheral neurotoxicity as well as tumour response. Investigations undertaken to elucidate these relationships found that infusion times as well as the duration of plasma levels above a certain 'threshold' are parameters that are related to neutropenia. AUCs, on the other hand, do not seem to be reasonable parameters to predict toxicity as they are similar for 3-h and 24-h infusions (Kearns et al., 1995). To date a relationship between pharmacokinetic parameters and tumour response has not been shown.

Carboplatin

Carboplatin or Cis-diamin (1.1-cyclobutandicarboxylato) platinum II is a second generation analogue of cisplatin that is characterised by a different toxicity profile.



Cisplatin Carboplatin

Fig. 1-4 Chemical structure of cisplatin and carboplatin

Carboplatin differs from cisplatin by the leaving groups as illustrated in Fig. 1-4. The two chlorine ligands are exchanged for a cyclobutandicarboxylato ligand. Carboplatin is less toxic than cisplatin. Oto-, nephro- and neurotoxicity occur rarely. The dose-limiting toxicity of carboplatin appears to be myelosuppression, especially thrombocytopenia (Van Echo et al., 1989; Highley and Calvert, 2000).

The antitumour effect of platinum compounds is thought to be due to interaction with DNA. Carboplatin and cisplatin appear to share a similar mechanism of action. As a first step aqua complexes are formed. The aquated compounds form bifunctional adducts with DNA (see Fig. 1-5). Intrastrand cross-links have been observed between two adjacent guanines (Pt-GG) or adjacent guanine and adenine (Pt-AG). For carboplatin the main adduct seems to be the intrastrand cross-link G-Pt-G in which carboplatin is bound to two guanines separated by another base. Monofunctional adducts (Pt-G) and interstrand bifunctional adducts were found as well (Vermorken et al., 1993; Blommaert et al., 1995; Fink and Howell, 2000). Due to the lesser reactivity

of carboplatin, a larger dose is required compared to cisplatin to obtain an equal effect (van der Vijgh, 1991).

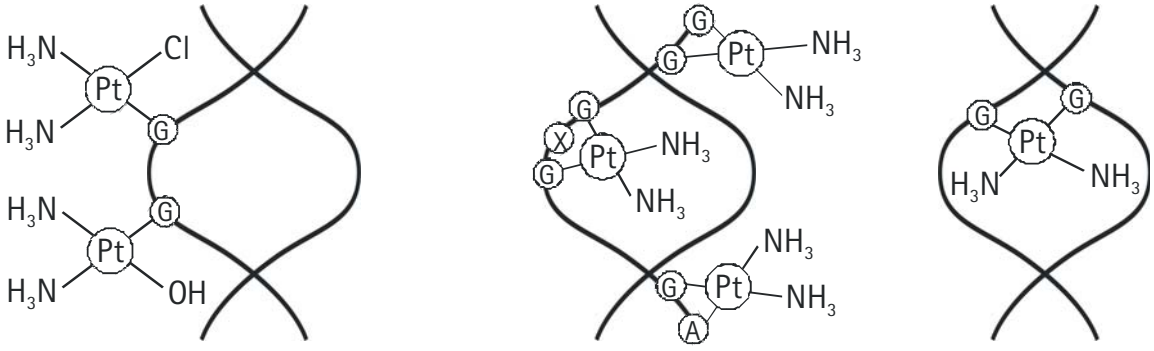


Fig. 1-5 Intra- and interstrand reactions of cisplatin with DNA

Carboplatin shows an antineoplastic effect in ovarian cancer, germ cell tumours, bladder cancer, small cell lung cancer and head and neck cancer (van der Vijgh, 1991; Highley and Calvert, 2000). It is administered intravenously.

Carboplatin exhibits linear pharmacokinetics according to an open two-compartment-model (van der Vijgh, 1991; Vermorken et al., 1993). It is mainly eliminated by renal excretion, entirely through glomerular filtration. Carboplatin is less protein-bound than cisplatin. This can be attributed to the lower reactivity of the substance. Within the first two hours post infusion the ultrafilterable concentration accounts for 60-80% which then slowly declines to 50% (Van Echo et al., 1989; Highley and Calvert, 2000). The elimination half-life is 6 h for ultrafilterable platinum. A correlation between the AUC of ultrafilterable plasma carboplatin and the extent of thrombocytopenia has been shown in clinical studies. Depending on whether the patient has previously been treated with chemotherapy or not, linear relationships were described which facilitate the prediction the extent of thrombocytopenia for certain carboplatin AUCs (Egorin et al., 1985; Van Echo et al., 1989; Jodrell et al., 1992; Egorin et al., 1994). Patients with carboplatin AUC 4 to 5 seem to have the lowest risk of developing thrombocytopenia (Jodrell et al., 1992). Additional studies suggest that no significant improvement in tumour response can be achieved by increasing the carboplatin AUC over 5 or 7 mg·min/mL in conventional chemotherapy for previously treated or untreated patients respectively (Jodrell et al., 1992; Jakobsen et al., 1997; du Bois et al., 1999).

1.2 Specific aspects of antineoplastic drug treatment

1.2.1 Safety of cytotoxic drugs

Antineoplastic therapy is associated with various desirable and undesirable outcomes. It is the main focus of the oncology care team to improve the desirable outcomes such as cure of the disease, slowing the disease progression, decreased symptoms, and to reduce the incidence of the undesirable outcomes such as mortality, disease progression, adverse effects, severe organ toxicity and drug resistance. Some toxicity may be dose-limiting and even lead to an interruption of the therapy. Thus, the success of the therapy is strongly connected to the severity of therapy-associated toxic effects. An efficient supportive care in order to control these adverse drug reactions (ADRs) is crucial for optimal treatment outcomes. The more complex drug regimens get the higher is the risk of experiencing drug-related problems (DRP). Drug-related problems in cancer chemotherapy can have severe consequences originating from the high toxicity of anticancer drugs. They may arise from lack of adherence to the protocols, may be associated with the chemotherapy itself or with inadequately applied supportive medication. Numerous attempts have been made to improve the prevention of medication errors in chemotherapy. Additional to systematic changes prevention strategies should also be applied on the individual basis.

1.2.2 Drug-related problems in systemic drug therapy

Whenever a patient receives a systemic drug therapy it is associated with a variety of potential risks. Strand et al. (1990) define drug-related problems (DRP) as problems which *exist when a patient experiences either a disease or symptom having an actual or suspected relationship with drug therapy*. They introduced eight categories of drug-related problems which physicians and pharmacists should be aware of. DRPs arise when (1) a patient does not receive a drug for an existing indication, (2) a wrong drug has been chosen for the indication, (3) under-dosage of the correct drug, (4) over-dosage of the correct drug, (5) a medical condition resulting from an ADR occurred, (6) a drug-drug, drug-food or drug-laboratory interaction is observed, (7) a medical condition occurs due to taking a prescribed drug or (8) a medical condition occurrs

because no valid drug has been prescribed.

Adverse drug reactions (ADR) represent a particular group among the DRPs. According to the World Health Organization ADRs are any noxious, unintended, and undesired effects of a drug, which occur at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, medication errors and abuse. Lazarou et al. found that fatal adverse drug reactions (ADRs) ranked between fourth and sixth leading cause of death in the United States in 1994 (Lazarou et al., 1998). Serious ADRs presented with an incidence of 6.7% (95% CI 5.2-8.2%) and fatal ADRs with an incidence of 0.32% (95% CI 0.23-0.41%). The authors explicitly checked ADRs which only account for a part of all potential drug-related problems. This impressively illustrates how crucial the prevention of ADRs and thus DRPs is.

Compared to the two terms discussed above another term has to be differentiated. Adverse drug events (ADE) are injuries which result from a medical intervention related to a drug, but compared to an ADR it also covers events if the drug has been used inappropriately and it also applies if it is not clarified whether the event is actually caused by the drug involved. Bates et al. published data of the incidence of ADEs in hospitalised patients (Bates et al., 1995). They detected 6.5% ADEs (related to hospital admissions) of which 30% were serious ADEs and 28% of all observed ADEs were judged as preventable. Only looking at the serious and life-threatening ADEs 42% were preventable. These results reflect that ADEs can be rated as common problems which have a good potential for optimisation. This conclusion can also be drawn from data of Gandhi et al. (2003). They surveyed the incidence of ADEs in ambulatory care. In total 25% ADEs (related to the number of patients) were detected of which 13% were rated serious and 11% preventable. The frequency of ADEs observed in ambulatory care is four times as high as in the comparable study for hospitalised patients. This is partly due to the fact that not only patient charts were reviewed but also patients reported ADEs. Another remarkable fact is that the main factor associated with the risk of an ADE was the number of drugs taken. The complexity of the treatment as a risk factor for adverse events has also been described by Leape et al. (1991). Applying these findings to the pharmaceutical care of ambulatory cancer patients offers many starting points. These patients receive a complex treatment and have an additional risk of experiencing ADEs in the ambulatory

setting.

Not only for safety reasons it seems important to reduce the incidence of ADRs, DRPs and ADEs. Studies conducted in American nursing homes have shown that with every dollar spent on drugs 1.33 US$ have to be afforded for treating adverse drug events (Alliance for Aging Research, 1998). Therefore, the prevention or the detection of drug-related problems at an early stage has also a large saving potential.

1.2.3 From compliance to concordance

Another factor which influences the optimal treatment outcome is the way in which a patient translates the recommendations of the healthcare provider into action. The patients' 'compliance' has been an issue for many years. Along with the development of a new patient role goes the development of a new term as a replacement for "compliance". The Royal Pharmaceutical Society of Great Britain published a report which addresses this topic (1997). The report is based on the assumption that about 50% of patients who suffer from chronic diseases do not take their medication in therapeutic doses and so do not derive the optimum benefits from their treatment. This being the cause for increased health services expenditure as well as a dissatisfying quality of health care should be surveyed and improved. One of the several reasons researchers have identified for the failure to achieve the potential benefit from medication is the failure in communication with patients. They suggest, that the most salient and prevalent influences on medicine taking are the beliefs that people hold about their medication and medicines in general. These beliefs often differ from the best evidence from medical science. Yet they are firmly rooted in the personal, familial and cultural experiences of our society. The concept of compliance does not take this cognition into account and more or less asks of the patient for absolute obedience to the recommendations of the healthcare provider. Concordance in the opposite is based on the notion that the working relationship between the healthcare provider and patient is a negotiation among equals and that therefore the aim is a therapeutic alliance between them. Its strength is the relationship between the doctor and the patient. Together they can proceed on the basis of reality and not of misunderstanding, distrust or concealment. This new perspective goes along well with the goals of pharmaceutical care which aims at meeting the patients' needs and at developing the treatment plan in cooperation with healthcare providers and patients.

1.2.4 Evidence-based drug therapy

The most common definition of evidence-based medicine (EBM) is taken from David L. Sackett. He describes EBM as the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research (Sackett, 1997). Clinical expertise calls for life-long learning and the willingness to communicate with others involved in the care of the patient in order to gain as much information as possible to be able to make the right decision. The patient brings to the encounter his or her own personal and unique concerns, expectations, and values which should also be considered in the treatment decision in order to improve the compliance and to meet the patient's needs.

The best evidence is usually found in clinically relevant research that has been conducted using sound methodology. For the practitioner it is rather time-consuming to do profound searches in every day practice. This problem is addressed by societies for the medical specialities which compile evidence-based therapeutic guidelines and treatment algorithms. The Cochrane collaboration has developed this approach since 1993. They produce and maintain systematic reviews in many areas of health care (The Cochrane collaboration, 2003) which are available to the practitioner in the Cochrane library. The Oxford Centre of Evidence-based Medicine published the so called 'Levels of Evidence' and according 'Grades of Recommendation' (2001). These serve as tools to classify the results of meta-analyses in a standardised way.

The elaboration of therapeutic guidelines in a multidisciplinary team approach with physicians, pharmacists and other healthcare professionals and their consequent implementation should contribute to improve the patients' quality of life and help reduce unnecessary drug costs. Among others Dranitsaris et al. (2001) showed in a prospective intervention study that the implementation of evidence-based antiemetic guidelines with the support of pharmacists could promote the clinically appropriate use of $5HT_3$ receptor antagonists. The therapeutic outcome for the patient was improved and drug costs were reduced.

1.2.5 Individualised chemotherapy

The generally narrow therapeutic range of antineoplastic agents holds a particular risk for the patient in terms of drug safety. The relationship between the systemic exposure of antineoplastic drugs and their toxic and therapeutic effects is widely recognised. For drugs such as fluorouracil, mercaptopurine and methotrexate a relationship between pharmacokinetics and treatment outcome has been shown. For other anticancer drugs such as platinum complexes, anthracyclines and some antimetabolites a relationship between the serum concentrations and the respective dose-limiting toxicity is described (Hon and Evans, 1998). In general all antineoplastic drugs should be dosed as high as tolerable for the patient in order to achieve a maximum antitumour effect. Optimally, the adverse effects should be limited to a minimum.

Three basic dosage strategies can be distinguished which are illustrated in Fig. 1-6. The empirical dosage strategy applies a definite dose to each patient which results in variable plasma concentrations and consequently even greater variability in the achieved effect. The common dosage strategy for adults in oncology is based on body surface area (BSA) according to Du Bois and Du Bois (1916). The observed variability using this method is often not much less than by using the empiric dosage strategy which leads to either over- or under-dosage with the according consequences (Gurney, 2002; Jaehde, 2003). In order to provide optimal treatment to cancer patients there is a strong need to find more precise dosage strategies. Conceivable approaches are pharmacokinetically or pharmacodynamically guided dose individualisation. Using the latter, the dose is adjusted based on the measurement of the desired effect. In oncology however, this approach is not applicable. Thus, pharmacokinetic dose individualisation seems to be a reasonable approach.

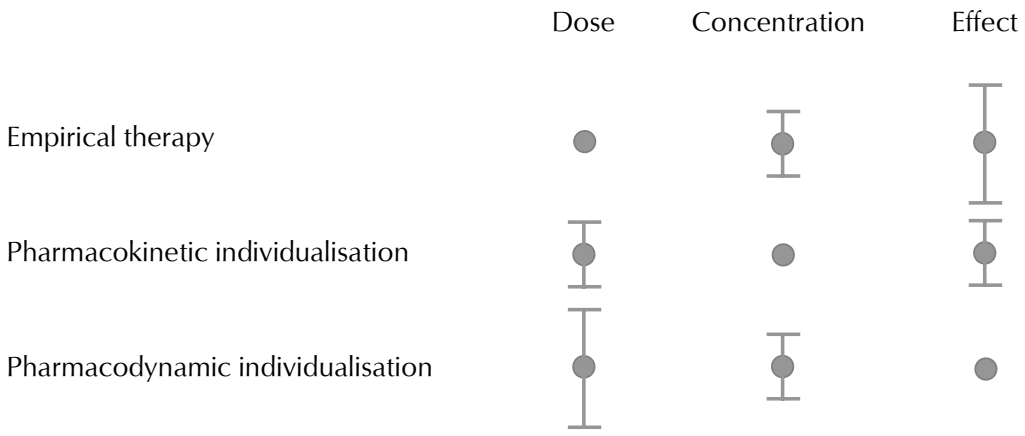


Fig. 1-6 Dose, concentration and effect variability using different dosage strategies (from Jaehde, 2003)

The measure which allows a prediction of drug exposure of an individual patient is the concentration of free drug in the plasma over a period of time (Area under the concentration time curve – AUC). The dose can be adapted accordingly. With this method the dose varies from patient to patient and even for an individual patient depending on the physiological conditions. The variability of the effects (desired and undesired) can be limited. In oncology, therapeutic drug monitoring (TDM) is being used on a regular basis already to control high-dose methotrexate therapy. Except this example, however, TDM does not yet have a broad application in antineoplastic chemotherapy treatment. Another example of a dosage method based on pharmacokinetic considerations is the target AUC approach. This will be described in detail in the following section.

1.2.5.1 Dose individualisation of carboplatin

Investigations on the pharmacokinetics and pharmacodynamics of carboplatin as mentioned above have led to the proposal for new methods of individualising dose. The reason for seeking an alternative dosage strategy was the observation of extreme variability in the AUC of the drug depending on the pre-treatment GFR of the individual patient (Calvert et al., 1989; van Warmerdam et al., 1996). Renal excretion is accomplished exclusively by glomerular filtration (measurable as GFR). Thus, the AUC of carboplatin is dictated primarily by the pre-treatment GFR. Several authors have

proposed dosage strategies based on the renal clearance of the drug (Egorin et al., 1985; Calvert et al., 1989; Chatelut et al., 1995; Huitema et al., 2000). The AUC correlates highly with drug-related toxicity especially thrombocytopenia and also with tumour response (Egorin et al., 1984; Jodrell et al., 1992; Calvert and Egorin, 2002).

Currently there are two principle methods being used to calculate the carboplatin dose. Calvert et al. derived a dosing formula based on the individual GFR:

$$\text{Dose}\,[\text{mg}] = \text{AUC}\,[\text{mg}\cdot\text{min/mL}]\cdot(\text{GFR}\,[\text{mL/min}] + 25) \qquad \text{(Eq. 1-1)}$$

The absolute dose is determined from the target AUC and the GFR. The constant of 25 represents the average non-renal clearance for adults. Calvert used the ^{51}Cr-EDTA method to estimate the GFR. As this method is rather inconvenient it did not establish in clinical practice. Another method to determine the creatinine clearance is to collect 24-h urine and analyse the contained creatinine. Similar to carboplatin, creatinine is primarily excreted by glomerular filtration. This method is not widely used either as it requires a 100% patient compliance in order to collect the urine completely. Alternatively there are two other methods being used to estimate the GFR. Cockcroft and Gault (Eq.1-2) as well as Jelliffe (Eq. 1-3) derived equations to estimate creatinine clearance (CL_{cr}) taking into account the serum creatinine concentrations and other patient-specific factors such as body weight, sex and age (Jelliffe, 1973; Cockcroft and Gault, 1976). Subsequently, the estimated creatinine clearance is equated with the GFR in Eq. 1-1. This assumption is not permitted if patients have been pre-treated with cisplatin, as renal function is most likely to be affected by cisplatin-exposure.

$$\text{CL}_{\text{Cr}}[\text{mL/min}] = \frac{(140 - \text{age}\,[\text{years}])\cdot\text{weight}\,[\text{kg}]}{72\cdot\text{Serum creatinine}\ [\text{mg/dL}]}\cdot 0.85\,[\text{female}] \qquad \text{(Eq. 1-2)}$$

$$\text{CL}_{\text{Cr(Jelliffe)}}[\text{mL/min}] = \frac{98 - 16\cdot\left(\frac{\text{age - 20}\,[\text{years}]}{20}\right)}{\text{Serum creatinine}\ [\mu\text{mol/L}]}\cdot 0.9\,[\text{female}] \qquad \text{(Eq. 1-3)}$$

The Cockcroft-Gault equation is currently the most commonly used method to estimate the GFR for use in the dosage method established by Calvert et al..

Chatelut et al. developed a method for the prediction of the carboplatin clearance in order to calculate the optimal dose for a patient to achieve a definite AUC based on population pharmacokinetic data.

They start with the basic pharmacokinetic equation AUC = dose/CL:

$$\text{Carboplatin dose}\,[\text{mg}] = \text{Target AUC}\,[\text{mg}\cdot\text{min/mL}]\cdot \text{CL}_{\text{Carboplatin}}\,[\text{mL/min}] \qquad \text{(Eq. 1-4)}$$

Based on this equation, carboplatin clearance is estimated to obtain the optimal carboplatin dose.

For the development of the method the data were analysed using a non-linear mixed-effect model (NONMEM). A two-compartment linear model was used which integrated potential co-variates such as gender, age, height, weight, BSA, serum protein levels, cisplatin pre-treatment and serum creatinine concentration. The resulting equation is (w = weight, a = age):

$$\text{CL}_{\text{Carboplatin}}\,[\text{mL/min}] = 0.134\cdot \text{w}[\text{kg}] + \frac{[218\cdot \text{w}[\text{kg}]\cdot(1-0.00457\cdot a[\text{years}])\cdot(1-0.314\cdot \text{sex})]}{\text{Serum creatinine}\,[\mu\text{mol/L}]} \qquad \text{(Eq. 1-5)}$$

Depending on the gender of the patient a factor of 0 for male and 1 for female patients is inserted in the equation. This equation has been approved by Cahtelut et al. for the use in adult patients. In contrast to the Calvert formula this method is applicable to patients with impaired renal function and patients that are pre-treated with cisplatin.

1.2.6 Therapeutic drug monitoring

As mentioned above the dose calculation based on body surface area goes along with an unpredictable inter-patient variability in drug exposure. The consequences can either be over-dosing and increased toxicity which is usually quite easy to detect or unexpected under-dosing which leads to reduced efficacy of the chemotherapy. Estimations suggest an approximate under-dosing rate of 30% when BSA is used (Gurney, 2002). On the other hand, an unnecessary over-dosing does not necessarily improve the antitumour effect as many cytotoxic drugs show a plateau in the dose-response curve. This has been described for carboplatin in the treatment of ovarian cancer. An AUC between 5 and 7 mg·min/mL might be associated with maximal

response rates (Duffull and Robinson, 1997).

Therapeutic drug monitoring (TDM) aims at optimising individual dosage strategies by including plasma concentration measures. However, the strategy has its limitations for a number of reasons. For one thing the drugs are usually given in combination and it is difficult to assess the pharmacodynamic effects of single agents. Furthermore, the target tissues are often remote from the plasma used for analysis, which may confound the interpretation.

TDM for carboplatin is not yet part of the clinical routine. In some clinical studies the AUC of carboplatin has been determined, but generally dose is calculated using the introduced methods described in 1.2.5. Since the introduction of the target AUC, inaccuracies in dosage have been observed. Studies addressing this question have shown that under-dosage resulted from using the modified Calvert method predicting the GFR with either the Cockcroft and Gault or Jelliffe equation. The equation developed by Chatelut et al. might also result in inaccuracies, but to a lesser extent (van Warmerdam et al., 1996; Panday et al., 1998; Donahue et al., 2001). This knowledge suggests reconsideration of the common practice.

1.2.7 Supportive therapy

The goal of supportive care is to prevent, control, or relieve complications and adverse effects and psychological, social, and spiritual problems associated with the treatment or disease in order to improve the comfort and quality of life of people who receive antineoplastic therapy. Adverse effects or complications of treatment cause inconvenience, discomfort, and occasionally even fatality to patients. Furthermore, they may also cause a delay in the delivery of the prescribed dose of therapy at the specific time and in the treatment-schedule.

The debate about ‘cure’ and ‘care’ entailed in 1987 the development of the concept of supportive care. Realising that cure is not always possible the concept of care gained more significance. Supportive care concepts aim at ameliorating the patient’s situation by trying to alleviate the treatment- and disease-associated symptoms (Senn and Glaus, 2002).

1.2.7.1 ADRs associated with chemotherapy in gynaecological malignancies

The ADRs associated with chemotherapy vary depending on the combination of drugs administered. Thus, the supportive therapy offered to the patient much depends on the toxicity profile of the administered regimen. Tab. 1-4 outlines the common ADRs associated with the two selected chemotherapy regimens.

Tab. 1-4 Toxicity associated with the two selected standard chemotherapy regimens (du Bois et al., 1997; Neijt et al., 2000; Piccart et al., 2001; Partridge et al., 2001; Ozols et al., 2003)

	Breast cancer	Ovarian cancer
	Epirubicin/ Cyclophosphamide	Paclitaxel/ Carboplatin
Leukopenia (Increased risk of infections)	+++	+++
Thrombocytopenia (Increased risk of bleeding)	+++	+++
Anaemia	n.s.	+++
Fatigue	+++	+++
Nausea and Emesis	+++	+++
Diarrhea	++	++
Constipation	+++	++
Mucositis	+++	++
Damage on skin, nails, mucous membranes	++	++
Alopecia	+++	++
Cystitis	++	-
Peripheral neuropathy	-	+++
Myalgia/arthralgia	n.s.	+++
Allergic reactions	+	+++

+++	very common (> 10%)
++	common (1-10%)
+	occasional (0.1-1%)
-	rare (0.01-0.1%)
n.s.	not specified

1.2.7.2 Prophylaxis of nausea and emesis

Of all ADRs associated to chemotherapy patients rate nausea and emesis as one of the most distressing events (Senn and Glaus, 2002). This is the reason for focusing on these adverse effects in the present context. Every patient receiving chemotherapy should therefore receive appropriate antiemetic prophylaxis. A considerably large number of drugs is available to the prescriber in order to achieve this. Depending on the emetogenic potential of the administered chemotherapy these drugs can be combined. The main classification system for the emetogenicity of antineoplastic drugs has been set up by Hesketh (Hesketh, 1999). It is based on empirical data and also includes an algorithm to estimate the emetogenicity of combination regimens. The guidelines for antiemetic treatment differentiate between high, moderate and low emetogenicity.

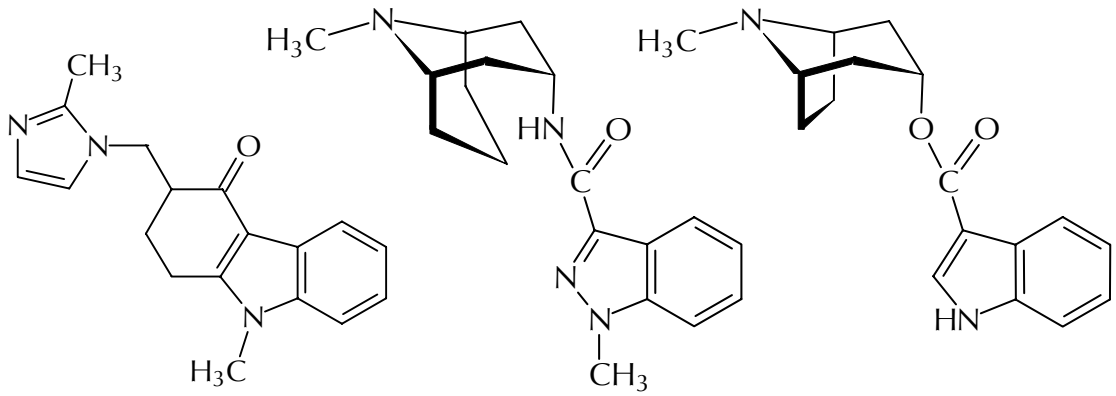
The selection of a drug combination also depends on the kind of nausea and emesis. Three types are differentiated. Acute nausea and emesis occur within the first 24h post chemotherapy. Delayed nausea and emesis emerge per definition from day two to five after chemotherapy. A third type is denominated anticipatory nausea and emesis, developing after previous undesirable experiences with therapy-associated nausea and emesis. All three types of nausea and emesis are based on different pathomechanisms and thus are treated differently.

To be precise it must be mentioned that nausea and emesis are different symptoms which are strongly connected. In this context both symptoms are considered in combination. Still, nausea is not so well investigated and therefore not as well controlled as emesis. The pathomechanism of acute emesis is fairly well understood. Cytotoxic agents as well as radiation therapy cause the release of serotonin from enterochromaffine cells of the small intestine. Serotonin binds to $5HT_3$ receptors on vagal afferent neurons thereby initiating the emetic reflex arch (Herrstedt, 2002). The pathomechanism of delayed emesis is not fully understood yet. Serotonin seems to play a minor role in this phase. However, more and more evidence is gained which suggests that neuropeptides are involved in the pathomechanism of delayed emesis. The neuropeptide substance P has been discussed for a while and the recently approved first NK1-receptor antagonist aprepitant has shown efficacy in the control of delayed emesis. Also high levels of endogenous noradrenaline cause

delayed emesis. A study showed that reserpine can also prevent delayed emesis (Tanihata et al., 2000).

5HT$_3$ receptor antagonists

Since the early 1990s this new group of drugs has changed the antiemetic prophylaxis and therapy immensely. Fig. 1-7 shows the currently most commonly used substances ondansetron, granisetron and tropisetron. These drugs have proved to be effective particularly in acute emesis. Their significance in the prevention of delayed nausea and emesis is discussed controversially. Studies suggest that in delayed nausea and emesis they are equipotent to corticosteroids and dopamine antagonists (Ioannidis et al., 2000).



Ondansetron Granisetron Tropisetron

Fig. 1-7 Chemical structures of 5HT$_3$ receptor antagonists

Serotonin receptors of the 5HT$_3$ type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is uncertain whether the 5HT$_3$ receptor antagonists' antiemetic action is mediated centrally, peripherally, or at both sites.

The 5HT$_3$ receptor antagonists themselves may cause ADRs. Commonly observed are headache, malaise, somnolence, constipation or diarrhea and dizziness. In rare cases hypersensitivity reactions, effects on the central nervous system or cardiac effects have been reported.

Corticosteroids

Of the corticosteroids especially dexamethasone plays a significant role in the antiemetic treatment. Ioannidis et al. undertook a metaanalysis in order to identify the potential of this corticosteroid (Ioannidis et al., 2000). Their result convincingly showed that dexamethasone in combination with a $5HT_3$ receptor antagonist prevents acute emesis more effectively than the respective $5HT_3$ receptor antagonist alone. For the control of delayed emesis the findings even suggest superiority over $5HT_3$ receptor antagonists. Roila et al. recommend to base prophylaxis and therapy of delayed emesis on dexamethasone which can be combined with either $5HT_3$ receptor antagonists or dopamine antagonists such as metoclopramide in high emetogenic chemotherapy regimens (Roila et al., 2002).

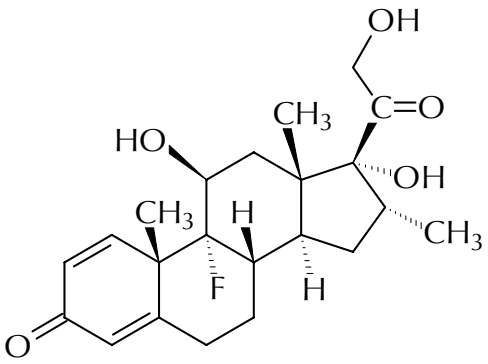


Fig. 1-8 Chemical structure of dexamethasone

The mode of action of dexamethasone is not yet elucidated. Dexamethasone causes the adverse reactions typical for corticosteroids. Ioannidis et al. found that the administered doses of dexamethasone vary within a wide range. The differing doses were not related to a variability in treatment effects which suggests that low doses might already achieve a protective effect (Ioannidis et al., 2000).

Dopamine antagonists

Among this group of drugs metoclopramide is a commonly used drug in antiemetic treatment and prophylaxis.

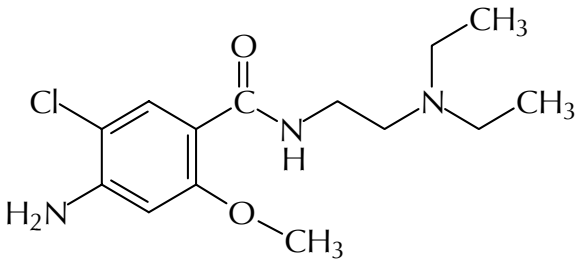


Fig. 1-9 Chemical structure of metoclopramide

Dopamine antagonists minimise the effect of dopamine at the D_2 receptor in the chemoreceptor trigger zone, thereby limiting emetic input to the medullary vomiting center. Although dopamine antagonists are inexpensive and have broad efficacy, they have an extensive adverse effect profile that includes sedation, orthostatic hypotension, and extrapyramidal symptoms such as tardive dyskinesia. In the treatment of nausea and emesis doses of 10 to 20 mg are recommended in order to make use of the additional antiserotonergic effect which occurs at higher dose levels.

Other drugs

Antihistamines have shown only limited effects in the control of nausea and emesis. None of the guidelines includes them in their primary recommendations. Benzodiazepines (e.g. lorazepam) have an effect in anticipatory emesis. Propofol and metopimazine are drugs discussed for the control of breakthrough and therapy-refractory emesis whereas the evidence is still sparse (Herrstedt, 2002).

Therapy guidelines

In times of increased awareness of the importance of evidence-based drug therapy a number of expert panels and scientific societies devised therapeutic guidelines for the prophylaxis and treatment of chemotherapy-induced nausea and emesis (Antiemetic Subcommittee of the MASCC, 1998; ASHP Commission on Therapeutics, 1999; Gralla et al., 1999; ESMO guidelines task force, 2001). Some problems emerge with the so far existing guidelines. Data of high quality, requested for the establishing of EBM guidelines, is often lacking. Instead the guidelines often have to rely on 'expert opinions'. Additionally the existing guidelines are not congruent. This causes irritation among the prescribing physicians which leads to 'non-compliance' to the best

available evidence (Roila, 2002). The MASCC initiated the formulation of mutual therapeutic guidelines of the main scientific associations. In March 2004 a consensus conference was held in Perugia, Italy addressing this task (Gralla, 2004).

1.2.8 Complementary medicine

Complementary medicine summarises a variety of treatment options which are based on different medical philosophies. They have in common that they are not part of the conventional medicine as they often still lack sound scientific evidence regarding efficacy and safety. In contrast to the causal approaches of the conventional medicine most complementary treatment options pursue holistic approaches. Over the past years complementary medicine has reached an increased consciousness among health care providers in oncology. This can have several reasons. As described above the requirements of the modern health care system increased and consequently the demands on health care providers to offer a high quality and needs-based service. As studies demonstrate cancer patients' needs for complementary medicine is especially in Germany fairly high. In a patient-oriented view where a patient is addressed as a competent partner it is mandatory to accept and integrate patients' needs also in terms of unconventional methods. Weis et al. showed that 58.4% of the asked patients had experience with complementary medicine after they had been diagnosed with cancer. The highest rate of users of complementary medicine was found among the breast cancer patients (72%). Of the different methods mistletoe (61.1%), vitamins (45.2%) and trace elements, such as selenium, zinc or others (40.4%) ranked on the first places (Weis et al., 1998).

In their study Weis et al. addressed the question why complementary medicine is significant to the cancer patient (1998). They found that the two main reasons for seeking support in complementary medicine are to strengthen the immune system and to contribute self-commitment to the therapy process.

All patient-oriented services offered to cancer patients should keep these aspects in mind. Nevertheless it has to be kept in mind that sufficient and reliable data for most complementary treatments is sparse and that a critical appraisal in an individual case is mandatory.

1.3 Changes in health systems

1.3.1 Patient-focused approaches

In recent years a paradigm shift towards a patient-focused rather than a disease-focused approach occurred in many health care systems. Patient-focused approaches are designed to meet the needs and wishes of the individual receiving care and treatment. Currently discussed care concepts such as case- and disease-management programmes or pharmaceutical care strategies aim at improving patients' outcomes by following evidence-based therapeutic guidelines, by trying to meet patients' needs and by taking into account economic aspects (Hepler and Strand, 1990). All models advocate patients' active participation in the therapeutic process and try to integrate quality assurance measures. Jackson and Kroenke describe the classic triad of quality care based on structure, process and outcome (Jackson and Kroenke, 1997). The former focus was on the structure and process of care, but it is changing towards the evaluation of the achieved outcome due to increasing patient enrollment and more sophisticated consumers. The competent patient should be well-informed and thus be able to make informed decisions regarding treatment. The Ottawa Charter for health promotion initiated this new way of thinking (International Conference on Health Promotion, 1986). It claims equal conditions for people to improve their health and well-being. In addition, it emphasises the importance of access to information for patients to increase control over their health and to be able to take on responsibility for their personal well-being.

1.3.2 Patients' needs

The WHO defined 'health' to be *a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity* (World Health Organization, 1948). Any disorder of health might be associated with reduced quality of life (QoL). It is desirable to not only pay attention to the symptom control when treating a person, but also consider the tolerability of the chosen treatment for the patient. Recently QoL evolved to be a popular outcome parameter in clinical trials. Still, a universally accepted definition is lacking. Investigators argue that in the Western world most

people are familiar with this expression and have an intuitive understanding of what it stands for. One associates with QoL predicates such as well-being, happiness and satisfaction with life. It has to be kept in mind, that it means different things to different people depending on the context and situation. Hence in health care science it is referred to as health-related quality of life. When mentioning QoL in the context of this project health-related QoL is meant. Health-related QoL includes a variety of aspects such as general health, physical functioning, physical symptoms and toxicity, emotional functioning, cognitive functioning, role functioning, social well-being, sexual functioning and also existential issues. Depending on the type and objectives of the conducted trial individual aspects are selected (Fayers and Machin, 2000).

The special situation of cancer patients has been taken into account with the development of specific instruments. Already in 1947 the Karnofsky Performance Scale was introduced to assess patients beyond physiological and clinical examinations. The European Organisation for Research and Treatment of Cancer (EORTC) developed and validated a basic module – the QLQ C30 questionnaire – and cancer type specific modules to assess cancer patients' quality of life (Aaronson et al., 1993).

Especially for cancer patients information on their disease and treatment plays an important role. Cassileth et al. found that the majority of cancer patients wants as much information as possible (Cassileth et al., 1980). The information appears to be relevant for developing coping strategies (van der Molen, 1999) and to initiate self care behaviour (Dodd, 1983). Moreover, satisfaction with the available information appears to be associated with an improved QoL (Annunziata et al., 1998).

The WHO indicates in its report on 'Quality of care: Patient safety' that health care interventions in general are intended to benefit the patients (World Health Organization, 2001). They remark that the modern health care delivery systems with their complex combination of processes, technologies and human interactions can bring significant benefits for the patients. Nevertheless, it involves inevitable risks of adverse events of different kinds and origins. The WHO summarises the core goals of most of the current health policy trends which will be introduced in the following.

1.3.3 Current health policy trends

With increased expectations regarding quality of care and an increasing pressure on public health care institutions to compete with private institutions, the evaluation of offered services has become a necessity. Therefore, applicative outcome parameters capable of assessing the quality of care have been developed. The use of outcome parameters such as patient satisfaction and quality of life are mainly driven by two rationales: cost containment and competition. In Germany the enactment of the 'Gesetz zur Reform der gesetzlichen Krankenversicherung ab dem Jahr 2000', a law which gives the health system a new structure, introduced the legal obligation to assure and further develop a high quality standard for health care services by implementing §135a in the code of social law V (Bundesministerium für Gesundheit, 1999).

A variety of models have been introduced to achieve this goal. Donabedian discussed the different prospects of the quality of health care (Donabedian, 1990). The efficacy and effectiveness of care should be preferably high, which means that the requirements for an optimum of care need to be established and the conditions need to facilitate the best possible realisation. Due to the financial pressure the efficiency has to be considered as well. It is a measure of the cost at which any given improvement in health care is achieved. Still, the optimum should be aimed at. This means that costs and benefits ought to be in a reasonable relation. Additionally, Donabedian refers to the quality of care from the patient's perspective. Accessibility to care, the patient-carer relationship, the amenities of care, the patient's preferences of the effectiveness and the costs of care should be taken into consideration when quality of care is addressed. All these factors need to be amalgamated to assure a high quality and affordable health care system. The following models integrate many of these factors.

1.3.3.1 Quality management

To enhance the quality of care, quality management systems which are known from industrial production sites have been adapted in several ways to health care (Süverkrüp, 2003). The idea of the total quality management builds the fundament of

most of the currently discussed concepts. As illustrated in Fig. 1-10 the delivery of any health care service, described as a 'product' from a 'supplier' (hospital, general practitioner, pharmacist etc.) to the 'customer', in case of health care usually the patient, is embedded in a continuous process of quality improvement. The supplier defines goals to achieve a high quality of the delivered product. The customer receives the product which is associated with a number of requirements. These can be objective requirements as well as subjective requirements. The described coherences are basic considerations. In reality additional influences such as monopolisation add to the complexity of the system.

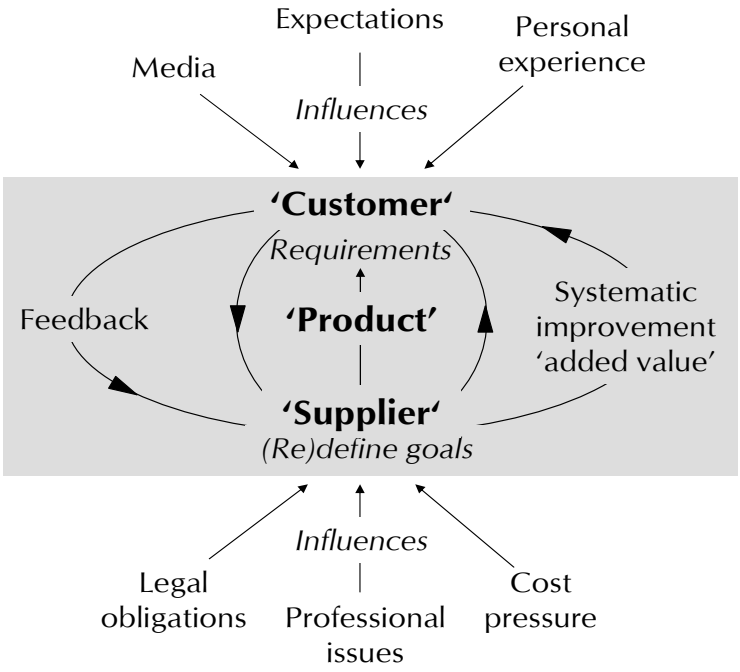


Fig. 1-10 Total quality management

The customer gives feedback to the supplier who redefines the goals accordingly in order to systematically improve the product. Both, the supplier and the customer, are influenced by several parameters, which direct their actions. Usually, especially in health care, they are also interchanging with other players. These might not necessarily be interacting, which complicates the described process. To assure a functioning quality management an effective information flow plays an important role. This is taken into account by implementing documentation systems and integrating networks which enclose all involved parties (Schmidt, 1998; DIN Deutsches Institut für Normung e.V., 2000; Süverkrüp, 2003; Engel et al., 2003).

The idea is to standardise the processes and to guarantee a continuous quality improvement to the customer. Standardisations like the DIN EN ISO 9001 have been set up to implement this philosophy into practice. Also legal obligations bind to quality management. As mentioned above the code of social law V in its current version calls for quality assurance and improvement of quality of the provided services. The services need to be based on actual scientific evidence and be presented in a professional manner. Cross-institutional measures to assure the quality, especially those which aim at improving the quality of outcomes should be taken and quality management systems should be implemented. According to §137b the quality assurance should be achieved in a cross-professional approach.

1.3.3.2 Integrated care

Disease management programmes (DMP) are based on the same considerations as described above. Todd et al. suggest that a common vision on what should be achieved is necessary to implement DMPs (Todd et al., 1997). The idea is based on continuous quality improvement. With the use of selected components, such as databases, evidence-based guidelines, outcome assessment, communication tools etc. this aim is to be reached. Again, in this context a consensus among all healthcare providers is seen inevitable. In Germany the code of social law V serves as a basis for the implementation of DMPs for various chronic indications, breast cancer being one of them. The government published consensus recommendations from a group of experts on the DMPs for breast cancer in 2002 (Koordinierungsausschuss, 2002). The DMPs should cover the whole care process which begins with the early diagnosis of the disease and aims at providing the optimal medical care by the implementation of evidence-based guidelines (Engel et al., 2003). In addition, preventive measures should be part of DMPs as well as the rehabilitation. In terms of breast cancer many disciplines contribute to the care process. Thus the consensus statement calls for cross-profession and cross-sector cooperation in order to improve the information flow. This seems to be especially important when looking at the intersection between hospital and ambulatory patient care. Breast cancer patients often switch from one to the other setting. Seamless care concepts which aim at optimising the handing over of the patient with the important information from one setting to another by implementing coordinating professionals such as nurses, social workers or pharmacists are

conceivable and are currently being surveyed. The code of social law V in its current version deals with the quality assurance in the ambulatory and hospital care and in during rehabilitation.

1.4 Oncology pharmacy

As other professions, the pharmacy profession experienced a change from traditional drug-oriented services such as drug distribution and preparation towards patient-oriented services. Within the last decade the speciality of oncology pharmacy developed and gained experience and knowledge to serve the expanding demands of the health system regarding cancer care. The setting-up of central cytotoxic services and standardisation of the chemotherapy order forms have been one of the first pharmaceutical contributions to decrease prescribing and dosing errors, and to increase the safety in handling cytotoxic drugs. Meanwhile the list of oncology pharmacy services expanded considerably as shown in Tab. 1-8.

Tab. 1-5 Pharmacy services in oncology

Central cytotoxic service
Drug information service
Therapeutic drug monitoring
Nutritional support
Parenteral medication (e.g. antibiotics, analgesia)
Unit dose system
Compiling medication histories
Pharmaceutical care

1.5 Pharmaceutical care

1.5.1 Definition

The recognition of the numerous risks to the individual patient associated with complex drug therapies has led to the development of a conceptual framework for an advanced pharmacy practice philosophy. In 1990 Hepler and Strand introduced the concept of pharmaceutical care as a further development of the pharmaceutical

profession (Hepler and Strand, 1990). They understand *pharmaceutical care as the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve patients' quality of life*.

The Fédération International Pharmaceutique (FIP) extended this definition in 1998, describing it as a collaborative process that aims to prevent or identify and solve medicinal product and health-related problems which can be regarded as a continuous quality improvement process for the use of medicinal products. Pharmaceutical care is a comprehensive practice model. It should be offered to the patient as a whole (Fédération International Pharmaceutique, 1998).

The American Society of Health System Pharmacists set up guidelines on a standardised method for pharmaceutical care to assure that pharmacists practicing pharmaceutical care work on the same quality level (1996). These guidelines amalgamate the aspects introduced above. The London oncology pharmacy group also introduced guidelines for the pharmaceutical care of the cancer patient which not only include the actual 'pharmaceutical care' as such, but also standardise the clinical pharmacy activities, dispensing, updating therapeutic policies, cytotoxic reconstitution, drug information, clinical trials and the oncology training of the pharmacists (Hoare and Beer, 1995). In Germany the Federal Chamber of Pharmacists (Bundesapothekerkammer) set up guidelines for the standardised application of pharmaceutical care (Bundesapothekerkammer, 2003a; Bundesapothekerkammer, 2003b). These are general recommendations and introduce the systematic approach. To support the pharmaceutical care of patient groups with special characteristics and needs such as asthma, diabetes or cancer patients, the Federal Union of the German Associations of Pharmacists (ABDA) initiated the publication of practice manuals which address the specific needs of such patient groups.

A fundamental development of pharmaceutical care compared to other pharmaceutical services is that pharmacists accept responsibility for the patient's pharmacotherapeutic outcome alongside the physicians. Consequently this concept only works in close collaboration with the other involved professionals as shown in Fig. 1-11.

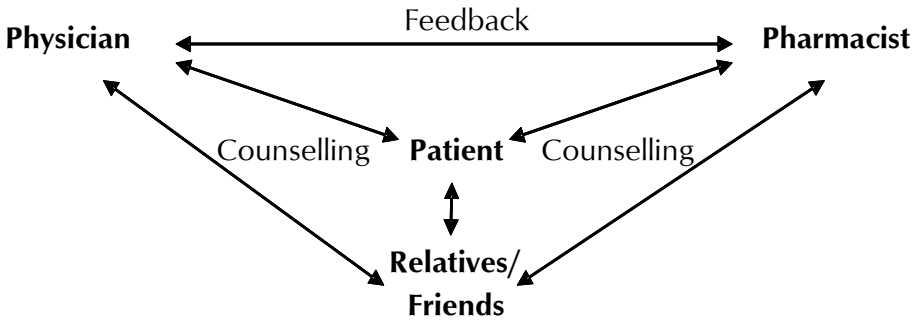


Fig. 1-11 Pharmaceutical care as a collaborative concept

Pharmaceutical care is a needs-based approach. For pharmaceutical care providers the main focus are the drug-related needs of the individual patient. The individual drug therapy should be appropriately indicated, effective, safe and convenient to the patient to assure good compliance and thus an optimal treatment outcome (Cipolle et al., 1998). These drug-related needs are not necessarily met, which can result in a variety of drug-related problems (see Tab. 1-9).

Tab. 1-6 From drug-related needs to drug-related problems (modified from Cipolle et al. (1998))

Drug-related needs	Drug-related problems
Indication	Additional drug therapy
	Unnecessary drug therapy
Effectiveness	Wrong drug for the indication
	Dose too low
Safety	Adverse Drug Reaction
	Dose too high
Compliance	Non-compliance

To detect potential DRPs and prevent or solve them, the therapeutic outcome monitoring serves as a helpful tool (Hepler, 1997). The medication record listing all drugs a patient is taking at a time gives an overview and helps interprete the patient's situation. A number of problems can be detected just from analysing the record.

In collaboration with the prescribing physician and the patient the goals of the drug therapy are to be defined and added to a therapeutic plan as shown in Fig. 1-12. Desired outcomes, such as reduction of emetic episodes and degree of nausea, patient knowledge about a certain drug, compliance etc. are selected to monitor this plan. The monitoring plan is structured following the SOAP method. Subjective information and objective parameters which characterise the patient are analysed and integrated in the plan.

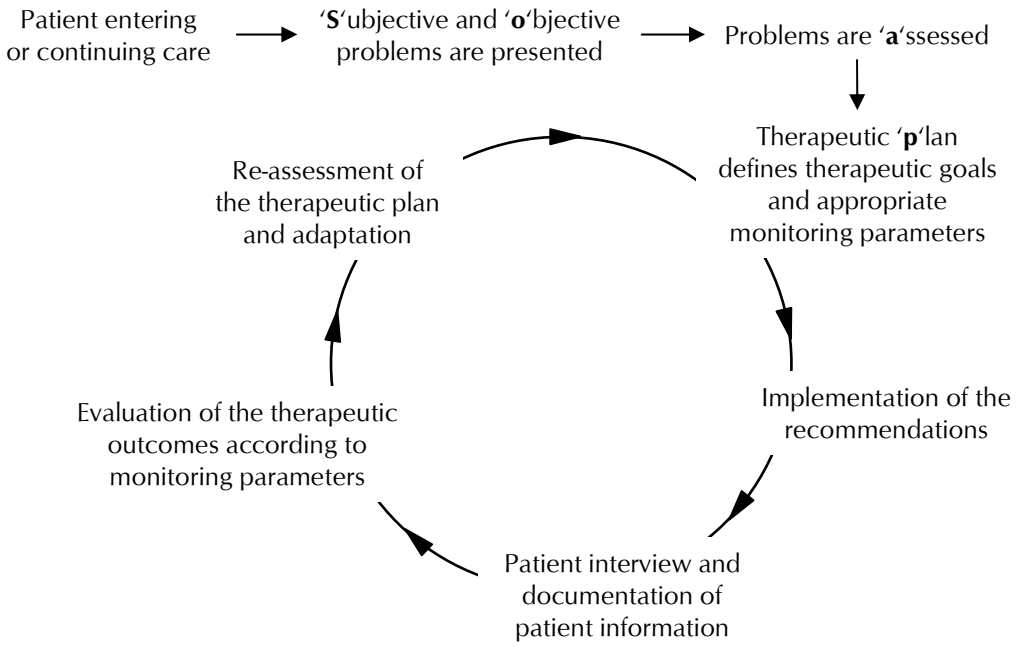


Fig. 1-12 Therapeutic outcome monitoring based on the SOAP method

The care concept is designed as a continuous process. Regular appointments with the pharmacist throughout the therapy are integrated to follow up the therapeutic plan. The primary plan needs to be re-evaluated and if necessary adjusted according to the patient's needs. It can be described as a comprehensive drug therapy management.

The continuity can only be achieved with a thorough documentation of the patient-specific data. Not only the medication-related information should be collected, but also demographic data, information on the life style (e.g. diet, exercise, social drug use), religious affiliations and the social background should be recorded. This information allows to get a realistic picture of the patient and to assess the situation.

It seems that in particular patients with complex drug regimens and/or chronic diseases and those who frequently need to be hospitalised benefit from pharmaceutical care. These characteristics apply to many oncology patients.

1.5.2 Integration in current health policy trends

Currently discussed care concepts such as case and disease management programmes (DMP) aim at improving patients' outcomes by following evidence-based therapeutic guidelines, by trying to meet patients' needs and by taking into account economic aspects. All models advocate patients' active participation in the therapeutic process and try to integrate quality assurance measures (see 1.3).

In terms of drug therapy, disease management aims to integrate the upper mentioned therapeutic goals in a much standardised manner to obtain transparency for the patient and the third-party payers. It fosters interdisciplinary approaches in order to achieve these goals.

Pharmaceutical care concepts seem to have a good potential of supporting the idea of DMPs. To be integrated in these programmes it is mandatory to document the impact of pharmaceutical care on patient outcomes in order to comply with the demand for transparency.

1.5.3 Integration in a societal context

Due to the above mentioned changes in the health care systems pharmacy profession has been endeavouring to adapt its profile accordingly over the past decades. In1987 the German Pharmacy Practice Ordinance (Apothekenbetriebsordnung) was amended by §20 which introduced the duty of pharmacists for consultation on medicines. A long debate preceded the enactment of the changed ordinance on the topic which in one way or the other still continues (Schubert, 1995). In this process, pharmaceutical care is a consistent practice concept which has the potential of amalgamating the legal obligations of the pharmacist and the described requirements of a modern health system. In addition, it supports the professional legitimation of the pharmacy profession which has been discussed controversially in recent times.

1.5.4 Pharmaceutical care for the cancer patient

Within the anticancer therapy concepts the drug regimens are administered following established protocols which have been generated in clinical trials and proved to be efficient for the respective indication. The administration of supportive therapies is not as controlled as the antineoplastic therapy itself. Various settings emphasise supportive care in a different manner. Furthermore, in supportive care evidence-based therapy is not usual practice, yet. Additionally main parts of the supportive therapy are not carried out by the oncology clinic, but from the general practitioners or the patients themselves. Many things have to be taken into consideration which often leads to less effective protection from adverse effects and thus to a decreased quality of life. That is why supportive care has been considered a field for the oncology pharmacist offering pharmaceutical care to the cancer patient. The two concepts work well together comparing the initial objectives.

Especially in ambulatory care the continuous monitoring of the medication use process should be mandatory. Patients receiving care in the community often experience fragmented services. The prescriber often does not see the patient until the next visit in the clinic or outpatient department which might be after a few weeks. Meanwhile ADRs can occur which might not be detected in time. Furthermore, patients tend to see more than one physician involved in the cancer care process as well as alternative practitioners. Patients are also exposed to a tremendous choice of products which are available to the customer without prescription (over-the-counter - OTC).

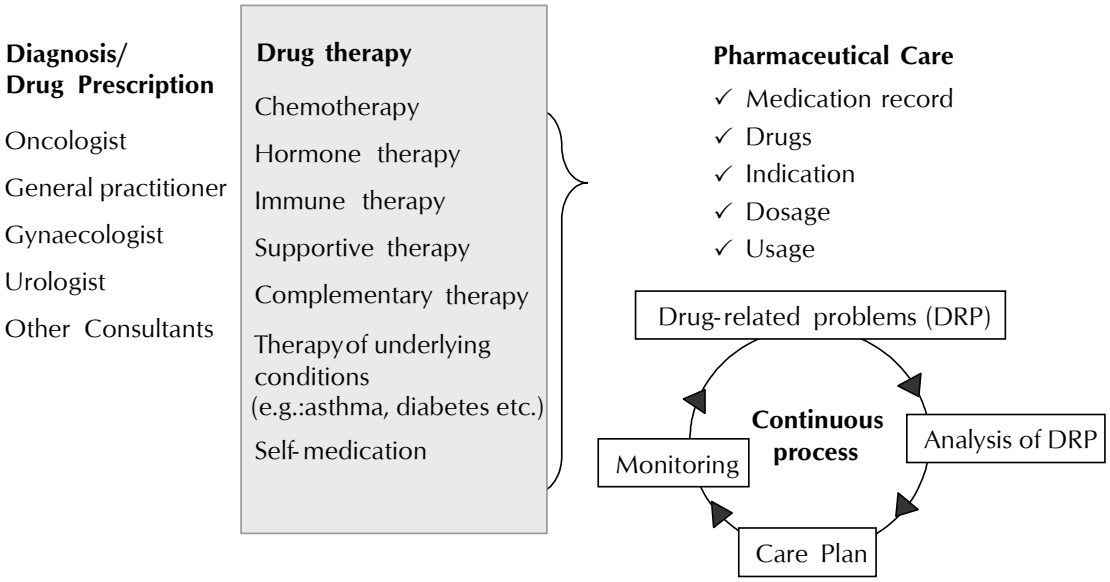


Fig. 1-13 Pharmaceutical care in oncology therapy

Fig. 1-13 illustrates the complexity of cancer patients' drug therapy and the possibly resulting drug-related problems which are addressed by the therapeutic outcome monitoring.

The different prescribers, nurses and relatives and the patient with self-medication are all part of the individual drug therapy team. Thus, they all need to be included in the collaborative process. A group of British experts drew up a policy framework for commissioning cancer services. They suggest the establishment of structures which support the seamless care of cancer patients in the community setting in a network of all parties in order to make use of the respective speciality knowledge (Working Party Report, 1997). Accordingly the information flow at discharge from hospital to the ambulatory setting should be optimised utilising pharmaceutical care plans to make sure that the efficient distribution of the medication to the patient is not interrupted.

Tab. 1-7 Pharmaceutical aspects of supportive care

Supportive Care (examplary)	Traditional pharmaceutical tasks	Patient-oriented tasks
Nutritional support	Distribution of appetite stimulating drugs	Calculation of nutritional regimens
	Distribution of hypercaloric products	Preparation of total parenteral and enteral nutrition
		Individual nutrition counselling
Pain management	Distribution of drugs	Preparation of parenteral medication (patient controlled analgesia PCA, different pump systems etc.)
		Counselling on taking modalities
		Non-medical advice on preventive behavior
Mucositis prophylaxis and therapy	Preparation of mouth washes	Patient education on oral hygiene algorithms
		Non-medical advice on preventive behavior
Antiemetic prophylaxis	Distribution of drugs	Elaboration of therapeutic algorithms
		Counselling on taking modalities
		Non-medical advice on preventive behavior

A few examples on how pharmacists' activities in supportive care expanded from the traditional tasks towards the patient-oriented tasks in the framework of pharmaceutical care are listed in Tab. 1-7. Within the pharmaceutical care process the application of agreed therapeutic algorithms can be assured on the individual basis. The adherence of the patient can be improved by patient education before and during the treatment cycles combined with patient counselling regarding drug therapy, adverse effects and complementary treatment options.

1.5.5 Pharmaceutical care research

There are numerous publications on the philosophy and theoretical background of pharmaceutical care. Additionally there are many reports on the experience with the implementation into practice settings. The major gap seems to be the lack of scientific

evidence of the impact of pharmaceutical care on health care provision. Kennie et al. addressed this problem and critically analysed pharmaceutical care research literature in order to determine deficiencies in study design and research methods and to formulate recommendations to improve the situation (Kennie et al., 1998). Among other recommendations they emphasised the importance of using the term 'pharmaceutical care' properly. In the evaluated studies they found that the term had been used to describe other pharmacy services such as pharmacokinetic services or patient counselling which on their own do not constitute pharmaceutical care. They also called for scientific standards such as controlled study designs, which should be implemented. In the literature only a few studies can be found which were conducted following research standards. Especially on asthma and COPD, studies were conducted and the results were published in renowned journals (Knoell et al., 1998; Schulz et al., 2001; Weinberger et al., 2002). Moreover, pharmaceutical care for elderly people was investigated in a multicentred, randomised controlled trial (Bernsten et al., 2001). A further suggestion was the development of a pharmaceutical care network which could coordinate the international effort to improve the research and to identify fields of interest. The Pharmaceutical Care Network Europe (PCNE) has taken up these suggestions and meets annually to address these questions.

In oncology, there is little scientific evidence on the feasibility of pharmaceutical care and actual benefit to the patient so far. In Canada projects have been carried out which suggest to implement suitable outcome parameters to evaluate the impact of pharmaceutical services in oncology (Broadfield, 1995). These have stimulated a founded discussion in Canadian health care politics regarding the necessity of the offered services.

In Germany various research projects are being carried out or have been completed which survey the benefit and the feasibility of pharmaceutical care for patients with different indications. Fig. 1-14 illustrates the distribution of the projects within the country. Cancer patients are the focus of a project in Hamburg which is working on lung cancer patients and the present study.

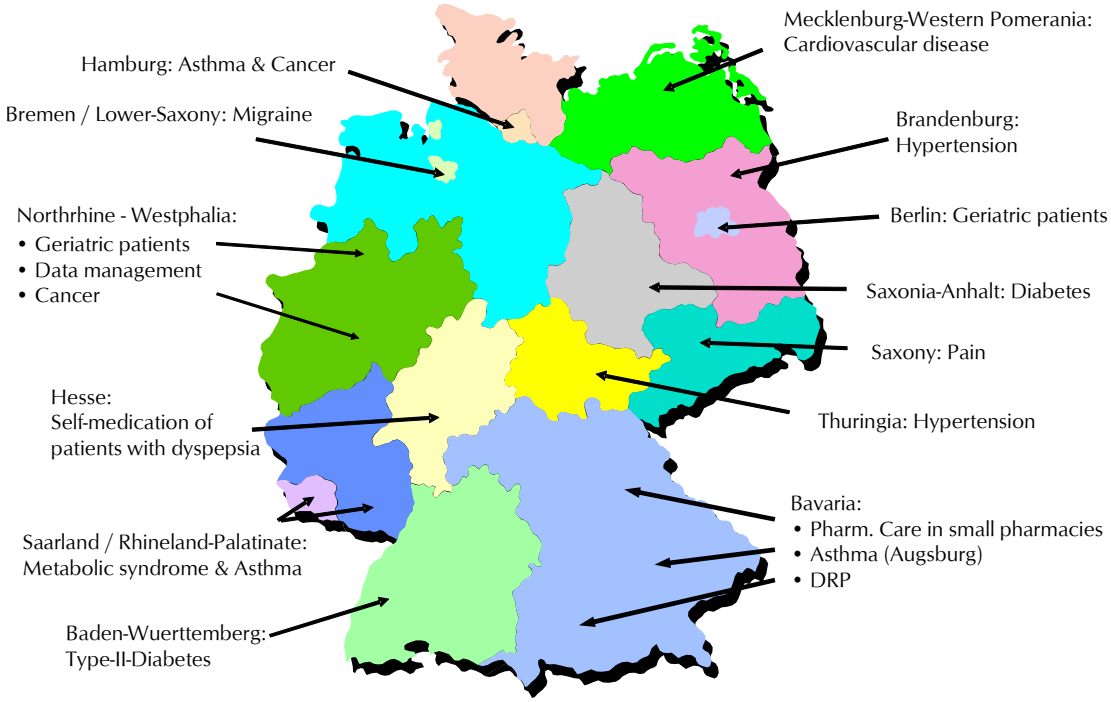


Fig. 1-14 Pharmaceutical care research projects in Germany [Schulz, personal communication]

[2] Aim & Objectives

2 Aim and Objectives

The present work is the first in the research field of pharmaceutical care in oncology in Germany and thus could not refer to much knowledge of previous projects. It is composed of three parts. Part one adapted a Canadian questionnaire on patient satisfaction with information on cancer treatment for German settings. The second main part of this pilot is the survey on the feasibility and benefit of pharmaceutical care for patients with gynaecological malignancies. Part three is the monitoring of carboplatin in patients with ovarian cancer. It can be viewed separately as well as integrated in the model of pharmaceutical care.

2.1 Patient satisfaction with information on cancer treatment

The objective of the first study of this thesis was to adapt the Canadian PS-CaTE questionnaire for use in German-speaking countries in order to provide a suitable outcome measurement instrument. In addition, the adapted questionnaire was applied to survey different cancer care settings across Germany and thus provides an assessment of the present situation in Germany. The results are intended to support the development of pharmaceutical care strategies for cancer patients by detecting and compensating information deficiencies.

2.2 Pharmaceutical care for patients with gynaecological malignancies

Pharmaceutical care in oncology aims at reducing treatment-related toxicity and at improving patients' quality of life. The aim of this work was to develop a specific pharmaceutical care model for breast and ovarian cancer patients including patient counselling on the management of treatment-associated adverse effects, optimisation of supportive medication and the implementation of a therapeutic algorithm for antiemetic prophylaxis.

2.3 Monitoring of carboplatin

Carboplatin is commonly dosed to achieve a defined target AUC. The estimations used in clinical practice proved to be inaccurate, consequently leading to either over- or more likely under-exposure to carboplatin. Therapeutic drug monitoring has a great potential for optimising individual drug therapy. This method is capable of improving the dosage accuracy as well as the safety of drugs with a narrow therapeutic range. It is the objective of this pilot study to assess the value of therapeutic drug monitoring for patients treated with antineoplastic agents, in particular carboplatin, the feasibility in outpatient settings and its contribution to pharmaceutical care.

2.4 Working hypotheses

The following working hypotheses were defined:

- The systematic optimisation of the supportive therapy by the pharmacist reduces incidence and severity of undesirable effects during and after chemotherapy.
- The minimisation of therapy associated toxicity improves the specific quality of life (symptomatic).
- Pharmaceutical care improves the communication regarding drug treatment and the global quality of life of patients.
- Individual dosage strategies based on pharmacokinetic parameters, e.g. therapeutic drug monitoring (TDM), are applicable to outpatient settings.

[3] Material & Methods

3 Material and Methods

3.1 Patient satisfaction with information on cancer treatment

In order to develop patient-oriented standards for a care process, it is necessary to know what type of information patients want and to what extent patients need to be informed. In addition, quality assurance plays an increasingly important role in the care of cancer patients. In order to obtain a high standard in cancer care it seems to be reasonable to establish measures that are capable of assessing the performance of care. Patient satisfaction may act as an indicator of the quality of health care services. It reflects the ability of the care provider to meet the patients' needs.

3.1.1 PS-CaTE questionnaire

In Germany, there are presently no appropriate instruments which measure patient satisfaction with the information given on cancer treatment. The British Columbia Cancer Agency, Vancouver, Canada, developed the 'Patient Satisfaction with Cancer Treatment Education (PS-CaTE)' questionnaire (Pohar and Taylor, 2000). This instrument was established to measure patients' satisfaction with the information they received within the framework of a cancer treatment education programme.

Intensive discussions with experts about the methodology of measurement scales resulted in the decision to translate an existing instrument rather than to develop a new one. This also facilitates comparing the status of cancer care in different countries as it has already been done with quality of life measures, such as the QLQ-C30 from the European Organisation for Research and Treatment of Cancer (EORTC) (Aaronson et al., 1993).

3.1.2 Translation of the PS-CaTE questionnaire

The Canadian questionnaire was translated using a systematic approach. Literal translation may result in different meanings as it might introduce subtle forms of distortion into the scales. To address this concern the Canadian 'Patient Satisfaction with Cancer Treatment Education (PS-CaTE)' questionnaire was translated into German

following the forward/backward translation method as shown in Fig. 3-1 (Streiner and Norman, 2000). Two bilingual translators who were familiar with the textual background of the questionnaire were asked to translate the original version into German. These independent versions were compared and the translators agreed upon one version. In this way possible misinterpretations could be detected and eliminated. The agreed German version was then translated back into English by two other bilingual speakers. They too compared their results and compiled an agreed English version. The last step in the procedure was to compare the original version with the English version translated back from the German version. All involved translators discussed uncertain aspects and adapted the German translation accordingly. Selected socio-demographic variables, including educational status, marital status, age, diagnosis, time since diagnosis, were added to the original version of the questionnaire to facilitate subgroup analysis.

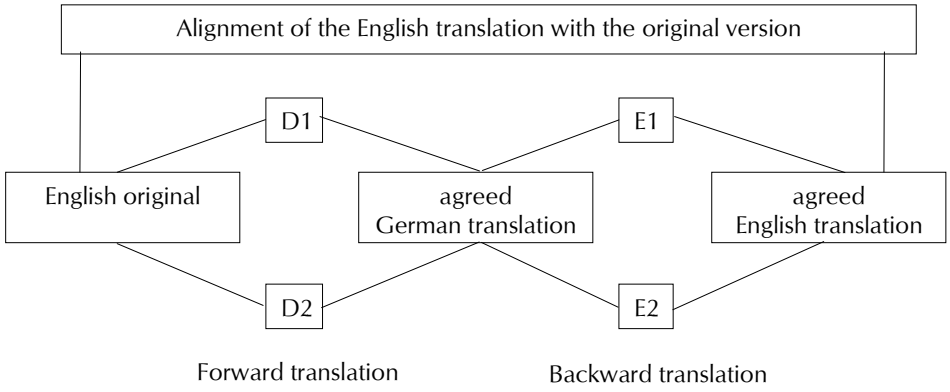


Fig. 3-1 Translation process of the questionnaire

3.1.3 Psychometric properties

Due to the translation process, the psychometric properties of the scales such as reliability and validity can be affected. It is therefore mandatory to reassure these test quality criteria.

The reliability of a questionnaire or a scale refers to the precision or homogeneity of the instrument, leaving questions of content out of consideration. It reflects the reproducibility of the scale measures across repeated administrations of the same test

or parallel test forms (Crocker and Algina, 1986). The reliability coefficient is defined as the ratio of the true score variance to the total variance of the test scores (Lord and Novick, 1968). Two commonly used reliability estimates are the Spearman Brown split-half reliability and the internal consistency coefficient (Cronbach's alpha). These coefficients were assessed both in a pre-test and in the main test. The procedures are described under 3.4.

The validity is the extent to which a measurement instrument actually measures the underlying concept it is supposed to measure. In our study the so-called face validity (or content validity) was assessed. Face validity indicates that an instrument appears to assess the desired dimension because of the semantic content of the items. It represents a subjective judgement based on a review of the instrument by one or more experts (Streiner, 2000). The German version of the questionnaire was handed out to experts of pharmacy practice, medical practice and patient speakers for reviewing. These experts were asked to critically appraise whether each item and the whole questionnaire were suitable to measure patient satisfaction with information on cancer treatment.

3.1.4 Patient selection

Patients with all types of cancer were asked to participate in the survey. A main criterion of inclusion was the ability to complete the questionnaire without help from others. Thus patients needed to be able to read and write German and to be mentally healthy. For the pre-study, patients did not have to give written informed consent. The patients were assured that anonymity would be maintained and that a refusal to participate would not in any way affect the quality of their care. A short letter preceding the questionnaire informed the patients about the content of the study (see appendix J).

3.1.5 Distribution among cancer centres in Germany

The questionnaire was distributed among patients of 11 cooperating hospitals, oncology practices, pharmacies and self-aid groups across Germany.

Persons entrusted with the distribution of the questionnaires encouraged patients to complete the questionnaire independently in order to minimise the tendency for

socially desired answering. Where possible, the individuals distributing the questionnaire were not involved in patient care. The completed questionnaires were either collected on the ward, in the general practitioner's office or in the pharmacy to be sent back by the distributor, or they were sent back by the patients themselves in previously addressed and stamped envelopes. All questionnaires were sent to the University of Bonn for analysis.

3.2 Pharmaceutical care for patients with gynaecological malignancies

The present project was initiated as the first study to survey pharmaceutical care for cancer patients in Germany. In addition little scientific evidence was available on pharmaceutical care research in general. Therefore this work was planned as a pilot study. Infrastructural aspects had to be solved and a suitable design had to be selected before the actual work could be started.

3.2.1 Study protocol

Two universal binding regulations determine the principles for clinical research with humans. The World Medical Association (WMA) constitutes in their 'Declaration of Helsinki' ethical principles which safeguard patients' rights in clinical research. They declare that medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. The WMA claims the application of basic principles for the medical research in order to protect patients' rights, including the scientific principles, the thorough formulation of an experimental protocol and an approval of an independent ethics committee (World Medical Association, 1964). The note for guidance on good clinical practice (GCP) comprises these principles likewise in order to assure a standardised quality (The European Agency for the Evaluation of Medicinal Products, 1996). In order to meet the requirements of these guidelines the principles mentioned above were considered in the planning of the study. A study protocol was worked out prior to the start of the study. The planning and realisation of the present work was accomplished by a research pharmacist.

3.2.1.1 Legal obligations

The German drugs act (Arzneimittelgesetz) regulates the protection of humans in clinical trials in §§ 40-42 (1976). According to this

- the expected risks for the involved person must be in relation to the expected benefit and must be justifiable.
- the patient needs to be thoroughly informed about the aim, content and associated risks of the study (see appendix E)
- the patient has to agree to participate by signing an informed consent (see appendix F)
- the study has to be supervised by a physician with at least two-year experience in clinical research
- a study protocol based on the current scientific evidence has to be set up and be approved by an ethics committee.
- an appropriate patient insurance has to be signed which covers € 500,000.

These requirements were considered in the present study. In order to obtain the same approach in all participating centres standard operating procedures (SOP) were set up (see appendix D).

Personal data of the participating patients were protected by applying §4, sect. 3 of the data protection act of North-Rhine-Westphalia (2000). The patients had to sign an agreement prior to the study allowing the caring pharmacist to inspect patient record and to analyse the collected data (see appendix G). All patient-associated data were anonymised with a specific code to assure complete data protection.

The ethics committee of the medical council of North-Rhine approved the study. Additionally, the ethics committees of the individual institutions, when existing, approved the study for their setting.

3.2.1.2 Selection of patients and drugs

To obtain a homogenous study population inclusion and exclusion criteria were defined (Tab. 3-1).

Tab. 3-1 Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Diagnosed breast or ovarian cancer	Diseases or mental states which impede that the patient completely understands the provided information on the study (e.g. Alzheimer's disease).
First chemotherapy	
Age 18–65 years	
Written informed consent	Impaired capability of reading and completing questionnaires self-administered
Ability to speak, read and write in the German language	

Moreover, only patients with predefined chemotherapy regimens were included in the study. Two chemotherapy regimens were selected that were regarded as standard regimens and presented a toxicity profile which required extensive supportive therapy. As described before the chosen regimens accomplish these considerations (Tab. 3-2). However, the prescribing oncologists were not influenced at all in their decision for an individual regimen. They were merely asked to inform about changes.

Tab. 3-2 Selected chemotherapy regimens

Breast cancer		**Ovarian cancer**	
Epirubicin	90 mg/m² BSA	Paclitaxel	175-185 mg/m² BSA
Cyclophosphamide	600 mg/m² BSA	Carboplatin	Target AUC 5-7.5

3.2.1.3 Study design

The use of gold standards in clinical research, such as double-blinded, randomised controlled study designs, is limited when applied to pharmacy practice research. Nevertheless, it is important to define and establish standards for pharmaceutical care research in order to obtain reliable data. It was aimed at approaching as close as possible to the standards of clinical research. Different study designs were surveyed regarding their suitability to evaluate the care model:

- pre-post comparison
- parallel control group
- preceding control group

During the developing process specialists with expertise in either pharmacy practice research or clinical research in oncology were consulted. Criteria for the developed study design were high scientific output, feasiblility of the study design in an ambulatory setting and ethical aspects. The pre-post comparison did not seem to be suitable as a disease progression would bias the results. The parallel control group design was decided to be unapplicable as 'learning effects' of the participating physicians could be expected regarding the therapeutic algorithm for the antiemetic treatment. Moreover, it appeared to be unethical to offer a comprehensive care to some patients while others would not receive it. This was particularly difficult as the patients who were treated concurrently intensively exchanged their experiences which could have led to major discontentment. Eventually an open prospective, multi-centred, sequential control group design as illustrated in Fig. 3-2 was chosen. The control group was studied before the intervention group in order to avoid the mentioned learning effects and the inequity among the patients. Both the control (CG) and intervention group (IG) received the explanations about the aim and content of the study. The patients were allowed a respite of at least 24h until they were asked to decide upon their participation.

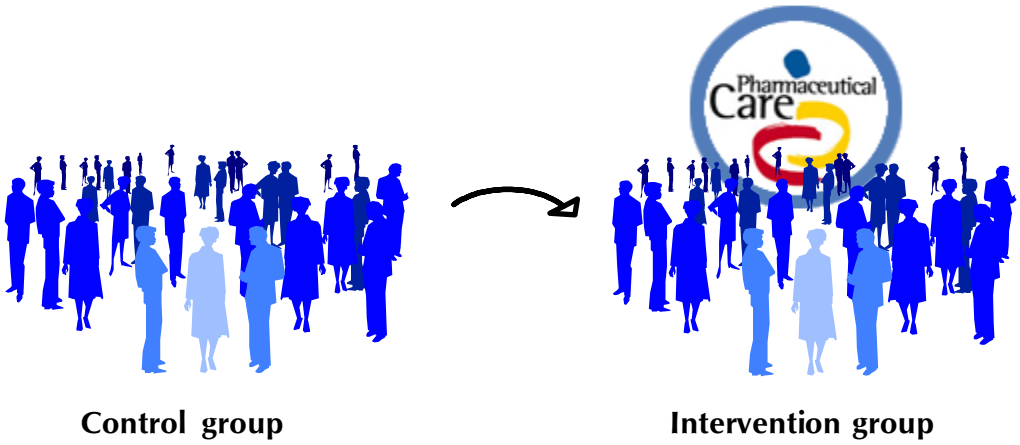


Fig. 3-2 Sequential control group design

All patients were asked to complete the questionnaires at predetermined times. The patients of the control group were then asked to send the completed questionnaires back to the study office in postage-paid and addressed envelopes, whereas the patients of the intervention group brought the questionnaires to the care

appointments. In case of the breast cancer patients the whole procedure lasted over a period of approximately nine weeks (four cycles with a three weeks interval). The ovarian cancer patients (OC) were in the care process for about 15 weeks (six cycles with a three weeks interval). Additionally, blood samples were drawn from ovarian cancer patients on the first, third and sixth cycle in order to determine the platinum concentrations in plasma (see 3.3 Monitoring of carboplatin).

For the intervention group, the following key interventions were defined:

- Regular appointments of the research pharmacist with the patients to define patient's needs and to detect and solve drug-related problems.
- The optimisation of supportive care and application of the acquired therapeutic algorithm.

The course of the study is illustrated in Fig. 3-3.

3.2.1.4 Study centres

Four gynaecological outpatient clinics and two oncological practices from the North-Rhine area participated in the study. The physicians had to agree to cooperate with the research pharmacist in terms of providing necessary patient information and being available for queries. Moreover, they needed to comply with the therapeutic algorithm for the antiemetic prophylaxis and treatment which the project team concertedly decided. The project team regularly met to discuss the process of the study. Between the meetings the research pharmacists communicated with the physicians mainly by telephone or by short visits in the clinics or physicians' offices.

3.2.1.5 Patient information material

Information on aim and content of the study

Prior to the study every patient received extensive standardised information material about the aim and the content of the study. The course of the study was explained and the individual effort in terms of completing the questionnaire and the expectable benefits for the patient were described. A sample of the information material for ovarian cancer patients is displayed in appendix F.

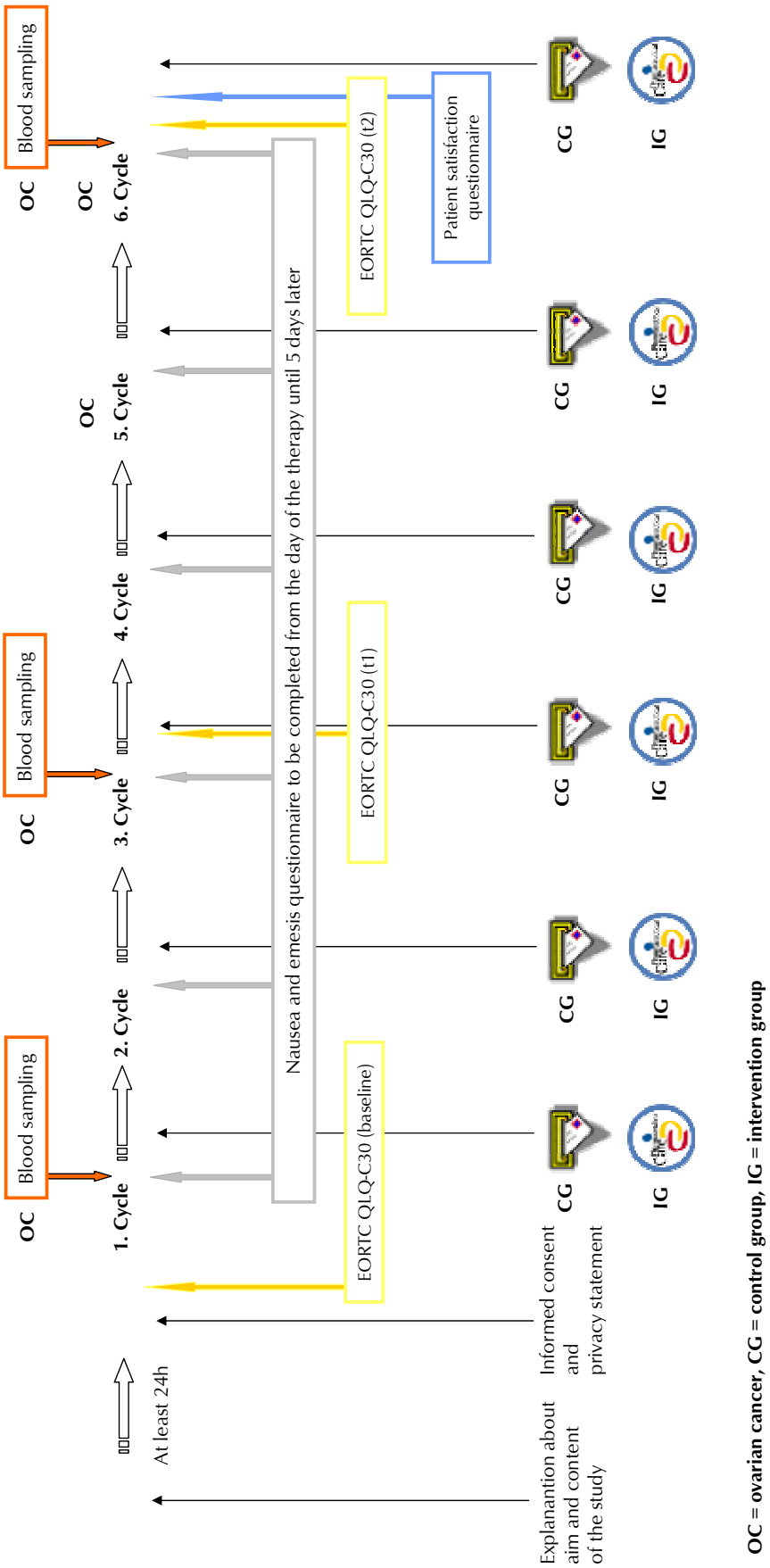


Fig. 3-3 Course of the treatment and outcome measurement

Information on expected adverse drug reactions

For the care process information material was prepared which explained the potential therapy-associated adverse drug reactions to the patient and gave recommendations for prophylactic measures as well as for emergency measures. An example is displayed in the appendix I. The content of these brochures was taken from a selection of cancer brochures from different cancer societies and textbooks (Margulies et al., 2002; Beckmann, 2003).

All patient information material was formulated in close cooperation with patient initatives. In order to prevent incomprehensibilities and inappropriate wording all material was proof read by patients from patient organisations (either 'Mamazone e.V.' or 'Frauenselbsthilfe nach Krebs e.V.'). In addition, the participating physicians approved the content of the information material.

3.2.1.6 Outcome measurement

In order to measure outcome in both groups, the following instruments were chosen: EORTC QLQ-C30 questionnaire to assess quality of life, a questionnaire to document nausea and vomiting for independent completion and the translated PS-CaTE patient satisfaction questionnaire referring to the given information (see 3.1). In addition, the kind of occurring DRPs and according pharmaceutical interventions were recorded.

Quality of life

Improvement of quality of life (QoL) is the main aim of pharmaceutical care. Different instruments are available to measure health-related quality of life (Fayers and Machin, 2000). The EORTC QLQ-C30 (version 3.0) questionnaire (see appendix J) was developed for research in oncology and reflects the special needs of cancer patients (Aaronson et al., 1993). Not only the fact that it is a disease-specific instrument made it suitable for this study, but also that it is widely used in international cancer research. It was translated in different languages including German and tested regarding its test-quality criteria. It was found to be reliable and valid.

It was important to be able to image the development of the QoL over the treatment period. Still the load for the patients should be minimised. Therefore three points of time were defined for the measurement of the QoL: at baseline just before the

beginning of the chemotherapy, at half time (after the second cycle for breast cancer patients and after the third cycle for ovarian cancer patients, respectively) and at the end of the treatment (after the fourth (BC) or sixth cycle (OC)). For the second and third measurement the patients were asked to complete the QLQ-C30 questionnaire a week after the chemotherapy cycle. This seemed to be reasonable as patients suffer most adverse effects within the first week after chemotherapy. Therefore, earlier measurements would bias the global QoL too much. Still the measurements should not be performed too long after these experiences. As it is a subjective assessment and influenced by many factors it also seemed to be important to measure all patients in the same manner in order to obtain reliable data.

The questionnaire consists of multi-item scales as well as single-item measures as listed in Tab. 3-3. Raw data were transformed into scores from 0 to 100 where a high scale score represents a higher response level (Fayers et al., 1999). For functional scales a high score represents a high degree of functioning, as well as a high score in global health status and QoL stand for high QoL. Compared to these a high score in a symptom scale or item represents a high degree of symptomatology.

Tab. 3-3 Scales of the QLQ-C30 version 3.0

	Scale	Number of items	Item numbers (v 3.0)
Global health status/QoL	QL2	2	29, 30
Functional scales			
Physical functioning	PF2	5	1-5
Role functioning	RF2	2	6, 7
Emotional functioning	EF	4	21-24
Cognitive functioning	CF	2	20, 25
Social functioning	SF	2	26, 27
Symptom scales/ items			
Fatigue	FA	3	10, 12, 18
Nausea and vomiting	NV	2	14, 15
Pain	PA	2	9, 19
Dyspnoea	DY	1	8
Insomnia	SL	1	11
Appetite loss	AP	1	13
Constipation	CO	1	16
Diarrhea	DI	1	17
Financial difficulties	FI	1	28

To obtain a score initially a raw score was calculated:

$$RS = RawScore = (I_1+I_2+I_3+...I_n)/n \quad \text{(Eq. 3-1)}$$

The score for functional scales is then determined by:

$$Score = \left\{1-\frac{(RS-1)}{range}\right\}\cdot 100 \quad \text{(Eq. 3-2)}$$

Both symptom scales and the global health status / QoL were scored by:

$$Score = \left\{\frac{(RS-1)}{range}\right\}\cdot 100 \quad \text{(Eq. 3-3)}$$

Item range is the difference between the possible maximum and the minimum response to individual items.

The results of the global health status/QoL and of the functional scales were calculated for the different time points (t_1, t_2) relative to the baseline value t_0.

$$t_1(rel) = \frac{t_1}{t_0} \cdot 100 \qquad t_2(rel) = \frac{t_2}{t_0} \cdot 100 \qquad \text{(Eq. 3-4)}$$

For the symptom scales the absolute values were used.

The changes in the different subscales over the treatment period were determined by subtracting the baseline value from the values at t_1 and t_2. The difference of the global health status/QoL and of the functional scales was related to baseline

$$t_1(change) = \frac{(t_1 - t_0)}{t_0} \cdot 100 \qquad t_2(change) = \frac{(t_2 - t_0)}{t_0} \cdot 100 \qquad \text{(Eq. 3-5)}$$

Nausea and emesis

The questionnaire for reporting of nausea or emesis had two purposes in the present study. For one, it served as an outcome measure. Additionally, it was used as a tool in pharmaceutical care to monitor the antiemetic prophylaxis and treatment. Some considerations had to be made to accomplish both tasks.

The assessment of nausea and emesis requires different methods (Morrow, 1992). Whereas emesis is an objective criterion, nausea is certainly subjective. Emesis can simply be measured by the enumeration of the emetic episodes. Strictly speaking it must be defined whether retching accounts for an emetic episode or not. The stringent criterion 'complete control emesis' (no event of retching nor emesis) avoids these definition problems. This parameter can be better recalled by patients and is also better comparable among different studies. Morrow describes in his meta-analysis different ways of measuring nausea. Frequency, severity and duration of nausea can be assessed.

Moreover, the way on how to get the information on the experienced nausea and emesis has to be considered. A very common way is to ask patients at the

following appointment. This, however, is biased by incomplete recalling. Another way is by self-reporting on patient diary cards. This seems to reflect the real situation much better.

Freidank established a patient diary for the self-recording of both nausea and emesis. It has successfully been used in the clinical setting and seemed applicable for the present study (Freidank, 1999). Patients were asked to report the emetic episodes and classifiy the experienced nausea from degree 0 to 4 ('no nausea' to 'severe nausea, which makes everyday life impossible').

In the present study a modified version of Freidank's patient diary was used (see appendix J). For nausea the sum scores of the reported degrees of nausea were compared whereas for emesis the achieved complete response rates were compared between the two groups. Still patients were asked to report all emetic episodes in order to evaluate the success of the antiemetic prophylxis and therapy. Patients were instructed to count episodes which were one minute apart as two, retching and/or vomiting accounted for one episode if lasting less than five minutes and for two if longer than five minutes. Complete response was defined as no event of retching and emesis over a defined period.

Nausea and emesis were documented after every cycle. This allowed monitoring as well as the longitudinal evaluation of the collected data. In order to record both acute and delayed nausea and emesis patients were asked to fill in the patient diary over a period of 5 days starting at the day they received chemotherapy.

Patient satisfaction with information on cancer treatment

The questionnaire measuring the patients' satisfaction with information on cancer treatment was completed once at the end of each chemotherapy cycle. The scoring of the questionnaire followed the system described inTab. 3-4.

Tab. 3-4 Scoring of the patient satisfaction questionnaire

Scale		Scoring
Global satisfaction		Sum score of all 14 items divided by the number of items
Scale 1	Satisfaction with information regarding cancer treatment	Sum score of items 1, 5, 6, 7, 12 divided by 5
Scale 2	Satisfaction with information regarding side effects	Sum score of items 2, 3, 8, 13 divided by 4
Scale 3	Satisfaction with information regarding vitamins, herbs and complementary therapy	Sum score of items 4, 9, 14 divided by 3
Scale 4	Satisfaction with information sources and the way information is provided	Sum score of items 10, 11 divided by 2

Pharmacists' interventions

An important aspect in pharmaceutical care is the detection and solution of drug-related problems (DRPs). Schaefer developed, comparable to Strand (Strand et al., 1990) and van Mil (van Mil and Tromp, 1997) a coding system for drug-related problems – PI-Doc® (Schaefer, 2002). This coding system is used in all German pharmacy software packages with a pharmaceutical care module. In the present study the detected DRPs and associated interventions were coded according to PI-Doc®.

This system is based on a set of codes (see appendix H) which can be extended by the operator for extra codes for specific care issues and DRPs. In case of the pharmaceutical care for cancer patients a supplementation of the existing codes was necessary. The additional codes are listed in Tab. 3-5.

Tab. 3-5 Supplementation of additional codes for PI-Doc®

G	**Other Problems (patient-related)**
GP7	Patient vomited the taken drugs
I	**General intervention**
I5	Recommendation of a drug
I5a	Recommendation to change a drug
I6	Recommendation of a preventive measure
I7	Information regarding complementary measures

I8	Drug information search
I9	Recommendation of a non-medical measure
IG	*Intervention: other problems*
	Patient-related problems
IGP4a	Information about nutrition
IGP4b	Information about physical training
IGP7	Recommendation regarding adaequate subsequent dosage
	Technical and logistical problems
IGT6	Clarification of a seamless therapy continuation

3.2.2 Therapeutic algorithm for the antiemetic prophylaxis and treatment

In order to optimise the antiemetic prophylaxis and treatment the currently available and evidence-based therapeutic guidelines of the scientific societies were applied (Tab. 3-6).

Tab. 3-6 Therapeutic guidelines for the antiemetic prophylaxis and treatment

American Society of Clinical Oncology	ASCO	Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines	Gralla et al., 1999
European Society of Medical Oncology	ESMO	ESMO recommendations for prophylaxis of chemotherapy-induced nausea and vomiting	ESMO guidelines task force, 2001
Multinational Association of Supportive Care in Cancer	MASC	Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia consensus conference	Antiemetic Subcommittee of the MASCC, 1998
American Society of Health System Pharmacists	ASHP	ASHP Therapeutic Guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery	ASHP Commission on Therapeutics, 1999

The research pharmacist studied the available guidelines and worked out a proposal which served as a basis for discussion within the project team.

Three questions had to be answered:

- How is the emetogenicity of the two selected chemotherapy regimens classified?
- What are the concordant recommendations of the scientific societies for the treatment of acute and delayed nausea and emesis?
- Do individual risk factors play a role in the treatment decision?

According to the consulted literature and taking the experience of the participating physicians into account the chosen regimens were classified (Hesketh et al., 1997; Antiemetic Subcommittee of the MASCC, 1998; ASHP Commission on Therapeutics, 1999; Gralla et al., 1999; ESMO guidelines task force, 2001). Epirubicin (90 mg/m^2) in combination with cyclophosphamide (600 mg/m^2) has a moderate to high emetogenic potential whereas paclitaxel (175 (185) mg/m^2) in combination with carboplatin (target AUC 5 – 7.5 mg·min/mL) is classified highly emetogenic.

The prophylactic treatment options for nausea and emesis recommended by expert groups of the different scientific societies were intensively discussed with the participating physicians until a consensus was reached in the project team. The consensus of the project team mainly applied these recommendations, which do not vary a lot. Regarding the significance of dexamethasone a deliberate modification was applied. Instead of dexamethasone metoclopramide was selected basic component of the antiemetic prophylaxis. The agreed therapeutic algorithm is illustrated in Fig. 3-4.

Regarding the individual risk factors only ASCO and ASHP mention the impact of young age, female sex, little alcohol intake and previous bad experiences which influence the symptomatology of nausea and emesis. Still, in neither of the studied guidelines these factors have an impact on the therapeutic recommendation. The project team therefore decided to act accordingly. In terms of the prophylaxis of anticipatory nausea and emesis the project team agreed that the mental condition of the patient prior chemotherapy should be considered. It was differentiated whether the patient was anxious or confident. Anxious patients received additional lorazepam.

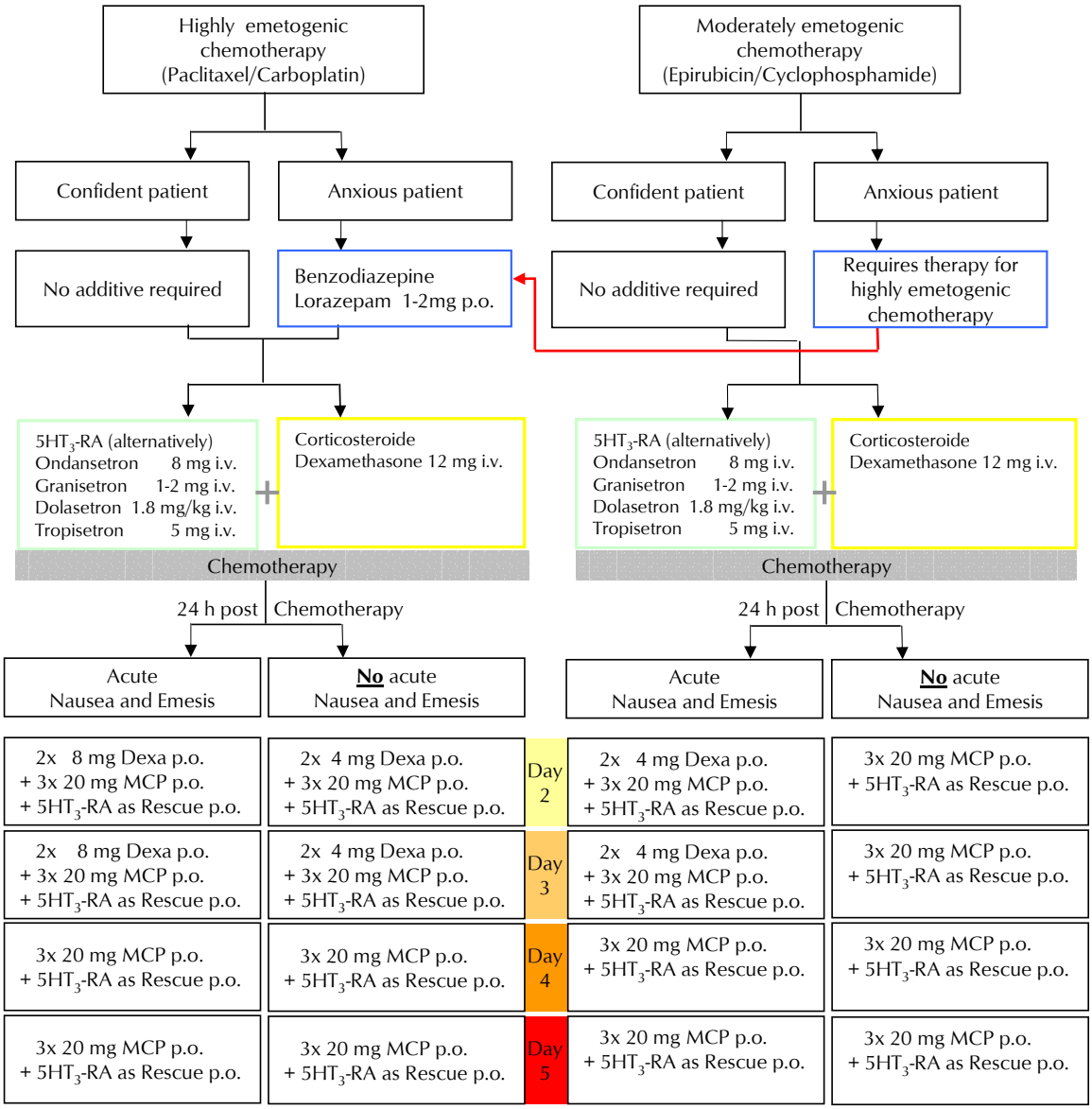


Fig. 3-4 Therapeutic algorithm for the antiemetic prophylaxis and treatment (RA = receptor antagonist, Dexa = dexamethasone, MCP = metoclopramide)

3.2.3 Evaluation of the collected data

The aim of this work was to study the feasibility and benefit of pharmaceutical care for patients with gynaecological malignancies. Little was known about the impact of pharmaceutical care on the selected outcome parameters. In the pilot phase pharmaceutical care was established and first knowledge on primary and secondary endpoints was obtained.

Due to the fact that information, necessary for a reasonable statistical planning, was lacking, a dual-stage adaptive design was chosen (Wassmer, 1999). In this

precursory pilot phase the important information was collected which than was used to thoroughly plan the subsequent main study. The advantage of this design is the opportunity to evaluate both patient groups together. This reduces the number of patients needed to show the difference between two groups regarding a selected effect.

As the improvement of the health related quality of life is per definition the aim of pharmaceutical care it was chosen to be the primary endpoint in the precursory phase of the study. Apart from the primary endpoint other parameters were regarded as secondary endpoints. Acute and delayed nausea, acute and delayed emesis, complete control of emesis and patient satisfaction were evaluated. To decide whether there is a difference in quality of life between control and intervention group the nullhypothesis H_0: QoLControl = $QoL_{Intervention}$,

that is, QoL in both groups is equal, has to be disproved in order to accept the alternative hypothesis

H_1 (two-sided): $QoL_{Control} \neq QoL_{Intervention}$,

that is, QoL in both groups is unequal.

Determination of α_0, α_1 and c_α and the decision-algorithm

The dual-stage adaptive design required the predefinition of threshold values α_0, α_1 and c_α which were part of the decision algorithm which was applied at the end of the pilot phase in order to decide how to proceed. It will also be used at the end of the main study. These threshold values resulted from the assumption that the total error should be less than 5%. According to Bauer and Köhne (1994) $\alpha = 0.05$ and $\alpha_0 = 0.50$ a critical value $\alpha_1 = 0.0233$ and $c_\alpha = 0.0087$ resulted.

This consequently led to the following decision algorithm:

If the p-value p_1 of the internal pilot study $p_1 \geq \alpha_0 = 0.50$, the study will be terminated accepting H_0.

If $p_1 \leq \alpha_1 = 0.0233$, the study will be terminated with the disaffirmation of H_0.

If $\alpha_1 < p_1 < \alpha_0$, the second phase of the study will be carried out. In the second phase H_0 will be rejected, if $p_1p_2 \leq c_\alpha = 0.0087$.

3.2.4 Pharmaceutical care process

3.2.4.1 Patient recruitment

The treating physician drew the patients' attention to the study and asked their permission to be contacted by the research pharmacist. The pharmacist then contacted the patient either in the clinic, practice or by telephone and made an appointment for an informative talk. Patients had 24h time to consider their participation until they were asked for their decision. They were informed that they would always have the chance to withdraw their consent without the need to explain the reasons or having to fear consequences for their treatment.

When patients agreed to participate in the study they were handed out a patient-folder which contained the

- Patient information
- Contact addresses of physicians and pharmacists
- Certificate of patient insurance
- Plan of the course of the study
- Copy of the written informed consent and the privacy statement
- Pre-printed form of a patient diary
- Questionnaires which had to be completed during the study period sorted by chemotherapy cycle
- Postage-paid and addressed envelopes to assure a complete return flow of the questionnaires

Some time was spent with each patient in order to explain the process and the questionnaires in detail. The questionnaires were filed cycle-wise in the same order in which they were meant to be completed by the patient. This measure was meant to improve the compliance of the participating patients to the study. Furthermore patients were offered the option to be reminded by the research pharmacist to complete the questionnaires either by phone or with a postcard.

3.2.4.2 Care appointments

The pharmaceutical care was conducted by two pharmacists in the following referred to as caring pharmacists. The care appointments took place on a regular basis according to the previously described study course. The first appointment was prior to the first chemotherapy whereas the following appointments usually took place about one week after the chemotherapy. This schedule was chosen to bridge the time between the patients' appointments with the oncologist in order to give the patient an immediate chance to discuss DRPs which might have occurred.

At the first appointment the focus was put on general information about the chemotherapy, the expectable adverse effects and the possibilities to avoid these. Patients were handed out written information (see appendix I) and patient brochures of the German "Krebshilfe". For the prophylaxis of nausea and emesis additional individualised information was given to the patient on when and how to take the prescribed medication. Time was taken to allow and answer patients' questions and concerns. This first appointment also proved to be important to establish a confiding relationship.

The following appointments were used to update on the well being of the patient. According to the concept of pharmaceutical care the past weeks were reviewed, drug related problems were discussed and mutual solutions were refined. In between the appointments patients always had the chance to get in contact with the caring pharmacist. Usually these contacts were by telephone and if necessary additional appointments were made.

3.2.4.3 Documentation

At the beginning of the care process the specific patient data were collected in a patient master file (see appendix K). The medical findings and laboratory data were documented as background information for an appropriate care process. All medication used by the patient was documented in a medication file and medication profile including prescribed and OTC medication(see appendix K). A care plan was developed according to the SOAP scheme.

The content and the time needed for each care appointment were documented in a protocol. Besides, the drug-related problems were documented and categorised using the PI-Doc®-System (Schaefer, 2002).

3.3 Monitoring of carboplatin

3.3.1 Patient selection

Patients with diagnosed epithelial ovarian cancer and a prescribed chemotherapy regimen of paclitaxel (175-185 mg/m²) in combination with carboplatin (target AUC 5-7.5 mg·min/mL) were included in the study. Study patients had to meet the inclusion criteria according to the study protocol. The patients were informed about the content of the study and the associated risks at least 24h prior to the study. Patients provided written informed consent. This part of the study was also approved by the ethics committee.

During the study period four patients agreed to participate in this part of the study and received all six cycles of the mentioned combination chemotherapy. The drug monitoring did not differ between the study groups. The statistical evaluation was descriptive, depicting the actual achieved AUC and the degree of thrombocytopenia.

3.3.2 Limited blood sampling

Blood sampling was planned in a way that was meant to integrate well with everyday clinical practice. Therefore, a limited sampling method was applied in order to reduce the number of necessary blood samples. Sørensen et al. developed a method to estimate the area under the concentration versus time curve of carboplatin requiring only two samples drawn at fixed time points, 15 minutes and 2 h and 45 minutes after the end of the infusion (Sørensen et al., 1993). AUC can be calculated from the respective ultrafilterable plasma concentration as follows:

$$AUC = 0.053 \cdot C_{0.25h} + 0.401 \cdot C_{2.75h} + 0.628 \qquad \text{(Eq. 3-6)}$$

The two-sample method is unbiased (MPE% ± SD: -2.2% ± 2.1%) and precise (RMSE%: 9.4%).

3.3.3 Drug analysis

3.3.3.1 Laboratory data

The routinely performed laboratory analysis of patients' blood was documented. In particular, the white blood cell count (WBC) and platelet count were documented.

3.3.3.2 Sample collection and preparation

Blood samples were drawn in line with the study protocol when cycle I, cycle III and cycle VI were administered. As the results did not have immediate consequences for the patients' individual dosage it seemed to be sufficient to obtain AUCs of three out of six cycles.

All blood samples were drawn from the opposite arm of the carboplatin infusion at 0.25 h and 2.75 h after the end of the carboplatin infusion in EDTA tubes (S-Monovettes®). Within 15 minutes after blood withdrawal, plasma was obtained by centrifugating the full blood at 3200 g for 10 minutes (at 20°C). Aliquots were taken from the plasma and 1 mL was used to obtain ultrafiltrate. Ultrafiltrate was used in order to measure the unbound platinum fraction. In an Amicon Centrifree® Millipore tube, plasma was centrifugated for another 20 minutes at 2000 g (at 20°C). The aliquots were stored at -20°C for transportation and afterwards at –80°C until analysis.

3.3.3.3 Atomic absorption spectrometry

Flameless atomic absorption spectrometry (FAAS) is a common method to detect traces of metals in different biological matrices. It has been used to quantify carboplatin in several pharmacokinetic studies (Kloft et al., 2002; Calvert et al., 1995; Obasaju et al., 1996; van Warmerdam et al., 1997; Boddy et al., 2001).

The quantification of metals in different matrices is based on their ability to absorb light of definite wavelengths after atomisation. This method uses light with the same wavelength that would be emitted by the element to be determined.

The correlation between the amount of light absorbed by the sample and the concentration of the respective metal is described by the law of Lambert-Beer:

$$A = \log \frac{I_0}{I} = k \cdot d \cdot c \qquad \text{(Eq. 3-7)}$$

A Absorption
I_0 Light intensity
I Light intensity after passing the sample
k Absorption coefficient
d Layer thickness
c Concentration of the analyte

This proportionality is only valid for low concentrations and a constant layer thickness.

Analytical conditions

In this study platinum was quantified in human plasma and ultrafiltrate using the flameless atomic absorption spectrometer SpectrAA® with a graphite furnace technique. The instrumentation and operating conditions are listed in the appendix L. The graphite tube was heated up by electric current. Argon served as an inert gas to prevent the self-inflammation of the graphite tube. The argon stream was interrupted during atomisation in order to avoid disturbance of the signal detection. A defined temperature programme was applied to eliminate potentially interfering substances such as proteins from the sample. The temperature programme was operated in five phases as described in Tab. 3-7.

Tab. 3-7 Temperature programme of the GF-AAS

Step	Phase	Temperature [°C]	Time [sec]	Gas flow [L/min]	Absorption recording
1	Drying	95	5.0	3.0	no
2		110	60.0	3.0	no
3		120	10.0	3.0	no
4	Pre-Ashing	650	15.0	3.0	no
5		650	20.0	3.0	no
6	Ashing	1300	10.0	3.0	no
7		1300	2.0	3.0	no
8		1300	2.0	0	no
9	Atomisation	2700	0.7	0	yes
10		2700	2.0	0	yes
11	Cleaning	2700	2.0	3.0	no

During drying and pre-ashing volatile components were eliminated from the sample matrix. Ashing followed. To guarantee constant initial temperatures for each analysed sample the graphite tube was cooled down following each atomisation and cleaning phase.

The hollow cathode lamp used had a current of 10 mA. The Zeeman correction assured the correction of background absorption caused by scattering of particles and absorption of organic molecules. The measurement was conducted with and without the presence of a magnetic field. Without the magnetic field the absorption of the element and background were measured, whereas in the presence of a magnetic field only the absorption of the background was measured. The difference of both values resulted in the intensity of the element's signal. Platinum absorbance was measured at a wavelength of 265.9 nm with a photomultiplier.

The described method enableses a sensitive platinum detection. The sample stays within the closed tube and is not carried away with the gas stream. This way a larger number of atoms can absorb the light of the hollow cathode lamp which leads to a lower limit of quantification. This is the particular advantage of the graphit-tube furnace (GF)-FAAS compared to conventional flame techniques.

3.3.3.4 Validation of the analytical method

The FAAS analysis was conducted according to a validated method (van Warmerdam et al., 1995; Kloft et al., 1999; Pieck, 2004). The lower limit of quantification, LLOQ, for platinum was 20 ng/mL in plasma and 5 ng/mL in ultrafiltrate. Recovery, linearity, accuracy and precision met the international requirements for the validation of bioanalytical methods according to the U.S. Department of Health and Human Services (2001) (see appendix L). The results were documented in a GLP-conform validation report.

The quantitative determination of platinum was performed after a single dilution step (modified according to Kloft et al. 1999). The chemicals and reagents used are listed appendix L. The aliquots of plasma and ultrafiltrate were prepared for the analysis. Plasma samples were diluted with an aqueous solution of 1% Triton™ X-100 to final concentrations in the calibration range.

Tab. 3-8 Sample preparation for platinum analysis

Plasma	Sample I	10 µL + 4990 µL Triton™ X 1% solution
	Sample II	10 µL + 990 µL Triton™ X 1% solution
Ultrafiltrate	Sample I	10 µL + 4990 µL nitric acid 6.5% solution
	Sample II	10 µL + 990 µL nitric acid 6.5% solution

Sample I = taken 15 min after carboplatin infusion
Sample II = taken 2 h and 45 min after carboplatin infusion

Samples of ultrafiltered plasma were diluted with nitric acid 6.5% to final concentrations in the calibration range (Tab. 3-8). The injection volume was 20 µL. The measurement of standards and samples was performed in the 'PROMT' mode (Precision optimised measurement time). All samples were measured at least twice. With a resulting deviation of > 5% a third measurement followed and if necessary a fourth one, if the standard deviation still was still < 15%.

3.3.3.5 Preparation of standards for calibration

A stock solution of carboplatin containing 10 mg/mL platinum (19.0 mg/10 mL) was used to prepare a standard solution containing 50 ng/mL platinum in plasma or ultrafiltrate. The stock solution was stable over a period of eight months at –20°C

(Pieck, 2004). The calibration standards of 5-50 ng/mL were prepared from blank matrix and the highest standard solution (50 ng/mL) by the programmable sample dispenser. The preparation was made by diluting the platinum-free plasma with Triton™-X solution 1% in the case of plasma and nitric acid 6.5% in the case of ultrafiltrate in the ratio 1:100. The calibration range reached from 500 to 5000 ng/mL. The calibration line was generated by performing linear regression analysis from the means of the peak heights of the absorption signal minus the zero value.

3.3.3.6 Quality assurance during the measurement

Plasma and ultrafiltrate blanks were spiked with adequate amounts of platinum, aliquoted and stored at -20°C in order to generated two different types of quality control samples. Processed quality controls (PQC) were samples which were processed immediately after their preparation in three concentrations (500, 2500 and 5000 ng/mL). They were stored in aliquots at -20°C until analysis. Spiked quality controls (SQC) were plasma or ultrafiltrate samples with concentrations of 500, 2000, 4000 and 20000 ng/mL. These samples were stored in aliquots at -20°C and were processed prior to analysis like clinical samples. Aliquots of PQC and SQC samples were analysed with each run.

According to the specifications of the international requirements for the validation of bioanalytical methods, 67% of the QC samples needed to be within 15% of their nominal values which was achieved in this study (appendix L).

3.3.3.7 From elementary platinum concentration to the carboplatin concentration

By means of FAAS the concentration of elementary platinum was measured. To derive the actual carboplatin concentration the measured platinum concentrations were converted using the molar mass of platinum (195.09 g/mol) and carboplatin (371.2 g/mol).

3.4 Statistical data analysis

3.4.1 Patient satisfaction with information on cancer treatment

Data entry and analysis were carried out using SPSS® 10.0 for Windows (SPSS Inc.,

Chicago, Illinois). The collected data were first analysed using descriptive statistics, determining frequencies, medians and percentile scores.

To measure the split-half reliability, the items of the test were first randomly divided into two equally large item subsets. The correlation of the sum scores of these subsets is an estimate of the reliability of the test halves in order to obtain an estimate of the whole test reliability; the correlation of the test halves is then adjusted using the Spearman-Brown formula. If the scale is internally consistent the two halves should correlate highly. The Spearman-Brown formula corrects the bias which results from the fact that the sub-scales being correlated are only half the length of the full version. This would normally result in too low correlations (Streiner and Norman, 2000). The used formula is

$$r_{tt} = \frac{2 \cdot r_{12}}{1 + r_{12}} \qquad \text{(Eq. 3-8)}$$

r_{tt} = Reliability of the complete test
r_{12} = Correlation of 1st and 2nd half of the test

The split-half reliability should not be the only measure to assess reliability as it does not determine the items which contribute to a low reliability. Therefore, it is combined with the coefficient alpha.

The coefficient alpha, in contrast, is based on the ratio of the sum of the single-item variances to the total test score variance (Lord and Novick, 1968). Cronbach's alpha can be used when there are more than two response alternatives.

$$\alpha = r_{tt} = \frac{c}{c-1}\left[1 - \frac{\sum_j s_j^2}{s_x^2}\right] \qquad \text{(Eq. 3-9)}$$

α = Cronbach´s alpha
r_{tt} = Reliability of the complete test
c = number of equal parts in which the test is divided
s_j^2 = Variance of the j-part of the test
s_x^2 = Variance of the test

The implication is usually made that the higher the coefficient the better. Both the Spearman-Brown corrected split-half coefficient and Cronbach's alpha can range between 0 and 1, with values larger than 0.7 indicating acceptable reliability (De Vellis, 1991).

In addition the alpha-if-item-deleted test was performed (Streiner and Norman, 2000). This way the influence of each item on the homogeneity of the scale was tested. Stepwise one after the other item was eliminated from the scale and Cronbach's alpha was determined. Thus, items which influence the reliability can easily be identified and if necessary be eliminated from the scale.

A stepwise multiple regression analysis was performed using the total satisfaction scores as the dependent variable to determine the predictors of satisfaction with information.

3.4.2 Pharmaceutical care of patients with gynaecological malignancies

Since it could be expected that data had a skewed distribution and therefore could not be described with a Gaussian distribution, non-parametric two-sample comparisons were applied for the hypothesis testing. Some of the data, QoL as well as nausea and emesis have a longitudinal dimension. It was evaluated cycle-wise regarding nausea and emesis, but also over time as the incidents are dependent.

3.4.2.1 Primary endpoint

Quality of life

The findings of the EORTC QLQ-C30 (v. 3.0) were descriptively evaluated. The relative changes in the different scales over the treatment period compared to baseline were evaluated by comparing the median and the 25% and 75% percentiles. Boxplots were chosen for the graphical presentation.

The non-parametric rank-sum test according to Mann and Whitney was used to compare the means of the two groups. To assess the difference between the two groups over time a non-parametric analysis of variance was performed (Brunner et al., 2001).

3.4.2.2 Secondary endpoints

All secondary endpoints were evaluated in an expolartory manner. Descriptive statistics were performed as well as statistical tests to compare the two groups (see above).

Complete control of emesis

The results of complete control of emesis between the two groups were evaluated from different perspective. The complete control was compared cyclewise and the achieved complete control rate was described in percent. The two groups were compared using contingency tables evaluated with Fisher's exact test (Motulsky, 1995; Bortz and Lienert, 1998). This was also applied when the number of cycles with complete response were compared.

To assess the difference between the two groups over time a non-parametric analysis of variance was performed (Brunner et al., 2001).

Acute and delayed nausea and emesis

From the collected data sum scores of experienced degrees of nausea and episodes of emesis in the acute and delayed phase were compiled. These were evaluated using descriptive statistics.

Acute and delayed

From the collected data sum scores of experienced in the acute and delayed phase can be compiled. These have been presented using descriptive statistics.

Patient satisfaction with information on cancer treatment

To compare the two equal sized groups the Mann-Whitney U-test, a robust non-parametric test, has been used.

3.4.2.3 Sample size estimation for the main study

For the pilot phase a sample size of 20 patients per group was chosen. Presuming a drop-out-rate of maximum 25%, 25 patients per group were required. This sample size was not statistically estimated, as in the pilot phase mainly the feasibility of pharmaceutical care was to be shown and knowledge about the distribution of the

primary and secondary endpoints should be obtained. The information will then be used for the adaptive sample size estimation for the main phase.

The pilot study was designed as an explorative observation. An alpha adjustment for multiple testing was therefore not required although different endpoints were evaluated.

So far no algorithms or programmes are available to calculate the sample size for non-parametric analysis of variance. The sample size estimation for the following main study was therefore performed by power simulation. For this purpose, different combinations of the group size (n), the prevalence in the control group (p) and the expected difference (Δ) 10,000 simulations were performed at a time and the power was calculated for a type I error $\alpha = 5\%$. The simulations were performed by S-Plus® 2000 (MathSoft Inc., Cambridge, MA).

[4] Results

4 Results

4.1 Patient satisfaction with information on cancer treatment

Parts of the following results were generated in the course of the diploma thesis of Eckhardt (2002).

4.1.1 The German version

Like the original Canadian version, the German questionnaire consists of three parts (see appendix J). Part one contains fourteen items and evaluates the patients' perception of the information provided during cancer treatment. On a five point Likert scale ('strongly disagree' to 'strongly agree') patients were instructed to rate how much they agree/disagree with the statement made in the item. Part two contains two questions referring to the information sources utilised by the patients. Several answers are possible. The last part of the questionnaire determines the socio-demographic characteristics of the patients.

4.1.2 Response

61 questionnaires were returned for the pre-test and 232 questionnaires for the main survey. The response rate of the questionnaires distributed by a self-aid group via mail was 65%. 47 questionnaires from the pre-test were completed entirely and could be used for the psychometric tests. Due to incomplete answering 14 questionnaires were excluded from the analysis. The socio-demographic and disease-related patient characteristics of the sample in the main survey are listed in Tab. 4-1 and Tab. 4-2.

Tab. 4-1 Socio-demographic patient characteristics in the main survey (n=232)

Socio-demographic variable		n	%
Age	< 50 years old	62	26.7
	50-60 years old	83	35.8
	> 60 years old	86	37.1
	No answer	1	0.4
Sex	Female	171	73.7
	Male	60	25.9
	No answer	1	0.4
Marital status	Married/partner	170	73.3
	Single	20	8.6
	Divorced	21	9.1
	Widow	21	9.1
Current living situation	Living alone	47	20.3
	With family or partner	182	78.4
	No answer	3	1.3
Education	Elementary school	47	20.3
	Secondary school	16	6.9
	O-levels	56	24.1
	Journeyman	23	9.9
	Master of a trade	9	3.9
	Bachelor	14	6.0
	University/ College	62	26.7
	No answer	5	2.2
Profession	Housewife	32	13.8
	Worker	8	3.4
	Employee	74	31.9
	Self-employed	25	10.8
	Public servant	19	8.2
	Pensioner	65	28.0
	Craftsman	7	3.0
	No answer	5	2.2

Tab. 4-2 Disease-related patient characteristics in the main survey

		n	%
Diagnosis	Breast cancer	125	53.9
	Ovarian cancer	11	4.0
	Others	53	27.2
	No answer	33	14.2
Time since diagnosis	< ½ year	75	32.3
	½ year to 2 years	79	34.1
	> 2 years	47	20.2
	No answer	31	13.4
Therapy setting	Inpatient treatment	29	12.5
	Outpatient clinic	94	40.5
	Primary care oncologist	80	34.5
	No answer	29	12.5
Self-aid group	Yes	39	16.8
	No	175	75.4
	No answer	18	7.8

4.1.3 Psychometric assessments

The results of the pre-test reliability analysis of the whole scale and of the subscales adapted from the Canadian questionnaire are shown in (Tab. 4-3). The whole questionnaire and the subscales 1 to 3 obtained reliability coefficients larger than 0.80. Only the subscale 4 'information sources' showed rather low reliability coefficients of 0.57 (split-half reliability) and 0.52 (Cronbach's alpha). The reliability analysis of the main survey revealed convincing reliability coefficients larger than 0.77 for all scales.

Regarding the face-validity, the consulted experts and the patients rated each item and the questionnaire in total as understandable and concordant with its task to measure several aspects of satisfaction with information.

Tab. 4-3 Reliability coefficients

Scale	Pre-test		Main survey	
	Cronbach's alpha	Spearman Brown split-half reliability	Cronbach's alpha	Spearman Brown split-half reliability
Global satisfaction	0.92	0.92	0.95	0.91
Satisfaction with information regarding cancer treatment (scale 1)	0.80	0.85	0.88	0.89
Satisfaction with information regarding side effects (scale 2)	0.88	0.89	0.90	0.87
Satisfaction with information regarding vitamins, herbs and complementary therapy (scale 3)	0.90	0.87	0.87	0.84
Satisfaction with information sources and the way information is provided (scale 4)	0.52	0.57	0.78	0.78

4.1.4 Satisfaction with information

The majority of patients were satisfied with the information given on cancer treatment. The detailed results of the agreement/disagreement rating are shown in Tab. 4-4.

The subscale analysis elucidated the differences in satisfaction among different information areas. Overall satisfaction was characterised by a median of 3.5 on a scale ranging from 1 to 5. Satisfaction with general cancer treatment information (subscale 1) achieved a median score of 3.8. Subscale 2 measuring satisfaction with information regarding side effects of the cancer treatment exhibited a median score of 3.5. In contrast, subscale 3 assessing satisfaction with complementary therapies attained a median score of only 3.0. The satisfaction score was highest for subscale 4 referring to information sources (median score of 4.0).

Tab. 4-4 Results for separate items in the main survey

		Strongly disagree	Disagree	Uncertain	Agree	Strongly agree	n.s.	Median	Percentile
		(1)[1]	(2)[1]	(3)[1]	(4)[1]	(5)[1]			25 50 75
I am satisfied with the **information** I have been given about my **cancer treatment**.	S1	3.4	10.8	15.5	47.8	21.6	0.9	4.00	3.00 4.00 4.00
I am satisfied with the **information** I have been given about possible **side effects** of my treatment.	S2	5.2	14.7	17.7	44.4	17.2	0.9	4.00	3.00 4.00 4.00
I am satisfied with the **information** I have been given on **what to do** if **side effects** happen.	S2	9.5	14.7	25.9	31.9	14.7	3.4	3.00	2.25 3.00 4.00
I am satisfied with the answers to my questions about **vitamins, herbs, and complementary therapies**.	S3	11.2	28.9	18.1	23.3	9.9	8.6	3.00	2.00 3.00 4.00
I am satisfied with the explanations about possible **interactions** between my prescribed **cancer treatment** and **other treatments** I am using or thinking about using.	S1	7.8	15.9	15.5	40.1	10.8	9.9	4.00	2.00 4.00 4.00
I am satisfied with **the way treatment information is presented** to me. It is clear and easy to understand.	S4	4.3	12.5	13.4	43.5	24.6	1.7	4.00	3.00 4.00 4.75
I am satisfied that I get enough **opportunity to ask** questions about my **cancer treatment**.	S1	2.2	11.2	7.8	46.6	31.0	1.3	4.00	4.00 4.00 5.00
I am satisfied that I get enough **opportunity to ask** questions about how to manage **side effects**.	S2	5.6	13.4	21.1	35.3	10.7	3.9	4.00	3.00 4.00 4.00
I am satisfied that I get enough **opportunity to ask** questions about the use of **vitamins, herbs,** and **complementary therapies**.	S3	10.3	23.7	16.4	26.3	15.9	7.3	3.00	2.00 3.00 4.00
I am satisfied with the available **information resources** such as the handouts and staff.	S4	4.3	12.1	15.5	45.3	20.3	2.6	4.00	3.00 4.00 4.00
Overall, I am satisfied with **the manner in which the information is provided**. It is friendly, respectful and non-judgemental.	S4	2.6	7.8	6.9	44.0	37.1	1.7	4.00	4.00 4.00 5.00
I am satisfied that I am able to make **informed choices** about my **cancer treatment**.	S1	3.9	7.8	17.7	41.8	24.6	4.3	4.00	3.00 4.00 5.00
I am satisfied that I am able to make **informed choices** about how to manage **side effects**.	S2	3.0	9.9	28.4	34.5	15.9	8.2	4.00	3.00 4.00 4.00
I am satisfied that I am able to make **informed choices** about **vitamins, herbs,** and **complementary therapies**.	S3	6.5	12.9	24.6	30.6	15.5	9.9	4.00	3.00 4.00 4.00

[1] *Frequency of responses are indicated as percentages (n.s.=not specified)*

4.1.4.1 Predictors of satisfaction with information

A stepwise multiple linear regression analysis was used to determine the relative influence of socio-demographic variables on the satisfaction with information. The overall satisfaction score was used as the criterion variable. The stepwise regression procedure showed that only a few variables contributed significantly to the satisfaction scores of the patients. Patients with breast cancer and patients who received treatment through a primary care oncologist seemed to be less satisfied than patients with other types of cancer or a different therapy setting. In addition, patients who were diagnosed less than half a year ago seemed to be more satisfied compared to those diagnosed more than half a year ago. The other variables included in the analysis (including age, sex, educational level) did not predict the satisfaction of the patients. As shown in Tab. 4-5, the predictors included in the regression equations explained a maximum of 22% of the variance (corrected R^2) in patient satisfaction. These were the predictors 'presence of breast cancer' and 'diagnosis less than half a year ago' for the subscale 'information regarding side effects'. For the remaining scales, the significant predictors explained less than 22% of the variance in patient satisfaction. Obviously, satisfaction with treatment information can only partially be explained by the type of disease, the time of diagnosis, and socio-demographic variables. It seems that other factors exist which are important predictors of satisfaction with treatment information.

Tab. 4-5 Results of the stepwise multiple linear regression analysis

R^2	Corr. R^2	F	Independent variable	Constant	Non-standardised regression coefficient	Standardised regression coefficient	p value
Global satisfaction scale							
0.158	0.136	7.323		4.222			
			breast cancer		-0.742	-0.315	0.003
			primary care oncologist		-0.411	-0.231	0.029
Scale 1 : Satisfaction with general treatment information							
0.150	0.130	7.826		3.825			
			breast cancer		-0.544	-0.243	0.019
			diagnosis < ½ year		0.450	0.242	0.019
Scale 2: Information regarding side effects							
0.237	0.220	14.263		0.3686			
			diagnosis < ½ year		0.628	0.321	0.001
			breast cancer		-0.734	-0.310	0.001
Scale 3: Information regarding vitamins, herbal products and complementary therapies							
0.045	0.034	4.221		3.646			
			breast cancer		-0.611	-0.212	0.043
Scale 4: Satisfaction with information sources and way information provided							
0.170	0.145	6.636		4.086			
			breast cancer		-0.542	-0.236	0.217
			inpatient therapy		-1.487	-0.262	0.006
			diagnosis < ½ year		0.394	0.201	0.036

4.1.4.2 Information sources

As shown in Fig. 4-1 patients utilised their oncologist, books, family doctors and TV programmes as their main sources of information. Pharmacists were scarcely perceived as information sources in the patients' view.

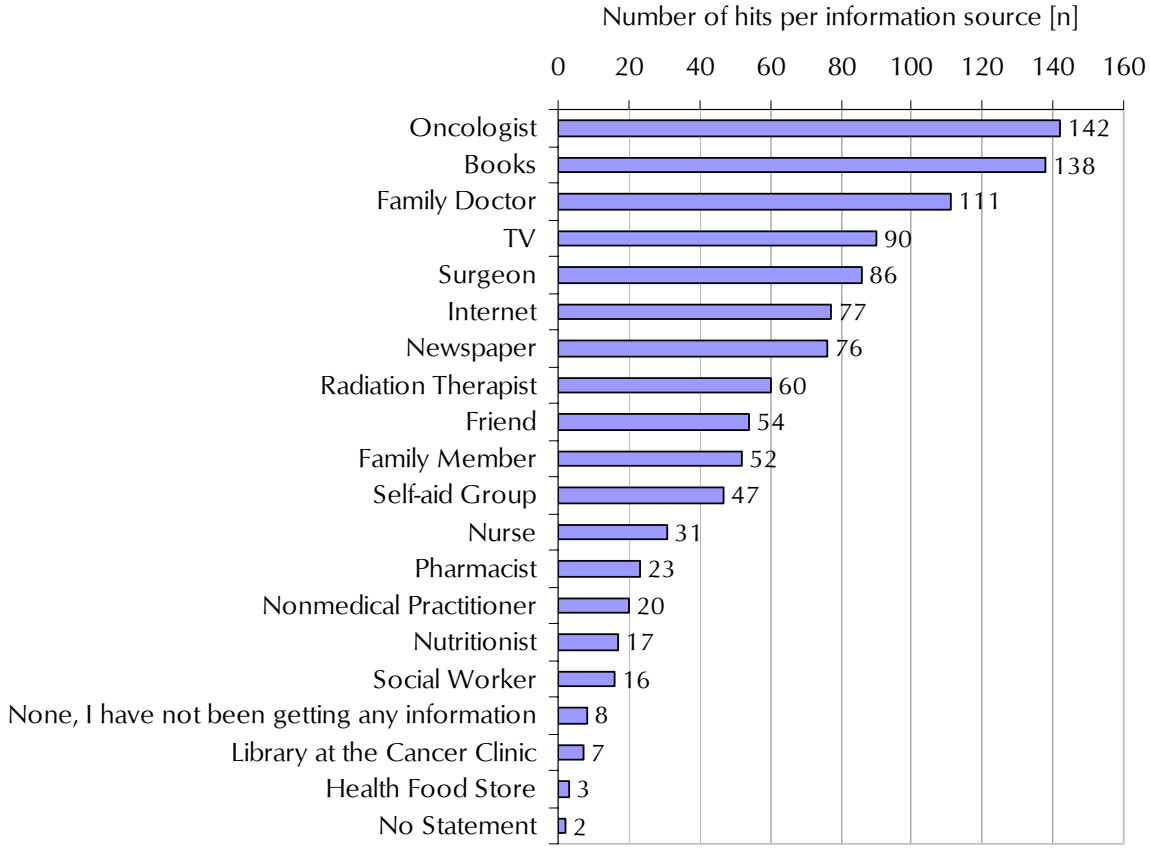


Fig. 4-1 Information sources used by cancer patients

4.1.4.3 Free Comments

Many patients took the opportunity to provide free comments. These were usually in line with the results of the first part of the questionnaire. Patients who provided a low score on the subscale 'satisfaction with information on vitamins, herbs and complementary therapy' desired more information on complementary treatment options. In general, they would favour a more open-minded discussion about complementary therapies with their oncologist. This result supports the validity of the questionnaire. In addition, many patients expressed their need for more psychological

assistance and for automatic provision of information without having to request it.

4.2 Pharmaceutical care of patients with gynaecological malignancies

The patients recruited for the pilot study form a rather homogenous population with no major differences in the distribution regarding the socio-demographic variables. The patient characteristics are documented in Tab. 4-6.

Tab. 4-6 Patient characteristics of the pilot study

Socio-demographic variable		Control group				Intervention group			
Age		$\bar{x}$	SD	min	max	$\bar{x}$	SD	min	max
		51.3	12.1	24	67	52	11.3	27	73
		n		%		n		%	
Sex	Female	21		100		20		100	
Marital status	Married/partner	16		76		16		80	
	Single	2		9.5		2		10	
	Divorced	1		5		1		5	
	Widow	2		9.5		1		5	
Living situation	Living alone	1		5		4		20	
	With family/partner	20		95		16		80	
Education	Elementary school	8		37		6		30	
	Secondary school	1		5		2		10	
	O-levels	5		24		5		25	
	Journeyman	1		5		2		10	
	Master of a trade	1		5		0		0	
	Bachelor	2		9.5		2		10	
	University	2		9.5		3		15	
	No answer	1		5		0		0	

to be continued on the following page

Profession	Student	0	0	1	5
	Housewife	6	28	10	50
	Worker	1	5	1	5
	Employee	9	43	5	25
	Self-employed	2	9.5	0	0
	Public servant	1	5	1	5
	Pensioner	2	9.5	2	10
Diagnosis	Breast cancer	18	86	19	95
	Ovarian cancer	3	14	1	5
Time since diagnosis	< ½ year	16	76	13	65
	½ year - 2 years	5	24	7	35
Therapy setting	Inpatient treatment	3	14	0	0
	Outpatient clinic	15	72	14	70
	Primary care oncologist	3	14	6	30
Self-aid group	yes	1	5	1	5
	no	20	95	19	95

4.2.1 Quality of life

The EORTC QLQ-C30 questionnaire consists of 15 scales. One referring to the global health status and quality of life, five functional scales and nine symptom scales. In the following the results of the individual scales are presented.

Global health status /QoL (QL2)

Compared to the control group the global health status/QoL of patients in the intervention group remained in the median on a higher level as illustrated in Fig. 4-2. Comparing the absolut median score of the global health status and quality of life, the intervention group has initially a far lower level than the control group (CG = 75 vs. IG = 58)

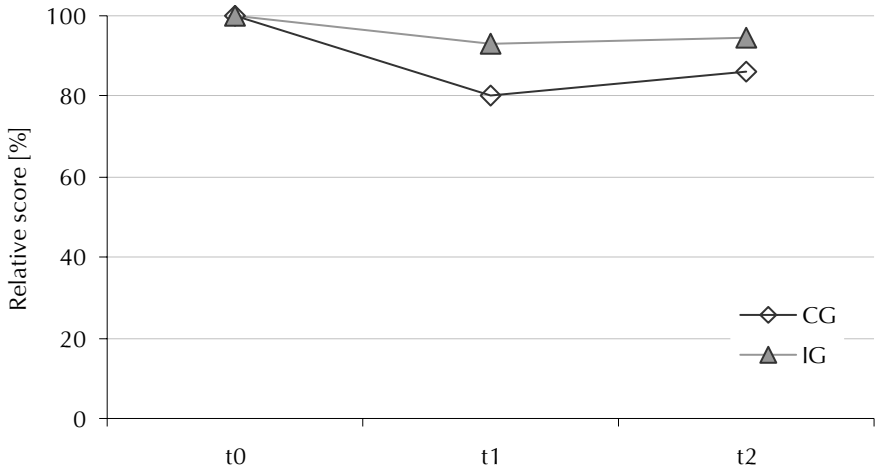


Fig. 4-2 Relative score of global health status/QoL in the median in control (CG) and intervention group (IG) over time (100% at t_0)

The boxplots illustrate that in the median the global health status/QoL decreased less in the intervention than in the control group (Fig. 4-3). This applies to both presented treatment periods. A remarkable variability of the relative changes was observed.

Within the first treatment period the global health status/QoL decreased relatively to baseline in the median by 20% (25% percentile = - 50%, 75% percentile = 0%) in the control group and only by 7% (25% percentile = - 36%, 75% percentile = 42%) in the intervention group. The difference of 13% in the relative change between the two treatment groups in the first treatment period was not statistically significant (p = 0.138, Mann-Whitney U-test).

Looking at the complete treatment period the global health status/QoL decreased in the control group in the median relatively to the baseline by 14% (25% percentile = - 53%, 75% percentile = 0%) and in the intervention group by 6% (25% percentile = - 57%, 75% percentile = 11%). The difference of 8% in relative change between the two groups was not statistically significant (p = 0.563, Mann-Whitney U-test).

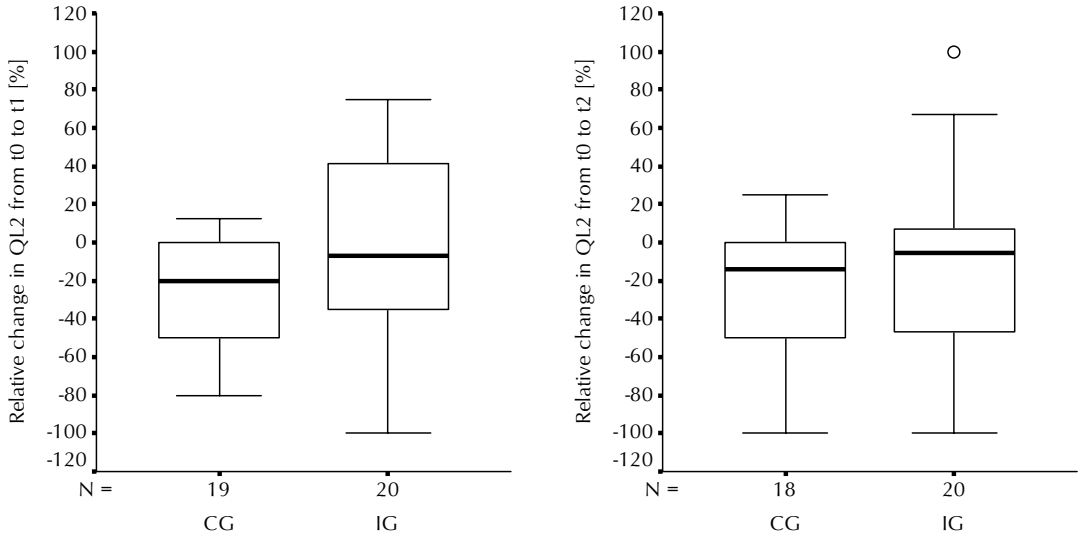


Fig. 4-3 Relative change of the global health status/QoL in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

No difference could be detected between the two treatment groups over time ($p = 0.218$; non-parametric analysis of variance). As $p < 0.5$ H_0 cannot be accepted according to the decision algorithm (see chapter 3.2.2.4). The p-value ranges between $\alpha_0 = 0.50$ and $\alpha_1 = 0.0233$. Therefore the second phase of the study will be carried out with a larger sample size.

Physical functioning (PF2)

The relative scores show that in the median the physical functioning of the patients in the intervention group was stable, whereas it decreased slightly in the control group (see Fig. 4-4).

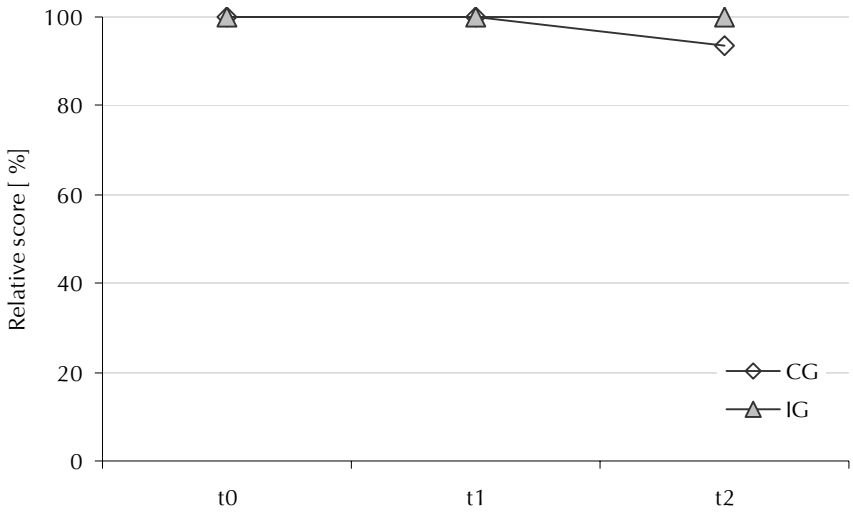


Fig. 4-4 *Relative score of physical functioning in the median in control (CG) and intervention group (IG) over time (100% at t0)*

The boxplots illustrate that within the first treatment period hardly any difference in the relative change was observed between the two groups, whereas for the complete treatment period the physical functioning of the patients tended to improve slightly in the intervention group (Fig. 4-5).

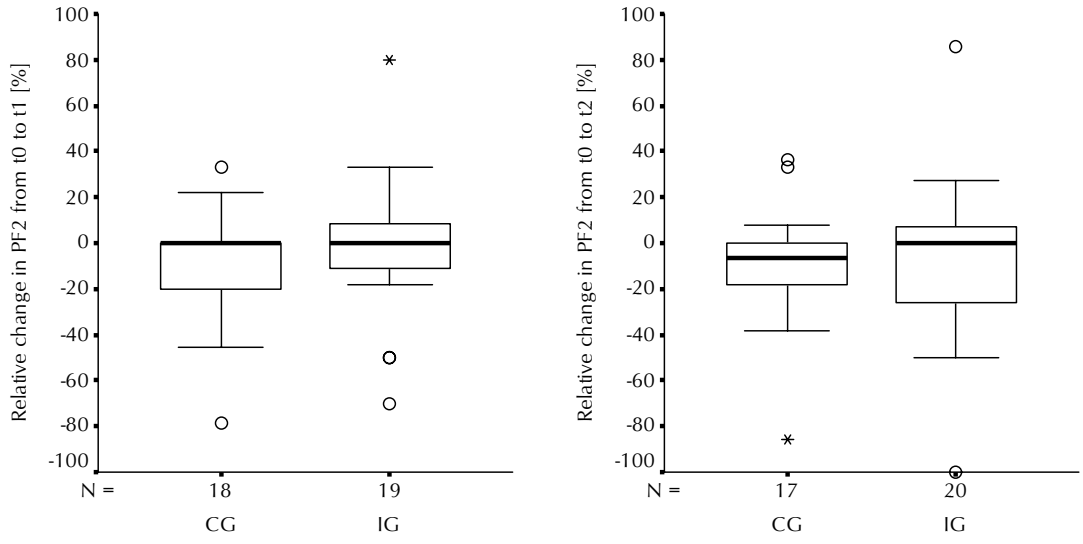


Fig. 4-5 *Relative change of physical functioning in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively*

Within the first treatment period physical functioning did neither change in the control group in the median (25% percentile = - 22%, 50% percentile = 0%, 75% percentile = 2%) nor in the intervention group (25% percentile = - 14%, 50% percentile = 0%, 75% percentile = 10%). The difference between the two groups in the first treatment period was not statistically significant (p = 0.465, Mann-Whitney U-test). Looking at the complete treatment period the physical functioning decreased in the control group in the median relatively to baseline by 7% (25% percentile = - 26%, 75% percentile = 4%). In the median the intervention group remained stable (25% percentile = - 27%, 50% percentile = 0%, 75% percentile = 8%). The differences were not statistically significant (p = 0.748, Mann-Whitney U-test).

Role functioning (RF2)

As with physical functioning Fig. 4-6 shows that there was no change in the median relative scores of role functioning in the intervention group, whereas the relative decreased slightly in the control group.

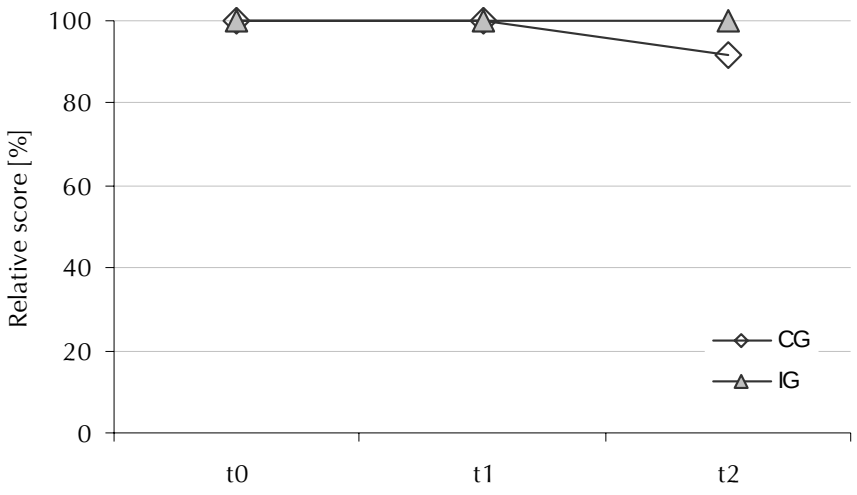


Fig. 4-6 Relative score of role functioning in the median in control (CG) and intervention group (IG) over time (100% at t_0)

The boxplots also show that there was hardly any difference in the change over the treatment period between the two groups (Fig. 4-7). Additionally, the results were highly variable.

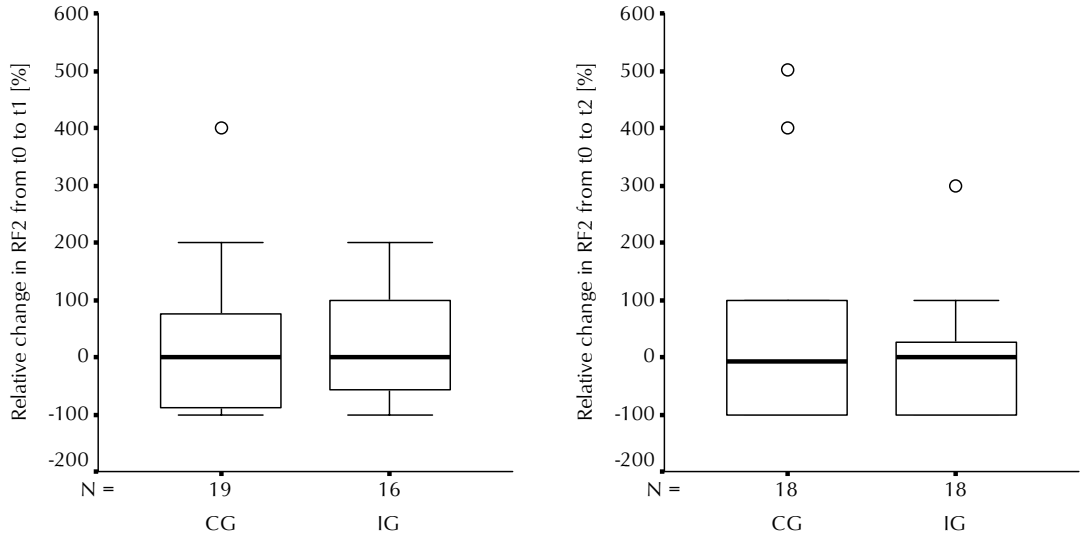


Fig. 4-7 Relative change of role functioning in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

Within the first treatment period the role functioning of patients in the control and intervention group in the median remained stable (CG: 25% percentile = - 100%, 50% percentile = 0%, 75% percentile = 100%; IG: 25% percentile = - 63%, 50% percentile = 0%, 75% percentile = 100%). The difference in the relative change between the two groups in the first treatment period was not statistically significant (p = 0.637, Mann-Whitney U-test). Looking at the complete treatment period the role functioning decreased in the control group in the median relatively to the baseline by 8% (25% percentile = - 100%, 75% percentile = 100%) and remained stable in the intervention group (25% percentile = - 100%, 50% percentile = 0%, 75% percentile = 35%). The differences, however, were not statistically significant (p = 0.760 Mann-Whitney U-test).

Emotional functioning (EF)

Fig. 4-8 illustrates that the emotional functioning of patients in the intervention group was considerably higher in the first treatment period compared to the patients in the control group. This difference was not observed anymore at the end of the treatment period.

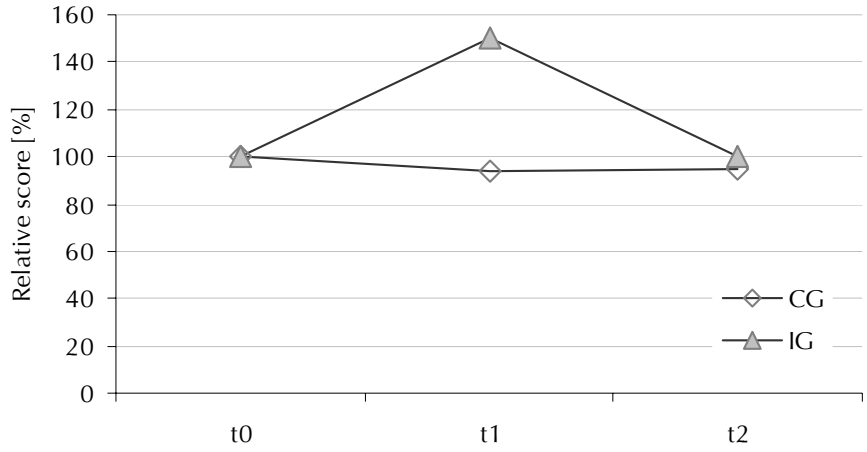


Fig. 4-8 Relative score of emotional functioning in the median in control (CG) and intervention group (IG) over time (100% at t0)

The boxplots show that the change of emotional functioning in the first half of the treatment period improved in the median for the intervention group by 50% (25% percentile = 0%, 75% percentile = 50%) compared to a deterioration in the control group of 6% in the median (25% percentile = - 32%, 75% percentile = 20%) (Fig. 4-9). The improvement of emotional functioning in the intervention group over the first treatment period compared to the control group was statistically significant (p=0.011, Mann-Whitney U-test). Looking at the complete treatment period the emotional functioning decreased in the control group in the median relatively to the baseline by 5% (25% percentile = - 38%, 75% percentile = 32%). In the median the emotional functioning in the intervention group remained stable (25% percentile = - 27%, 50% percentile = 0%, 75% percentile = 35%). The difference was not statistically significant (p = 0.551, Mann-Whitney U-test).

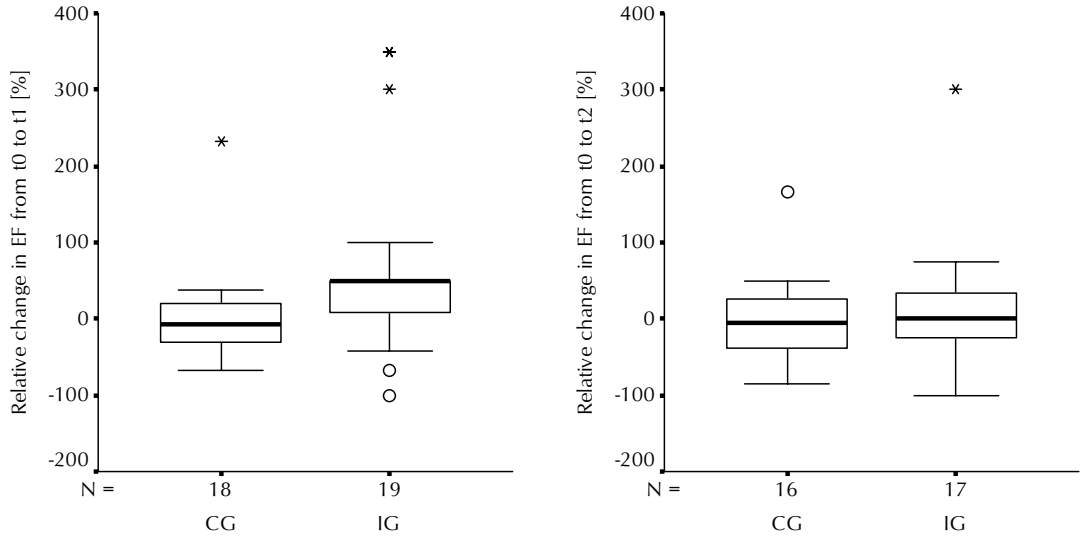


Fig. 4-9 Relative change of emotional functioning in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

Cognitive functioning (CF)

No difference in cognitive functioning was observed when comparing relative scores of the the median of the two groups (Fig. 4-10).

There was hardly any relative change in cognitive functioning in the median over the treatment period comparing the two groups. Particularly the data of the intervention group scattered widely as shown in Fig. 4-11.

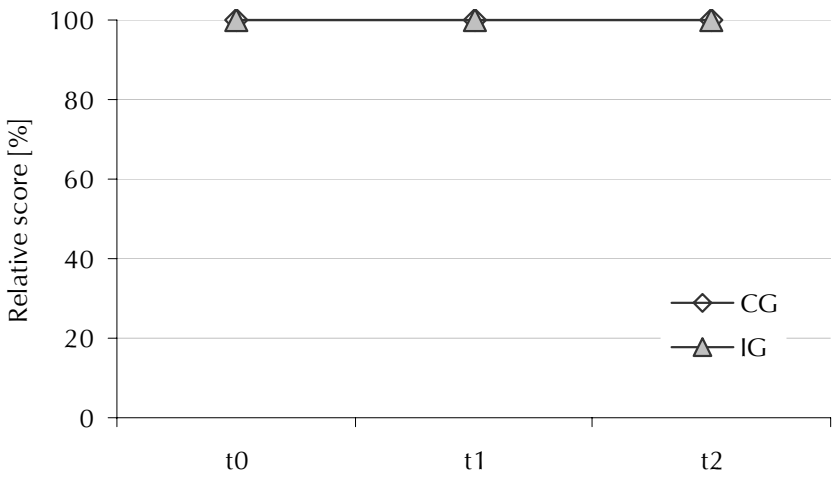


Fig. 4-10 Relative score of cognitive functioning in the median in control (CG) and intervention group (IG) over time (100% at t0)

Within the first treatment period there was no change in cognitive functioning in the control group (25% percentile = 0%, 50% percentile = 0%, 75% percentile = 0%). In the intervention group it also remained stable in the median (25% percentile = - 25%, 50% percentile = 0%, 75% percentile = 25%). The difference between the two groups regarding the relative change in the first treatment period was not statistically significant (p = 0.677, Mann-Whitney U-test). Looking at the complete treatment period the cognitive functioning was unchanged in the control group (25% percentile = - 20%, 50% percentile = 0%, 75% percentile = 0%) as well as in the intervention group (25% percentile = - 17%, 50% percentile = 0%, 75% percentile = 43%). The differences were not statistically significant (p = 0.331, Mann-Whitney U-test).

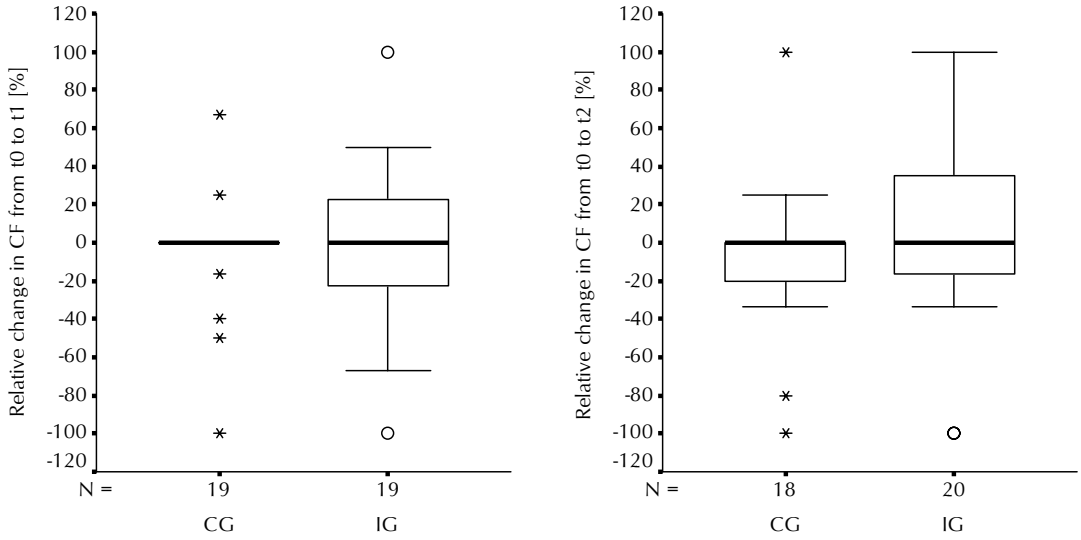


Fig. 4-11 Relative change of cognitive functioning in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

Social functioning (SF)

The patients of the intervention group deteriorated in terms of social functioning towards the end of the treatment whereas the patients of the control group improved in the median towards the end (Fig. 4-12).

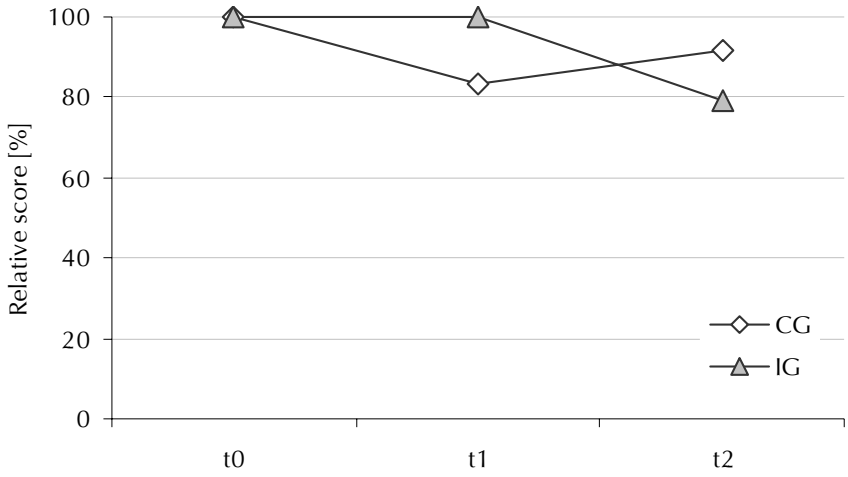


Fig. 4-12 Relative score of social functioning in the median in control (CG) and intervention group (IG) over time (100% at t_0)

The boxplots (Fig. 4-13) show that in the median the intervention group remained stable in the first treatment period (25% percentile = - 19%, 50% percentile = 0%, 75% percentile = 25%) whereas the patients of the control group deteriorated in the median by 17% (25% percentile = - 33%, 75% percentile = 0%). Looking at the whole treatment period the control group deteriorated by 8% in the median (25% percentile = - 40%, 75% percentile = 0%) whereas the patients of the intervention group deteriorated in the median by 21% (25% percentile = - 75%, 75% percentile = 0%). The differences in change were neither for the first treatment period (p = 0.078, Mann-Whitney U-test) nor for the completed treatment period statistically significant (p=0.529, Mann-Whitney U-test).

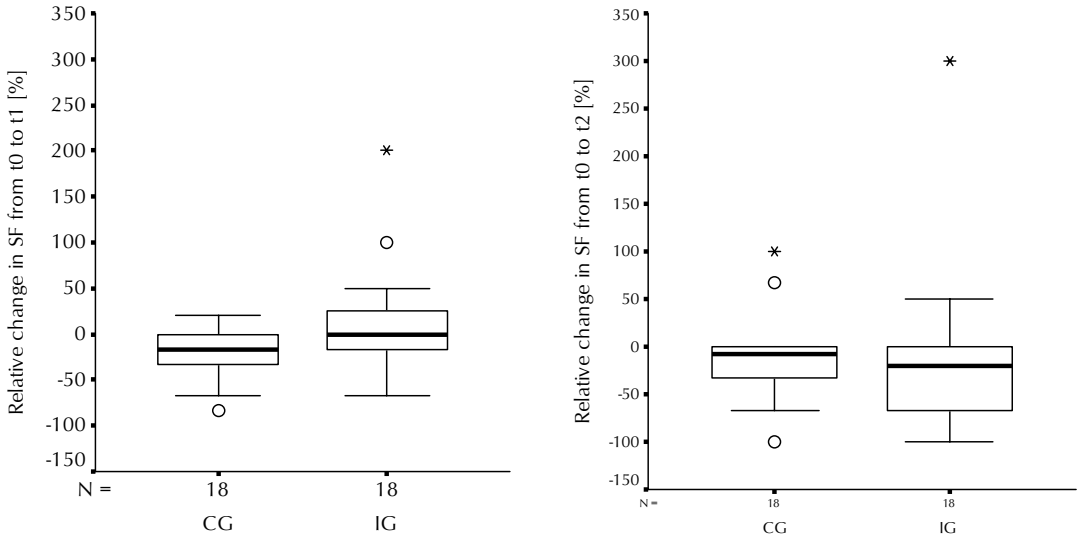


Fig. 4-13 Relative change of social functioning in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

Fatigue (FA)

In both groups patients increasingly experienced fatigue. The scores show that in the median the patients in the intervention group experienced more fatigue than in the control group. In both groups fatigue worsened within the first treatment period and emeded towards the end of the treatment.

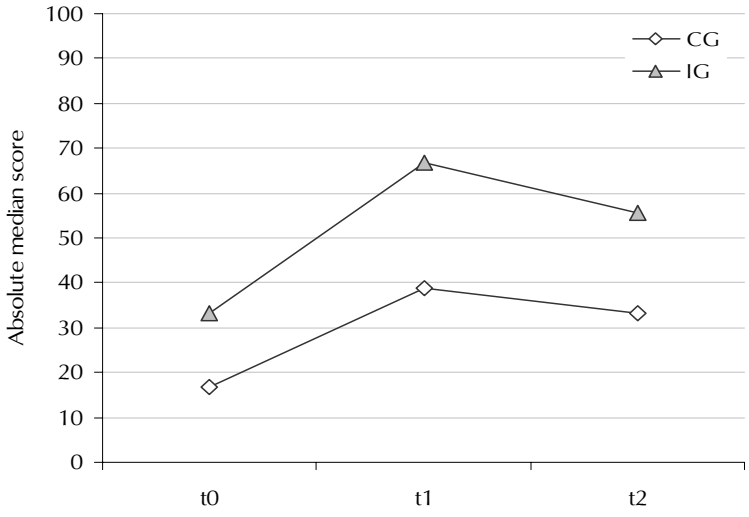


Fig. 4-14 Development of fatigue in the median in control (CG) and intervention group (IG) over time (100% at t0)

The boxplots illustrate the changes in fatigue over time (Fig. 4-15).

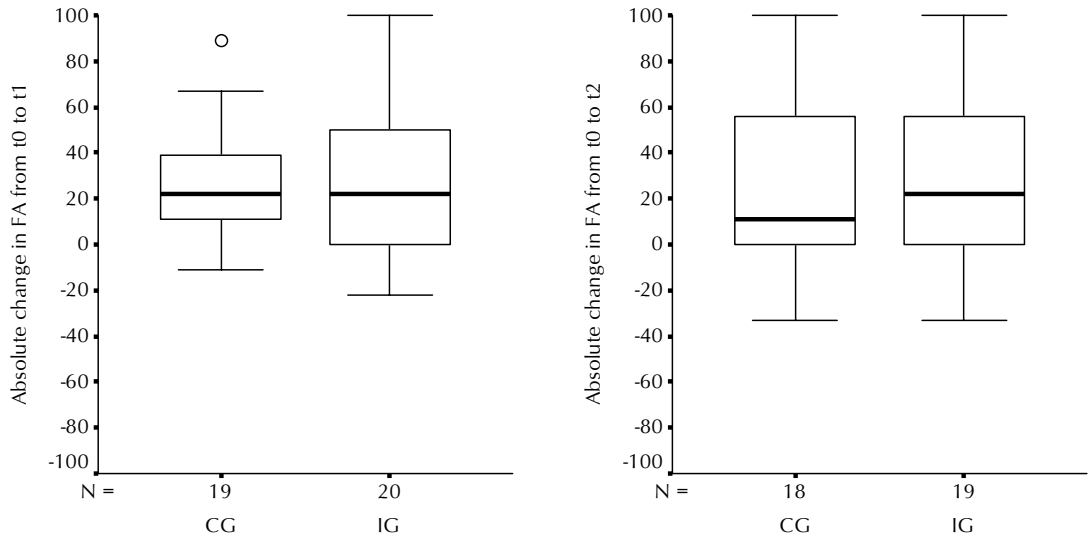


Fig. 4-15 Absolute change of fatigue score in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

Looking at the first treatment period the score of experienced fatigue increased in the median by 22 compared to baseline (25% percentile = 11, 75% percentile = 44) in the control group as well as in the intervention group (25% percentile = 0, 75% percentile = 53). The difference in the change between the two groups in the first treatment period was not statistically significant (p = 0.943, Mann-Whitney U-test). Overlooking the complete treatment period the difference between the two groups was even larger. The score of experienced fatigue in patients of the control group in the median increased compared to the baseline by 11 (25% percentile = - 3, 75% percentile = 56) and in the intervention group by 22 (25% percentile = 0, 75% percentile = 57). The difference between the two groups was not statistically significant (p = 0.711, Mann-Whitney U-test).

Pain (PA)

Fig. 4-16 illustrates that in the median little reduction could be achieved in the experience of pain of patients in the control group, whereas pain of patients in the intervention group was reduced within the first treatment period. Pain increased again in the intervention group towards the end of the treatment, but did in the median not reach the initial value. Patients in the intervention group presented initially with higher

scores of pain than patients in the control group.

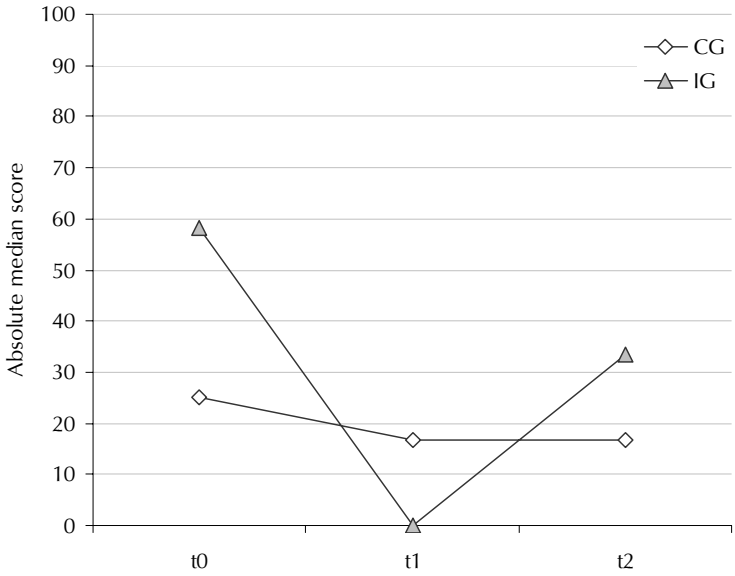


Fig. 4-16 Development of pain in the median in control (CG) and intervention group (IG) over time (100% at t0)

The boxplots show for the intervention group in the median a decrease of 17 score points (25% percentile = - 58, 75% percentile = 0) in the first treatment period as well as over the complete treatment period (25% percentile = - 33, 75% percentile = 0) (Fig. 4-17). The control group does not present considerable changes neither in the first half (25% percentile = - 17, 50% percentile = 0, 75% percentile = 0) nor over the whole treatment period (25% percentile = - 21, 50% percentile = 0, 75% percentile = 17). Data exhibited large variability. In both observed treatment periods the differences between the two groups were not statistically significant ($p = 0.153$ and $p = 0.402$, Mann-Whitney U-test).

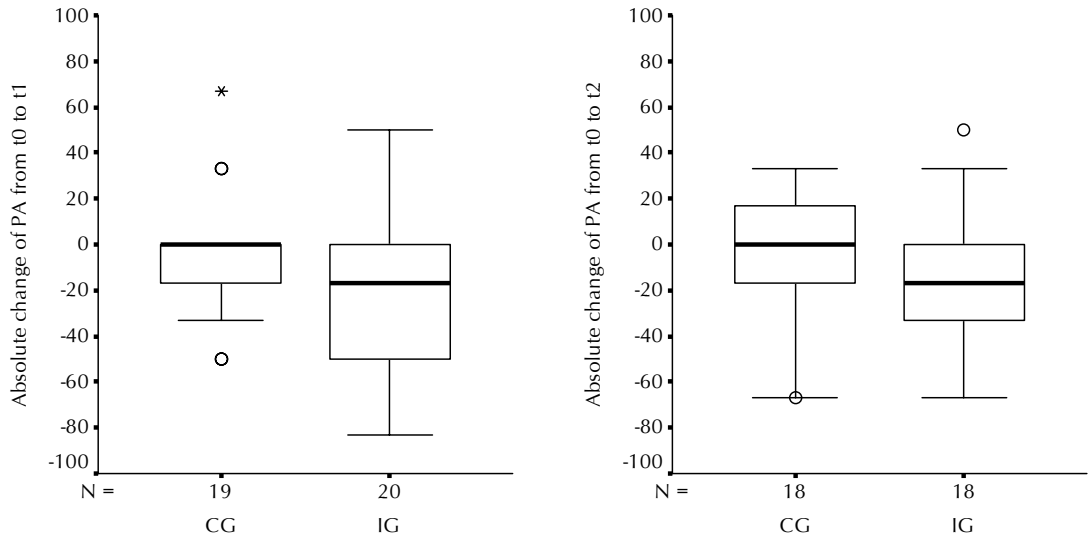


Fig. 4-17 Absolute change of pain scores in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

Constipation (CO)

The median scores in the control group suggest that patients experienced a constant deterioration of constipation over the treatment period. The experienced constipation in the intervention group increased during the first treatment period but ameliorated towards the end (Fig. 4-18).

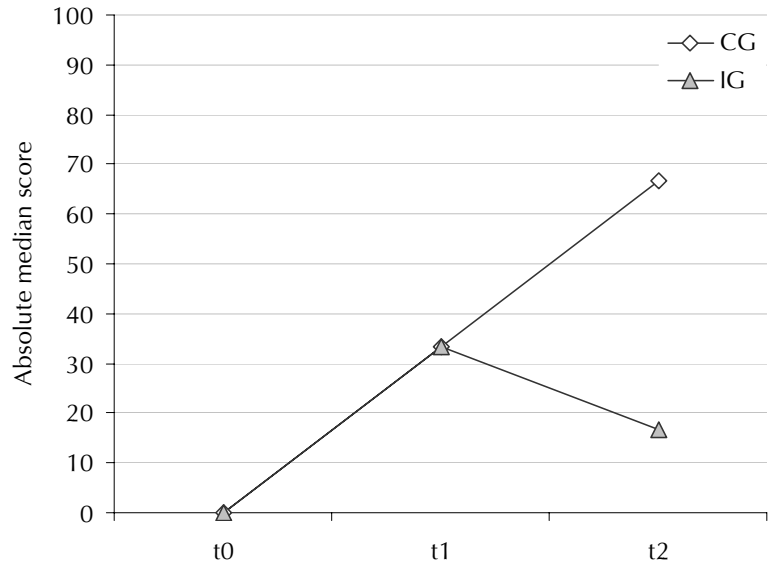


Fig. 4-18 Development of constipation in the median in control (CG) and intervention group (IG) over time (100% at t0)

The boxplots illustrate that the patients of the control group had an increased experience of constipation in the median by 33 score points compared to baseline (25% percentile = 0, 75% percentile = 100); compared to 17 score points in the intervention group (25% percentile = 0, 75% percentile = 33) in the first half of the treatment period (Fig. 4-19).

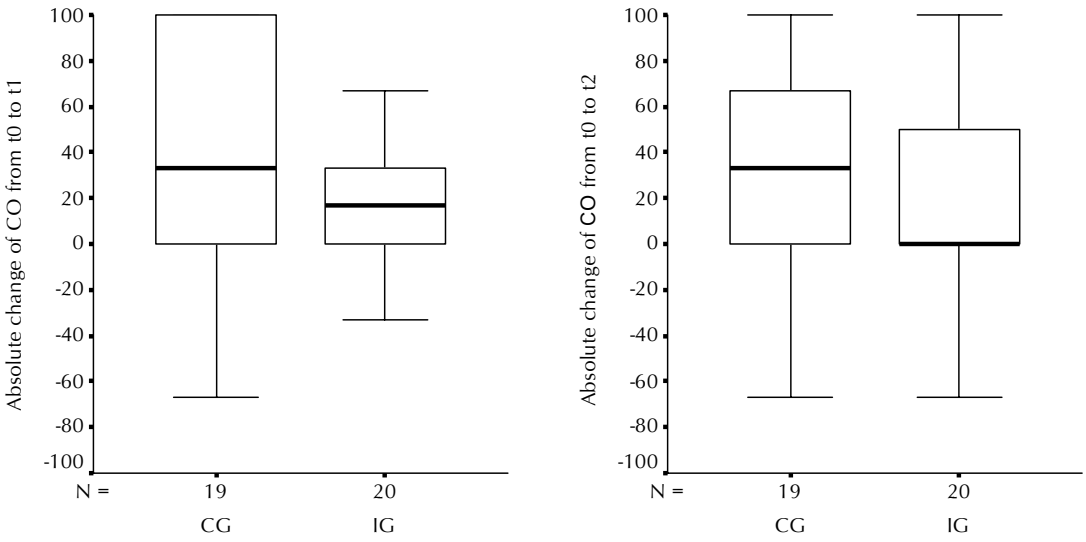


Fig. 4-19 Absolute change of constipation score in control (CG) and intervention group (IG) between baseline and t1 or t2, respectively

This difference even amplified looking at the whole treatment period. Patients of the control group had an increased experience of constipation in the median by 33 score points (25% percentile = 0, 75% percentile = 67%); compared to no change (25% percentile = 0, 50% percentile = 0, 75% percentile = 58) in the intervention group. The data scattered widely and the differences in change between the two groups were not statistically significant for both observed periods ($p = 0.069$ and $p = 0.188$, Mann-Whitney U-test)

The results of the scales dyspnoea (DY), insomnia (SL), appetite loss (AP), diarrhoea (DI) and financial difficulties (FI) are not presented as these symptoms were rare and hence no influence of pharmaceutical care could be expected for this particular group of patients. Nausea and vomiting (NV) was not evaluated in this context as a far more precise instrument was used to elucidate this aspect (see 4.1.1).

4.2.2 Nausea and emesis

The strongest criterion to assess the success of the prevention of nausea and emesis is the complete response (CR) to the antiemetic treatment. Looking at the full treatment period the chi-square trend test showed that in the intervention group an increase in the number of cycles with CR in emesis could be achieved. This increase was not statistically significant (p = 0.155).

Tab. 4-7 Number of cycles with complete antiemetic response (CR)

							total
Number of chemotherapy cycles with CR		0	1	2	3	4	
Control group	Number of patients	5	4	2	2	8	21
	%	23%	19%	9%	9%	38%	100%
Intervention group	Number of patients	1	2	3	7	7	20
	%	5%	10%	15%	35%	35%	100%

Looking at the separate cycles, Fig. 4-20 illustrates that in each cycle the CR rate could be improved. However, none of the cycle-wise improvements in CR was statistically significant ($p_{cycle\ I}$=0.058, $p_{cycle\ II}$=1.000, $p_{cycle\ III}$=0.505, $p_{cycle\ IV}$=0.326, Fisher's exact test).

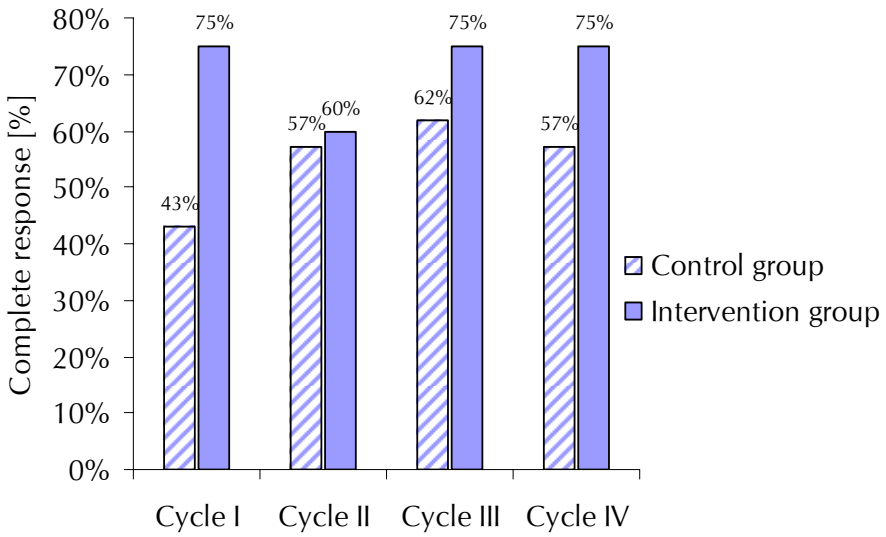


Fig. 4-20 Complete response to the antiemetic drugs (cycle-wise)

Acute and delayed emesis

Acute and delayed emesis are presented descriptively. The sumscores of acute and delayed emesis are presented in Fig. 4-21. The boxplots show that patients of the control group experienced in the median 2 acute emetic episodes (25% percentile = 0, 75% percentile = 10) whereas the patients of the intervention group experienced no acute emetic episode in the median (25% percentile = 0, 75% percentile = 3). The scattering of data was less in the intervention group than in the control group where one patient suffered from 29 emetic episodes. The data regarding the delayed phase indicated no difference between the two groups.

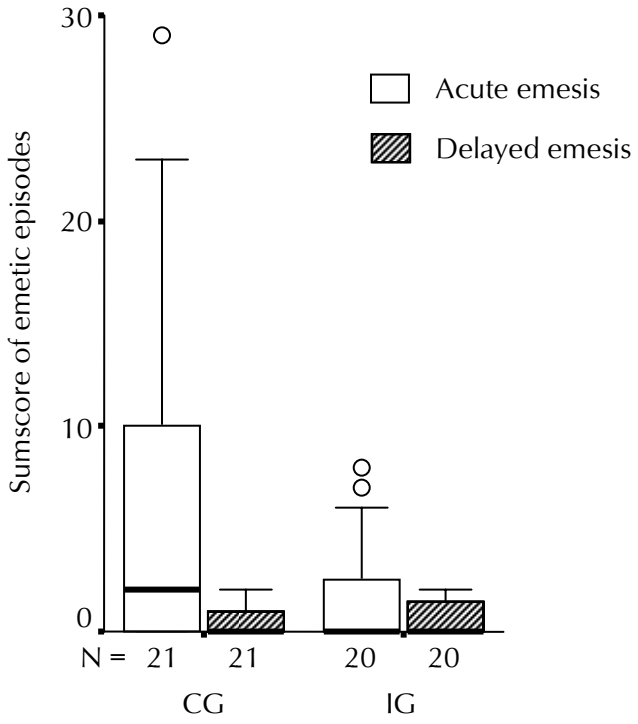


Fig. 4-21 Sumscores of acute and delayed emesis

Acute and delayed nausea

Acute and delayed nausea are presented descriptively. The results indicate no improvement for the patients of the intervention group. It rather seems that the patients of the intervention group suffered more from nausea in both phases.

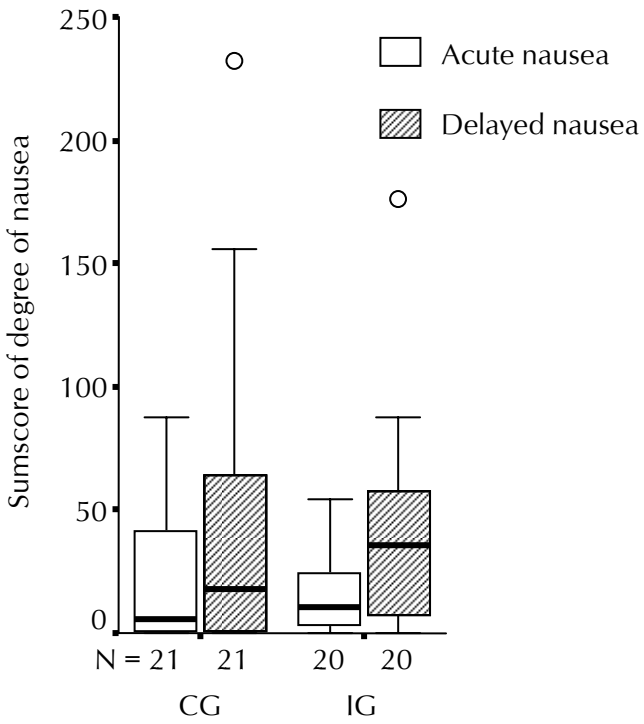


Fig. 4-22 Sumscore of acute and delayed nausea

4.2.3 Patient satisfaction with information on cancer treatment

The basic survey indicated that although the global satisfaction was rather high there still seemed to be possibilities to improve patients' satisfaction with information on cancer treatment. Fig. 4-23 illustrates the effect of the pharmaceutical care intervention on the satisfaction with information. Even the scales which showed good satisfaction in the control group were improved in the intervention group.

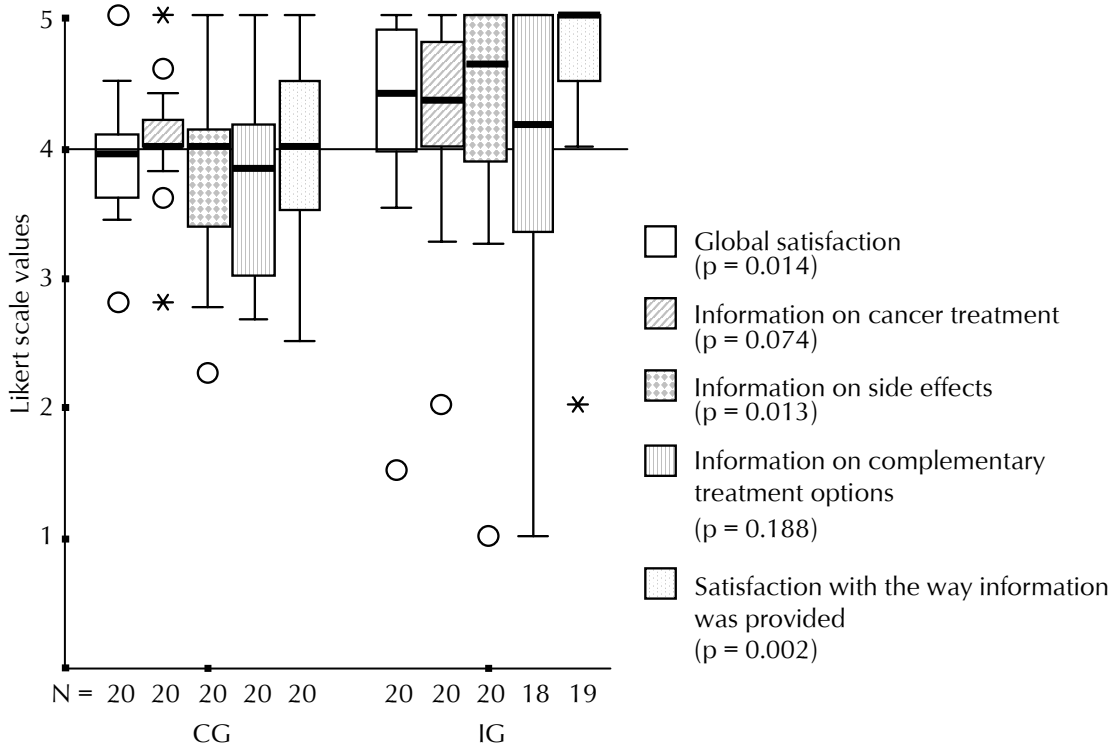


Fig. 4-23 Descriptive evaluation of patient satisfaction with information on cancer treatment

The global satisfaction with information on cancer treatment was in the control group in the median 3.94 (25% percentile = 3.58, 75% percentile = 4.13) compared to a median of 4.41 in the intervention group (25% percentile = 3.98, 75% percentile = 4.91). The difference was statistically significant (p = 0.014, Mann-Whitney U-test).

The relations were similar looking at the different subscales. With the information on the cancer treatment itself the intervention group was in the median more satisfied than the control group (IG: 25% percentile = 4.00, 50% percentile = 4.35, 75% percentile = 4.80; CG: 25% percentile = 4.00, 50% percentile = 4.00, 75% percentile = 4.2). For this subscale the difference was not statistically significant (p = 0.074, Mann-Whitney U-test). Patients of the intervention group also rated their satisfaction with the information on side effects higher as the patients in the control group (IG: 25% percentile = 3.81, 50% percentile = 4.63, 75% percentile = 5.00; CG: 25% percentile = 3.31, 50% percentile = 4.00, 75% percentile = 4.19). For this

subscale the difference was statistically significant as well (p = 0.013, Mann-Whitney U-test). The satisfaction with the information on complementary treatment options did not differ as much between the two groups (IG: 25% percentile = 3.25, 50% percentile = 4.17, 75% percentile = 5.00; CG: 25% percentile = 3.00, 50% percentile = 3.83, 75% percentile = 4.25). For this subscale the difference was not statistically significant (p = 0.188, Mann-Whitney U-test). The results shows that the patients of the intervention group were much more satisfied with the way the information was presented to them compared to the control group (IG: 25% percentile = 4.50, 50% percentile = 5.00, 75% percentile = 5.00; CG: 25% percentile = 3.50, 50% percentile = 4.00, 75% percentile = 4.50). For this subscale the difference was statistically significant (p = 0.002, Mann-Whitney U-test).

The basic survey indicated the limited perception of pharmacists as a source of information by the patients. This observation was confirmed in the pilot study. Only 15% of the patients in the control group described the pharmacist as one of their most important sources of information. In the intervention group 68.4% called pharmacists one of their most important sources of information. This increase was statistically significant (p = 0.001, Mann-Whitney U-test). It is also striking that the intervention group referred to the oncologist as a most important source of information a lot more than the control group. Fig. 4-24 illustrates all information sources which were most valuable to the cancer patients for both the control and intervention group.

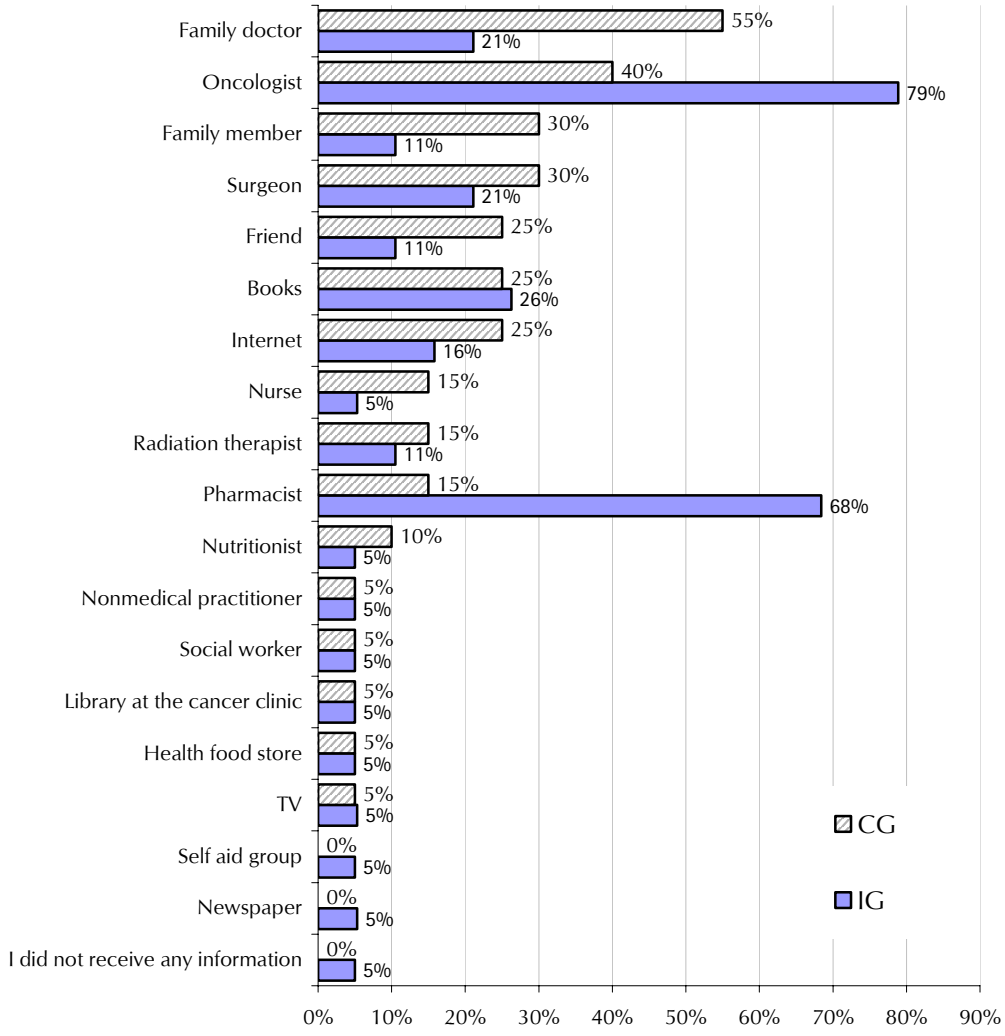


Fig. 4-24 Important sources of information utilised by the patients in control and intervention group (patients could choose more than one source)

4.2.4 Drug-related problems and pharmacist's interventions

During the intervention phase the caring pharmacists coded the detected drug-related problems and the according interventions using the PI-Doc® System (Schaefer, 2002). The detected drug-related problems are listed in the following tables (Tab. 4-8 to Tab. 4-13).

Tab. 4-8 Inappropriate drug choice

	∑
Unsuitable drug for indication	2
Physiological contraindication not considered	3
Contraindication by other disease not considered	1
Unsuitable package size	3

Tab. 4-9 Inappropriate drug use by patient/compliance

	∑
Insufficient knowledge about the application of the drug	1
Handling problems	1
Patient does not use a recommended drug (primary non-compliance)	6
Self-reliant change of the recommended dose by the patient	7
Unsuitable period of use	1
Unsuitable time of application	1

Tab. 4-10 Inappropriate dosage

	∑
Patient does not know his or her dosage	3
Underdosage	5

Tab. 4-11 Drug-drug interaction

	∑
Reference to an interaction by literature	1

Tab. 4-12 Adverse drug reaction

	∑
Patient's fear of adverse drug reactions	2
Symptoms of an adverse drug reaction	78
Medication stopped due to unacceptable adverse drug reaction	1

Tab. 4-13 Other problems

	∑
Patient-related	
Dissatisfaction with current treatment	3
Patient does not receive a drug although an indication exists	2
Patient vomits the taken drugs	1
Technical and/or logistical	
Problems with the sickness funds (refunding)	1

According to the drug-related problems the following interventions were undertaken by the caring pharmacists. Interventions had often a preventive character and were also initiated if no DRPs previously occurred. Interviewing and counselling of the patient, as well as documenting symptoms of adverse drug reactions were performed in every regular meeting with the patient. The interventions with a higher denomination such as 'interviewing and counselling of the patient' and 'documentation of symptoms of an adverse drug reaction', were part of the routine care programme. All interventions are summarised in Tab. 4-14 to Tab. 4-19.

Tab. 4-14 General interventions

	∑
Contacting the physician	21
Refer a patient to a general practitioner	8
Refer a patient to a specialist	1
Recommending other health care professionals	3
Refer a patient to self-help groups	1
Interview and counselling of the patient's relatives	10
Recommendation of a drug	19
Recommendation to change a drug	2
Recommendation of a preventive measure	39
Information regarding complementary treatment options	14
Drug information search	16
Recommendation of a non-medical measure	20

Tab. 4-15 Intervention: inappropriate drug choice

	∑
Selecting or recommending an appropriate drug for the indication	3
Clarification with regard to a physiological contraindication	4
Clarification with regard to a contraindication due to concomitant diseases	2

Tab. 4-16 Intervention: inappropriate drug use by the patient/compliance

	∑
Advice for correct application	2
Searching for the reasons for primary non-compliance and counselling	7
Searching for the reasons to change a recommended dosage by the patient and counselling	7
Advice with regard to optimal duration of use	22
Advice with regard to optimal time of application	20

Tab. 4-17 Intervention: inappropriate dosage

	∑
Advice to the patient with regard to dosing	24
Clarification with regard to an underdosage	5

Tab. 4-18 Intervention: adverse drug reaction (ADR)

	∑
Counselling patients fearing adverse drug reactions	2
Documentation of symptoms of an adverse drug reaction	74
Clarification with the physician	4
Suggesting a change in medication to the physician	1

Tab. 4-19 Intervention: other problmes

	∑
Patient-related	
Reducing fears and prejudices of a drug therapy	5
Searching for reasons for dissatisfaction with current treatment	2
Advice to the patient with regard to a health-supporting life style	2
Information about nutrition	23
Information about physical training	23
Advice with regard to treatment opportunities of ailments/recommendation to see a physician	1
Recommendation regarding adaequate subsequent dosage	1
Technical and logistical problems	
Clarification with the sickness fund	1
Ensuring a seamless therapy continuation	4

4.2.5 Time spent on appointments and rework

Fig. 4-26 and 4-27 illustrate the scattering of the time spent on the care appointments and on the rework.

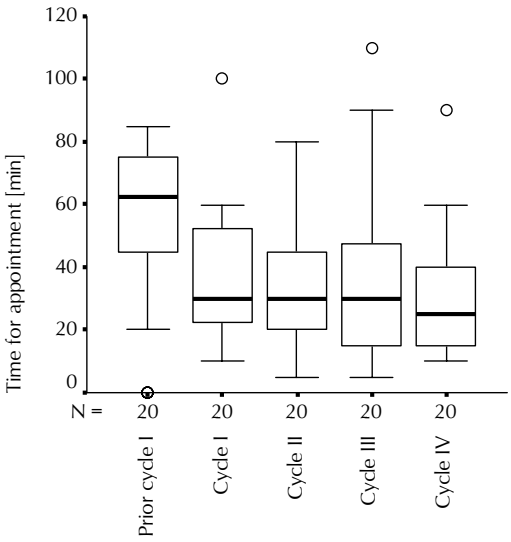


Fig. 4-25 Time for appointments

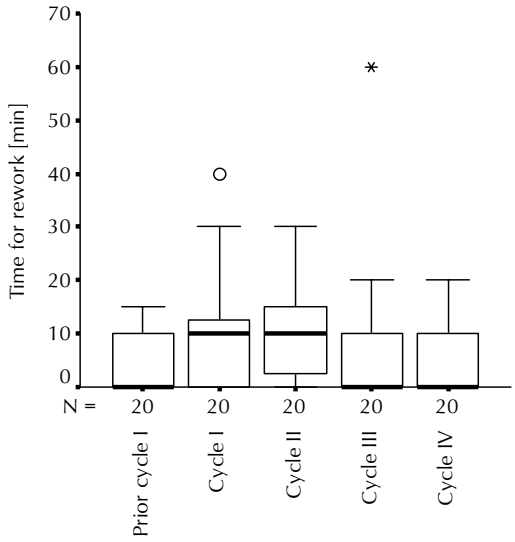


Fig. 4-26 Time for rework

The time necessary for the care appointments levelled in the median off at about an hour for the first appointment and at half an hour for the following appointments (see Tab. 4-20). For the rework after the appointments in the median between 0 to 10 minutes after each cycle were needed whereas there was seldom the need for rework after the first appointment (see Tab. 4-21).

Tab. 4-20 Time for appointments [min]

	Mean	Median	Min	Max
Prior Cycle I	55	63	0	85
Cycle I	38	30	10	100
Cycle II	35	30	5	80
Cycle III	36	30	5	110
Cycle IV	30	25	10	90

Tab. 4-21 Time for rework [min]

	Mean	Median	Min	Max
Prior Cycle I	5	0	0	15
Cycle I	10	10	0	40
Cycle II	10	10	0	30
Cycle III	8	0	0	60
Cycle IV	5	0	0	20

4.2.6 Sample size estimation for the main study

The sample size for the main study was calculated adaptive based on the results of the present pilot study. Other than in the present study a different endpoint has been chosen. This was declared in an amendment for the study protocol. For the future primary endpoint ‘complete control of emesis’, with a sample size of n = 50 per group and a prevalence of 40% to 60%, given an overall α of 5% (for both phases), an improvement of Δ=15% in the intervention group can be detected with and a power (1-β) of more than 99%.

4.3 Monitoring of carboplatin

During the pilot study four patients donated blood for the pharmacokinetic analysis. These patients presented with characteristics summarised in Tab. 4-22.

Tab. 4-22 Patient characteristics

Patient code	KOM01	KOD01	KOK11	KOS01
Age [years]	48	41	69	61
sex	female	female	female	female
Type of cancer	EOC	EOC	EOC	EOC
TNM	pT3c pN0, pMx, G3	pT1c, N0, M0, G2	pT3b, Nx, M1, G2-3	pT3c, G3
FIGO stage	IIIc	Ic	IIIb	IIIc
Chemotherapy regimen	Paclitaxel 175 mg/m² Carboplatin AUC5	Paclitaxel 175 mg/m² Carboplatin AUC5	Paclitaxel 175 mg/m² Carboplatin AUC5	Paclitaxel 175 mg/m² Carboplatin AUC5
Pre-treatment	none	none	none	none
Height [cm]	166	170	159	154
Weight [kg]	60	61	68	53
BSA [m²]	1.67	1.71	1.7	1.5

In all observed cycles for these four patients the achieved AUCs [according to Sørensen et al.] did not reach the level of the intended target AUC as shown in Fig. 4-27. The AUCs were determined based on the carboplatin concentration in the ultrafiltrate in order. The mean AUC had a variance of 23% (7.2-38.4%, SD 7.66%). In the median the AUC differed 21.7% with a 25% percentile of 20.4% and a 75% percentile of 25.3%. The measured platinum concentrations in plasma and ultrafiltrate and the resulting AUCs are documented in appendix M.

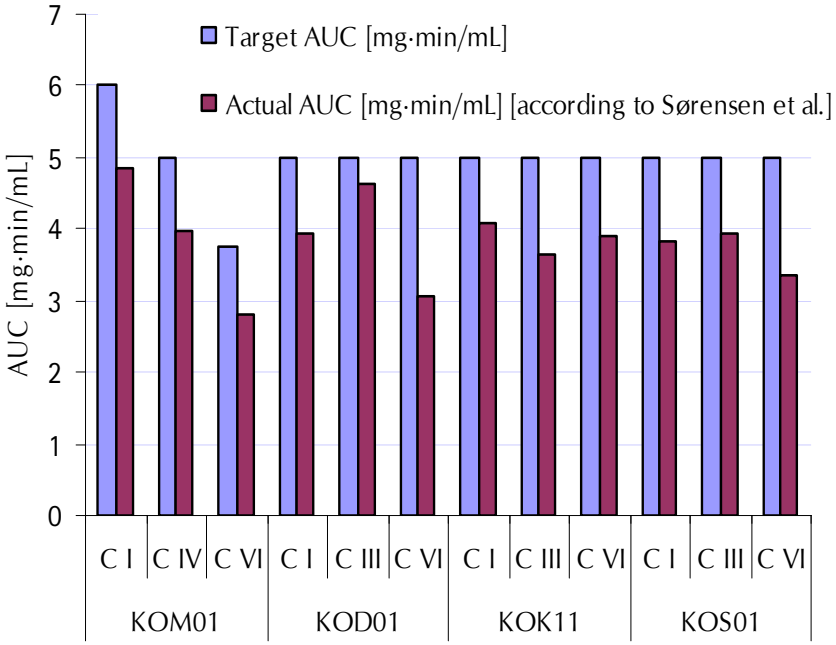


Fig. 4-27 Actual AUC (ultrafilterable plasma) vs. target AUC [mg·min/mL]

To get an idea of what doses would have been calculated with the other introduced methods these calculations were performed based on the available serum creatinine levels and the patient characteristics of sex, weight and age. Using the rule of proportion the according AUCs which would have resulted from these doses were also calculated. The results are listed in Tab. 4-23. The doses necessary to achieve the target AUC would need to be in the mean 31.1% (7.7-62.3%, SD 13.65%) higher than the actual dose given. All available serum creatinine levels are documented in Tab. M-2 of the appendix M. For some cycles there were no actual serum creatinine levels available. In these cases the doses and accordingly the AUCs could not be determined. In all cases the calculated dose was higher than the actual dose given, however, even with these higher doses the target AUC would still probably not have been achieved.

Tab. 4-23 Actually received carboplatin doses and measured AUCs and according calculated values

	KOM01			KOD01			KOK11			KOS01		
	C I	C IV	C VI	C I	C III	C VI	C I	C III	C VI	C I	C III	C VI
Target AUC [mg·min/mL]	6	5	75% of 5	5	5	5	5	5	5	5	5	5
Absolute dose [mg] received	800	640	460	750	750	750	390	420	410	430	430	430
Actual AUC [mg·min/mL] (according to Sørensen et al.)	4.85	3.96	2.82	3.93	4.64	3.08	4.09	3.66	3.90	3.83	3.94	3.37
Deviation from target AUC [%]	-19.2	-20.8	-24.8	-21.4	-7.2	-38.4	-18.2	-26.8	-22	-23.4	-21.2	-32.6
Dose [mg] necessary to achieve target AUC	991	809	612	955	808	1217	477	573	525	561	546	639
Deviation from the actually received dose [%]	+23.9	+26.4	+33.0	+27.3	+7.7	+62.3	+22.3	+36.4	+28.0	+30.5	+27.0	+48.6
Absolute dose [mg] calculated according to the modified Calvert equation (Cockcroft-Gault)	802	n. d.	501	762	729	n. d.	410	460	342	430	n. d.	n. d.
Possibly achieved AUC [mg·min/mL] using the modified Calvert equation (Cockcroft-Gault)	4.86	n. d.	3.07	3.99	4.51	n. d.	4.30	4.01	3.26	3.83	n. d.	n. d.
Absolute dose [mg] according to the modified Calvert equation (Jelliffe)	805	n. d.	503	769	736	n. d.	386	431	321	438	n. d.	n. d.
Possibly achieved AUC [mg·min/mL] using the modified Calvert equation (Jelliffe)	4.88	n. d.	3.09	4.02	4.56	n. d.	4.05	3.76	3.05	3.91	n. d.	n. d.
Absolute dose [mg] according to the Chatelut equation	841	701	525	790	790	790	439	439	439	435	435	435
Possibly achieved AUC [mg·min/mL] using the Chatelut equation	5.09	4.33	3.22	4.13	4.89	3.24	4.61	3.83	4.18	3.87	3.98	3.40

n.d. = not determined

In order to look for possible relationships between platinum exposure and toxic effects, myelotoxicity, in particular the platelet and white bood cell (WBC) counts were analysed in detail. As summarised in Tab. 4-24 the available laboratory data indicate that none of the participating patients suffered from thrombocytopenia. Neutropenia experienced can be considered as mild in most cases. In one case a grade 3 neutropenia was observed. However, AUC was not particularly high in this patient.

For patient KOM01 too few data were available to list in the table. This patient was not included in the evaluation of the experienced myelotoxicity. The common toxicity criteria according to the NCI v.2.0 for platelets and leukocytes are listed in Tab. M-3 of appendix M.

Tab. 4-24 Myelotoxicity observed in ovarian cancer patients

	KOD01			KOK11			KOS01		
Platelet count [$\cdot 10^9$/L]		NCI CTC Grade	days post CT		NCI CTC Grade	days post CT		NCI CTC Grade	days post CT
Before therapy	207	0		343	0		461	0	
CI	278	0	20	285	0	22	292	0	19
CIII	164	0	12	292	0	11	215	0	11
CVI	n.d.	n.d.	n.d.	270	0	13	n.d.	n.d.	n.d.
WBC count [$\cdot 10^9$/L]									
Before therapy	4.7	0		8.3	0		5.3	0	
CI	4.4	0	20	9.1	0	22	2.7	2	19
CIII	3.0	n.d.	12	3.2	1	11	2.7	2	11
CVI	n.d.	n.d.	n.d.	1.6	3	13	n.d.	n.d.	n.d.

n.d. = not determined

Normal ranges: Platelets 150–400$\cdot 10^9$/L; WBC 4-9$\cdot 10^9$/L

For platelets the nadir usually occurrs between days 14 and 22 after the chemotherapy, whereas the WBC nadir occurs between days 14 and 28.

[5] Discussion

5 Discussion

5.1 Patient satisfaction with information on cancer treatment

The basic survey primarily aimed at assessing the suitability of a German adaptation of the Canadian PS-CaTE questionnaire. Results on test homogeneity and test reliability indicated good psychometric properties of the German version. However, data concerning the validity of the instrument are still scarce and should be complemented by future research. Nevertheless, there are several reasons for accepting the current version for the time being. First, the German questionnaire appears to be psychologically equivalent to the original Canadian version which has already been used successfully for assessing patient satisfaction with treatment information. Second, the item content is obviously face-valid. Third, the spontaneous written comments of the patients were generally in agreement with the quantitative questionnaire results. It thus seems reasonable to use the adapted questionnaire for assessing patient satisfaction in Germany.

Strong validity criteria, such as criterion-related validity or construct validity, cannot be assessed at this time. One possible way of establishing criterion-related validity would be to compare results from this instrument with results of other patient satisfaction measures. Since the instruments intend to assess the same concept, patient scores should correlate highly. However, currently no other patient satisfaction with information measurement instrument exists in Germany that could serve as a reference. Moreover, construct validity is not fully applicable to our instrument as the concept behind the construct of patient satisfaction is not yet completely understood. Although Annunziata et al. found a positive correlation between satisfaction and quality of life, it does not seem to be advisable to use this result for validity assessments until further studies verify it (Annunziata et al., 1998).

One possible objection against the 5-point rating scales used in this instrument is that they might provoke a tendency for giving judgments corresponding to the mean rating category (Cassileth et al., 1980). However, as is well-known from the test construction literature, this tendency is typically a problem for bipolar rating scales

only that require decisions between two qualitatively different attitudes, opinions, or values (love-hate, fast-slow etc.). It is less of a problem in unipolar rating scales that require decisions between different degrees of a single attribute. Consistent with this view, our results show that patients did not tend to favour the third rating category.

Future research should also address the aspects of socially-desirable answering, correlation of patient satisfaction with information to measured quality of life and correlation between patient satisfaction with information on cancer treatment and the actual knowledge of the patient.

As previous studies illustrate, important information needs of patients include information about diagnosis, treatment, cure rate, side effects and complementary treatments (Gustafson et al., 1993; Luker et al., 1996; Pimentel et al., 1999; Hope et al., 2000; Bonnet et al., 2000). In general, needs regarding treatment information were obviously met in the present study population as the rather high satisfaction scores show. Since studies revealed that patients want as much information as possible (Dodd, 1983), the patients' role has become a more active one. A trend towards competent, well informed patients can generally be observed and patients are becoming increasingly involved in treatment decisions. The patients' responses in this study support this observation. Patients demand transparent information about all aspects of their treatment. They complained that a lot of information was supplied to them only upon request, which they experienced as tiring and unsatisfactory.

Our results reveal that the provision of information on side effects and complementary treatment options could be improved. It would be interesting to assess whether patients *de facto* receive less information about such aspects, or whether they simply perceive the information in a different way. Ried et al. found that patients' satisfaction can also be influenced by personal attention (Ried et al., 1999a). Perhaps information about side effects and complementary treatment options was not provided with the same emphasis as information regarding cancer treatment. Health care providers should increasingly offer this kind of information to cancer patients.

Whereas this part of the study showed that age, sex, educational status and living situation seemed to have no impact on patient satisfaction with information, other investigations have found that at a younger age patients seem to have higher information needs (Cassileth et al., 1980; Gustafson et al., 1993; Bonnet et al., 2000).

Breast cancer patients seem to be less satisfied than patients with other types of cancer. This result should be interpreted with caution. It could be biased due to the fact that most of the patients in our study were breast cancer patients and that other types of cancer were underrepresented. Breast cancer and especially mastectomies have a major impact on a woman's self-perception. Thus, compared to other cancer patients, breast cancer patients might generally have a lower satisfaction level, which, as a by-product, may induce lower satisfaction with information scores. In Germany, an increasingly stronger lobby is emerging especially for breast cancer patients. Modern mass media provide information about this disease, the diagnosis and treatment options and the patients' rights. In this way, lower satisfaction scores of breast cancer patients could be caused by the fact that media depictions lead to high expectations. If these expectations are not fully met, dissatisfaction could be the consequence.

Cancer patients with recent diagnosis (< six months) seem to be more satisfied than patients who were diagnosed longer ago. These results are consistent with the findings of Jänel et al. (2000). After about six months patients seem to realise that important information has been omitted, a fact that leads to dissatisfaction.

Our findings show that among the information sources used by patients, pharmacists still seem to play a minor role. This low score is of particular concern considering that patients knowing the background of the researchers undertaking a study tend to answer in a socially desirable manner. This could have resulted in higher scores since the professional background of the research group was not disclosed. It might well be, however, that patients were not able to draw the connection between the pharmaceutical institute mentioned in the heading of the enclosed letter and the questions regarding community pharmacists in the questionnaire since the two have different wordings in German. A reason for the low awareness of pharmacists as information source might be that in the patients' perception, pharmacists still focus primarily on the distribution of drugs. Unless additional information about the treatment, potential side effects and complementary treatment options is offered actively, patients cannot recognise the pharmacist as a valuable source of information. In particular, pharmaceutical care provides an opportunity to actively offer individualised information to patients. Häggmark et al. (2001) showed that

individualised information programmes significantly affect the satisfaction of cancer patient with information. Most importantly, all health care providers should cooperate, in order to offer such individualised information to their patients.

5.2 Pharmaceutical care of patients with gynaecological malignancies

Pharmaceutical care in oncology aims at reducing treatment-associated toxicity and at improving patients' quality of life. The aim of this project is to develop a specific pharmaceutical care model for breast and ovarian cancer patients including patient counselling on the management of treatment-associated side effects, optimisation of supportive medication and the implementation of a therapeutic algorithm for antiemetic prophylaxis. Already in the beginning of the 1990s outcome orientation and quality assurance in pharmaceutical care was claimed by several authors (Penna, 1990, Angaran, 1991, Donabedian, 1992). Especially in research it is important to support the proposed hypotheses with meaningful outcome parameters. Nevertheless, the main objective of this pilot study was to assess the feasibility of pharmaceutical care for cancer patients in the outpatient setting and to estimate its benefit for the patients as the number of patients whose data could be evaluated is by far too small to draw secluding conclusions.

5.2.1 Quality of life

Senn and Glaus described the paradigm shift from cure to care in oncology which reflects the change of attitudes and treatment goals (2002). Other outcomes than the standard endpoints survival and tumour response gain importance. Health-related quality of life is an aspect of the personal well-being of individuals. It can be described as a complex of functional and symptomatic experiences of patients. By definition health-related quality of life includes physical, psychological and social as well as functional dimensions (Ravens-Sieberer, 2002). The EORTC QLQ-C30 questionnaire is a disease-specific instrument which reflects all these dimensions. Rusthoven emphasised the importance of a differenciated interpretation of health-related quality of life data (1997). He called attention to the fact that the different dimension (either single items or scales) could be considered in its own rights. Thus, the investigator

must decide which of these dimensions are primary to the particular study. The present findings were evaluated accordingly.

Regarding the quality of life two hypotheses were set up prior to the present study. For one it was assumed that the global quality of life of patients can be improved by the enhancement of communication regarding drug treatment by pharmaceutical care. This hypothesis could not be confirmed with the present results. However, there were tendencies for a better preservation of quality of life during chemotherapy compared to the control group.

The other hypothesis was that the minimisation of treatment-associated toxicity improves the specific quality of life in terms of the symptomatology. This could actually be achieved although not statistically significant for the symptoms pain and constipation. These findings can be explained as follows. Regarding pain control, patients in the intervention group made use of the opportunity to ask about the compatibility of analgesics with the antineoplastic therapy. Pharmacists, after reconsulting with the physicians, suggested appropriate medication for the respective situation.

Constipation is a common adverse drug reaction associated with the use of $5HT_3$ receptor antagonists which have been used far more extensively in the control than in the intervention group. In addition to the controlled use of the $5HT_3$ receptor antagonists, mild laxatives were recommended as soon as patients suffered from constipation. Patients tended to not mention problems with their digestion of their own accord as they felt uncomfortable. It was important to ask them directly in order to get the information and to start the necessary measures.

As an alternative to the $5HT_3$ receptor antagonists high doses of metoclopramide were used to prevent delayed nausea and emesis in the intervention group. This caused most probably the obvious deterioration of the experienced fatigue in the intervention group compared to the control group (see chapter 1.2.7.2). The increased fatigue symptomatology in the intervention group is particularly concerning as this symptom complex was ranked 3^{rd} of the worst adverse events from patients perspective (Carelle et al., 2002). With a change of medication according to the international guidelines in favour of dexamethasone as main component of the antiemetic prophylaxis in the subsequent study and additional information for patients'

everyday life such as physical exercise and nutrition this symptomatology should be positively influenced.

The present data showed a large variability. This might be due to potential bottom and ceiling effects. No definite prediction can be made on which of these effects were predominant, though. These effects are often observed in QoL measurements when patients tend to choose the extreme values. Additionally, patients' differing coping strategies and personalities do affect the answering. This bias is difficult to avoid and it is even reinforced by additional incidents (positive as well as negative) which the patients experience. These experiences influence the results of quality of life measurements in particular as health-related quality of life is a multidimensional construct and thus tangent to a variety of areas of patients' lives. It is conceivable that for example the emotional functioning is negatively affected by the recent death of a family member, or in a positive way by the marriage of son or daughter. Examples like this exist for every dimension. This has also been shown by Determann et al. (2004). They observed in a prospective, randomised, controlled trial 106 patients with colorectal cancer which received in the intervention group additional psychooncological support. The assessment of the psychometric properties of the EORTC QLQ-C30 showed illustration of situational influences and therefore an insufficient illustration of effects of specific interventions. It would be worth considering a general QoL instrument which would possibly show less variability but probably also a reduced sensitivity. A comparison between a general and a health related QoL instrument would be useful to address this question in future studies.

Another aspect worth discussing is the sensitivity of the selected instrument. The sensitivity is the ability of measurement instruments to detect differences between patients or groups of patients (Fayers and Machin, 2000). Just as with the variability it is difficult to judge the sensitivity of the EORTC QLQ-C30 questionnaire in this context. With a larger number of patients the variability would even out and maybe a better predication of the sensitivity would be possible.

Another methodological question is the optimal time of administration of the questionnaire. Pater et al. addressed this question in a large antiemetic trial (1998). They found that the time of administration as well as the time frames have an impact on the results. The administration close to the maximum of experienced toxicity would

enhance the detection of the impact of the symptoms on QoL. As different types of toxicity occur at different times post-chemotherapy there is a risk of overlooking these in case they are not in the chosen time frame. The time of administration in this study was a week after chemotherapy looking at a timeframe of 7 days. This covers acute toxicity such as nausea and emesis but not delayed toxicity such as for example mucositis. As for this study the main focus was put on the prophylaxis of nausea and emesis the time of administration seemed to be reasonable.

It is questionable what impact on quality of life can be attributed to pharmaceutical care interventions, in such a short period of time and observing only a limited number of patients. Osoba discussed this in a review on this topic (1997). To date it is still uncertain to what extent health-related quality of life is actually affected for example by post-chemotherapy nausea and emesis or whether other factors such as the underlying disease have a greater effect.

Experts seem to agree upon the fact that the expressiveness of findings from quality of life measurements is much depending on the methodology of the questioning and the evaluation of the collected data (Osoba, 1997; Rusthoven, 1997; Ravens-Sieberer, 2002). Nevertheless, it is important to ask for patients' feelings in particular when aspiring an even partnership between health care professionals and patients.

As primary endpoint QoL does not seem to be appropriate, though, as it is influenced in various ways as mentioned above. Thus it is not capable of reflecting the influence of the intervention in a meaningful way. The decision was made to change the primary endpoint to 'complete control of emesis' as it is a much stronger parameter and the interdependency of intervention and change in this parameter is much better to interprete.

5.2.2 Nausea and emesis

The results of this study indicate that it is possible to optimise the antiemetic treatment and influence the outcome in a positive manner. To interpret the results it is necessary to distinguish between nausea and emesis as two different symptoms. Regarding emesis, patients in the intervention group had a clear benefit compared to patients in the control group. Although not statistically significant, the number of cycles with a

complete response to the antiemetic prophylaxis could be enhanced in the intervention group. The cycle-wise consideration and the comparison of the sumscores of experienced emetic episodes show the same tendency. In particular, acute emesis could be improved. The improvement of the antiemetic prophylaxis is the result of different interventions. First, the application of the evidence-based therapeutic algorithm was a mandatory presupposition. The physicians were asked to report and at best specify the reason for altering the antiemetic prophylaxis or treatment. Second, pharmaceutical care might have contributed by improving patients' knowledge and discernment in the therapy and thus enhancing the concordance to the suggested prophylaxis. In particular for the antiemetic prophylaxis patients received additional written information on how to take their medication and were asked to fill in the patient diary about their experience with nausea and emesis including the medication taken.

In contrast to emesis, nausea could practically not be affected in the intervention group. Looking at the results it even seems that the patients in the intervention group experienced higher degrees of nausea compared to the control group. This might be due to the fact that patients of the intervention group did not suffer emesis as much which might have led to a more sensitive rating of the experienced nausea compared to patients in the control group which experienced more emetic episodes and thus might not have experienced nausea as bad in comparison. In line with the current literature on patients' perception of side effects in cancer chemotherapy it is more important to control emesis as it is rated more distressing by the patients than nausea (Carelle et al., 2002). Still, in the early 21st century the patients' perception of cancer therapy-associated adverse events has changed considerably compared to 20 years ago. When at the beginning of the 1980's emesis and nausea were ranked first and second worst adverse events nowadays psychosocial aspects, alopecia and fatigue lead the list. Emesis is now on rank 11 and nausea even below 15. However, any effort should be made to minimise this toxicity.

Our results, that acute emesis can be influenced most, is in agreement with the current literature. Herrstedt discussed the present state of the antiemetic prophylaxis in an editorial (2002). He pointed out that delayed emesis and particularly acute and delayed nausea have remained to be unsolved problems. In the case of the present

study population at least delayed emesis might be controlled better by changing the therapeutic algorithm in favour of dexamethasone which will be applied in the subsequent study.

Additionally the recently approved NK1-receptor antagonist aprepitant has been implemented in current international guidelines of the MASCC (Gralla, 2004). It is indicated for the prophylaxis of acute and delayed nausea and emesis in highly emetogenic chemotherapy. However, currently published data show that it might also be effective in moderately emetogenic chemotherapy. Warr et al. conducted a worldwide multicentre randomised, double-blinded, controlled trial with breast cancer patients receiving an anthracycline in combination with cyclophophamide. Aprepitant was given to one group in addition to the standard antiemetic prophylaxis before chemotherapy and on days 2 to 3 after chemotherapy in order to prevent both acute and delayed emesis (day 1: aprepitant 125mg, ondansetron (OND) 8mg, and dexamethasone 12mg before chemotherapy and ondansetron 8mg 8 hours later; days 2-3: aprepitant 80mg four times daily). The other group received a standard treatment (day 1: ondansetron 8mg and dexamethasone 20mg before chemotherapy and ondansetron 8mg 8 hours later; days 2-3: ondansetron 8mg twice daily). The aprepitant regimen proved to be significantly more effective in both acute and delayed emesis compared to the standard treamtent (Warr et al., 2004). These findings are very promising and might lead to the application of this drug in the subsequent study.

The importance of the application of standardised and evidence-based therapeutic guidelines or treatment algorithms was shown in previous national and international studies. Dranitsaris et al. (2001), Kämmerer (2002) and Freidank (1999) initiated the implementation of such guidelines out of their pharmacy departments and achieved an improvement of the therapeutic outcome for the patients. As an additional effect considerable amounts of money were saved by implementation of guidelines. Kämmerer described savings of 100,000 € annually for the hospital by simply reducing the administered dose of granisetron from 3 mg to 1 mg as recommended in the literature (2002). The question whether there is a need for an update of the currently available therapeutic guidelines has been discussed by Roila, who was member of the panel of experts for the Antiemetic Subcommittee of the MASCC, in an editorial (2002). The currently available drugs are taken into consideration in the present guidelines. Attempts to set up new guidelines with the

available drugs do not let expect major new insights but may lead to more confusion among the practitioners.

5.2.3 Patient satisfaction with information on cancer treatment

The contents of the pharmaceutical care process for patients with gynaecological malignancies have been adapted according to the conclusions from the basic survey regarding information deficiencies of cancer patients. The results showed that in the intervention group the patients' satisfaction with the information improved. In four of five sub-scales the differences were statistically significant.

In the intervention group patients chose pharmacists as one of their most important sources of information significantly more often than in the control group. This is not surprising as the regular appointments with a pharmacist were a mandatory part of the pharmaceutical care process and usually took place in a familiar environment with enough privacy and time to ask questions. Still, the results showed that the information provided was not only accepted but also perceived as particularly valuable. Another aspect that should be taken into account is that the study pharmacists observed that often patients did not perceive them as 'pharmacists', as they did not meet the general image of a 'white coat' pharmacist in the pharmacy. This would explain why only 80% of all patients from the intervention group indicated the pharmacist as a utilised source of information.

Three important questions need to be addressed:

1) Did the pharmaceutical care intervention improve patients' satisfaction with information on the cancer treatment?

To answer this, some general considerations regarding the outcome variable 'patient satisfaction' need to be made. It is important to be aware of the many uncertainties still connected to the term 'patient satisfaction' when interpreting the data.

From the scientific point of view patient satisfaction should only be applied as an outcome parameter if its theoretical construct can be precisely described. The literature describes a variety of approaches which try to explain the construct of patient satisfaction (Cleary and McNeil, 1988; Leimkühler and Müller, 1996; Jackson

and Kroenke, 1997). They emphasise the many interdependencies of patient satisfaction with other influencing factors. Also the possible correlation between patient satisfaction and other outcome parameters such as quality of life and compliance have been discussed.

Patient satisfaction can be influenced by a variety of objective and subjective factors such as attitudes and expectations, relation to the caregiver, health status prior to care, patient characteristics such as age, social class, race or gender. At present no meaningful answers can be presented, though, which specify the impact of these factors on patient satisfaction.

The consulted literature introduces a fulfilment theory which suggests that the more the provided care conforms to patients' expectations the higher is the resulting satisfaction (Jackson and Kroenke, 1997). Transferring this to the present study it would support the conclusion that the pharmaceutical care intervention met the expectations of the study patients as intended.

It also has to be taken into account that the health status at baseline influences satisfaction. Applied to the available data this would even strengthen the observed difference as the intervention group had a median global health status below the control group. The influence of patient characteristics on patient satisfaction has been discussed under 5.1.

Diener et al. describe satisfaction as one of three major components of subjective well-being (SWB) (Diener et al., 1997). The other components are pleasant affect and low levels of unpleasant affect. People tend to experience similar levels of well-being across different aspects of their lives. If global satisfaction is measured the results will more likely be influenced by other components. Whereas the more narrow the measure is laid out the more sensitive the measure is to causal variables. Leimkühler and Müller point out that many studies measure global satisfaction which generally tends to be fairly high (Leimkühler and Müller, 1996). Cleary and McNeill describe the same observation in their review (1988). If the questionnaire is more differentiated other aspects may differ from the global satisfaction by all means. This assumption is supported by the observation of Williams and Calnan (1991). They compared the global and specific satisfaction and found out that although 95% of the patients were generally satisfied, 35% felt that the hospital doctors did not give

sufficient information. Our questionnaire refered to this aspect of care. Compared to instruments which measure only global satisfaction with health care service this can be considered an advantage. Although global satisfaction was at a high level as expected, the subscales provided different results. The results especially reflect that in terms of complementary treatment options, the satisfaction with the information received was still not as high as for the other scales. More attention should be paid in the future to this aspect.

Another phenomenon that has to be considered and may have influenced the response is that patients received the questionnaires from the pharmacists who provided the care. This could cause a socially-desirable answering. Although this held for both, the control and intervention group, the effect might be stronger in the intervention group as the relationship to the pharmacist is far more intense compared to the control group. This would consequently lead to improved outcomes in the intervention group.

Considering the potential bias discussed, it cannot be concluded that the pharmaceutical care intervention alone improved patients' satisfaction. Further research in this area will be necessary to elucidate the interdependencies and correlations of patient satisfaction in relation to other parameters.

2) Do the results allow the inference on the quality of the delivered pharmaceutical care in general?

For one thing 'quality' needs to be defined. One approach is to describe it as a composite of technical expertise, interpersonal skills and the ability to transfer information. Patients surely have difficulties to judge the technical expertise of the caregiver, whereas the interpersonal skills have a major influence on satisfaction (Jackson and Kroenke, 1997). Ried et al. showed that patients' satisfaction can be influenced by personal attention (Ried et al., 1999). This observation is in accordance with Cleary and McNeil (1988). They concluded that the more 'personal' the provided care is, the higher satisfaction levels are reached. This probably applies to the pharmaceutical care intervention. The authors emphasise that in terms of quality assessment an improved personal attention can be interpreted as improved caregiver-patient communication which is considered part of a high quality standard in health

care. Medical treatment depends to a great extent on accurate patient communication and active involvement in the treatment process.

Furthermore, the majority of studies interpret results based on two unproven assumptions. One assumption emanates from the fact that an objectively good reality is perceived as such and consequently results in high satisfaction and the second is that subjective satisfaction can be gathered from the declared satisfaction. Leimkühler and Müller discuss the topic in detail in their review (Leimkühler and Müller, 1996). They doubt whether patient satisfaction as it has been used in studies so far actually contributes to quality assurance as intended. At this time there seems to be no valid outcome parameter available which would allow the inference from patient's perception to the quality of health care services. Still it is true that there cannot be high quality care unless the patient is satisfied. Also patient satisfaction may serve as a valuable monitoring parameter of the quality of care over time.

3) Finally, do the results reveal whether the patients in the intervention group are actually better informed or educated about their disease?

The results from the patient satisfaction questionnaire alone do not allow this conclusion. Taking into account other outcome parameters evaluated in this study, the assumption that the patients from the intervention group might be better informed about their treatment is supported. In terms of nausea and emesis the intervention group experienced less toxicity than the control group. This effect cannot only be attributed to medication changes but also requires a good adherence to the suggested medication plan. The better the knowledge of the patient regarding her treatment is the more likely there will be good adherence to the medication plan.

Even if at this time the construct 'patient satisfaction' can not be sufficiently described it still seems reasonable to ask for the patients' subjective perception. Analogous, unevaluated conclusions, however, should not be drawn.

5.2.4 Drug-related problems and pharmacists' interventions

In the present study the drug-related problems and according pharmacists' interventions were documented descriptively in order to elucidate where the main contribution for this particular patient collective is. The major drug-related problem

were obviously the adverse drug reactions which, to a different extent, were experienced by every patient in almost every cycle. Knowing the antineoplastic treatment this was expectable. The PI-Doc®-system does not allow the classification of the degree of experienced adverse drug reactions. It would be interesting to document the drug-related problems also for the control group to be able to compare the two groups. Other drug-related problems occurred to a minor extent. Suseno et al. showed in their study that the systematical documentation of pharmacists' interventions does not only affect the quality of health care but has also an impact on cost savings (1998). The corresponding interventions made by the pharmacists do show a certain pattern. It is obvious that activities such as interviewing and counselling of the patient, recommendations on preventive or complementary measures as well as advice on the optimal duration of use of the medication, especially regarding the supportive therapy, were part of the routine care. These findings are valuable for the conception of care standards in the future. The amount of time spent on the care appointments adjusted at similar levels. In the median about one hour is necessary to educate the patient before the therapy starts. The follow-up appointments took in the median about half an hour time. The suggestion is that these times can even be reduced in everyday practice considering the increasing expertise of the caring pharmacist as well as the different working conditions in a study. The research pharmacists had many appointments in the private environment of the patients. Which might have lead to longer conversations as if held in a clinic or pharmacy. This defiinately biased these results. Still they give a rough estimation of what to expect if pharmaceutical is applied to this kind of patient collective.

5.2.5 Limitations of pharmaceutical care research

Data from pharmacy practice studies have to be interpreted with caution. Mobach explains the traps of pharmaceutical care research (PCR) (2001). He described it as a relatively new scientific field which needs to be defined and suggests that standards need to be created. PCR ranges between natural science and social sciences. Each of these directions have their own rules which need to be linked and adapted to achieve representative results. It is science in the field rather than in the laboratory and thus much more exposed to a variety of environmental influences. For these conditions

specific rules need to be established through studies. Van Mil emphasised in an editorial that this kind of research is often, in addition to the general problems connected to research, subject to uncontrolled settings, uncontrolled interventions and uncontrolled populations. This obviously increases the risk of influencing the reproducibility of the data (van Mil, 2003). When interpreting data from pharmacy practice studies van Mil calls for the consideration of an effect well known in sociological and psychological research as the 'Hawthorne effect'. This effect was observed in a series of studies undertaken between 1924 to 1927 at the Western Electric Company in Hawthorne, Illinois which aimed at finding conditions under which the productivity of the workers could be increased. Eventually they found that it were not the changes in the working conditions itself that resulted in increased productivity, but rather the fact that workers were influenced by the management's perception and the team spirit among co-workers. This effect was applied to a variety of situations in personel management but it is also transferable to sociological, psychological, medical and pharmacy practice research. What can be observed is that patients who participated in studies regardless of the treatment and whether they are assigned to the control or intervention group, seem to benefit. This is probably due to the fact that special attention is paid to them (Gnant, 2000). Di Blasi et al. described a similar effect referred to as 'context effect'. They concluded in their review that the manner in which patients are cared for in terms of emotional and cognitive care has a considerable effect on the treatment outcome. When interpreting study results these aspects have to be taken into account. It is a lot more difficult to show an effect of an intervention such as pharmaceutical care, since the patients of the control group are more likely to have better outcomes than the overall population. Nevertheless this is a problem which applies to all study populations. However, when results show statistical significance even in a small study population, the effect can probably be accredited to the intervention.

The present study was affected by all the effects mentioned above. They had to be considered when interpreting the data. In future research projects further effort should be made to test methods in order to reduce the bias discussed above. Nevertheless, the selected sequential control group design proved to be a suitable design for this kind of question. It oriented much on the research standards in cliinical trials. Due to the conditions in the clinical routine a randomisation was not possible.

This was a clear disadvantage. When planning subsequent studies it would be worthwhile thinking about randomising the study centres which would be unproblematic with a larger number of participating centres. However, sometimes it is difficult to convince study centres (e.g. participating pharmacies) to be the control group, as they hope to learn from the experience in participating in a study. Blinding, however, still remains a problem. One approach may be the 'placebo care' concept where patients in the control group also get contacted by an additional person who spends the same amount of time with them as for the provision of pharmaceutical care would take up in the intervention group. Someone without a pharmaceutical or medical education would have to perform the care to assure the 'placebo effect'. This might be difficult to achieve in daily practice for several reasons. First, people would need to be hired and somehow integrated into the routine so that it would not be obvious to the patient. Second, it is difficult to fulfil the expectations of patients participating in a study. Third, and perhaps most important is the ethical issue. Patients often exchange their experiences with other patients and it can thus easily end up discovering to which study group they belong. Under these circumstances it would not be justifiable to deprive extended care from one group of patients.

As described for quality of life research and research on patient satisfaction pharmaceutical care research faces the similar methodological uncertainties which have to be overcome in the future. So far very limited scientific evidence is available to judge the significance of the concept within health care particularly in cancer care. Mainly opinions of members of the pharmacy profession are available rather than profound scientific findings.

5.2.6 Pharmacoeconomic aspects

In recent times due to cost pressure in the health care sector treatment costs play an increasingly important role in supportive care. Pharmaceutical care of cancer patients seems to have potentials of saving costs in different ways. Two aspects have already been indicated above.

First, the antiemetic treatment has proven cost saving potential. Guidelines have been established which are not only based on randomised clinical trials but also include pharmacoeconomic evaluations. The general ability to reduce treatment costs

by implemeting pharmaceutical care in the ambulatory setting was shown by Lobas et al. (1992). In this particular case even more distinguished approaches are applicable. The 5-HT_3 antagonists in the treatment of chemotherapy-induced nausea and vomiting are a good example. Whereas for acute emesis 5-HT_3 antagonists show a pharmacoeconomic benefit compared to high doses of metoclopramide, they should not be used for the treatment of delayed emesis. A study by Berard and Mahoney showed that the implementation of a treatment algorithm for antiemetic prophylaxis, incorporating aspects such as treating delayed nausea and vomiting without using serotonin receptor antagonists or matching antiemetic prophylaxis with the emetogenic potential of the chemotherapy regimen led to a cost reduction of about 205,000 $ (US) in a 719-bed medical center in the first year (Berard and Mahoney, 1995). Thus, the right choice of treatment can save a substantial amount of money. Furthermore, the route of administration has a great impact on the treatment costs. Oral administration frequently is as efficient as intravenous administration but at significantly lower costs. Engstrom et al. showed that the implementation of an oral antiemetic regime saved about 18,000 $ (US) within the nine months study period on 52 patients both in in- and outpatient settings (1999). As mentioned earlier Kämmerer managed to save about 100,000 € by simply changing the dose of the $5HT_3$ receptor antagonist granisetron according to the guidelines (2002). A pharmacoeconomic analysis will be included in the subsequent study.

The second cost-saving effect by documented pharmacists' interventions was described by Suseno et al. (1998). These cognitions might not only have pronounced effects on the successful implementation of pharmaceutical care, but also for the future offering of supportive care to cancer patients. Elting and Tina Shih describe the economic burden of supportive care of cancer patients and call for more cost-effectiveness analyses in order to be able to judge the different measures (2004). Moreover, the proof of a pharmacoeconomic benefit of pharmaceutical care may be an additional argument for a reform of the current payment system (Rappaport, 2002).

5.2.7 Future prospect

Crooks et al. (2004) identified the gap in supportive care between the care delivery and the often unknown patients' needs. They developed and introduced the 'Initial

Health Assessment' form which helps the clinician to identify patients' supportive care needs systematically. A similar approach has been followed by Scottish scientists. Simons describes in his thesis the so called 'care issues' of cancer patients which are identified systematically and translated into a number of potential drug therapy problems in order to standardise the pharmaceutical care process for cancer patients. The findings of the present work showed that there is obviously a need of patients for optimised supportive care and individualised information. Nevertheless it is important to elaborate in more detail the particular needs of certain groups of patients in future projects. This could be for example for different cancer entities or for different age groups of patients. The results of the patient satisfaction questionnaire showed that with individual information the satisfaction can be significantly improved. It would be interesting to further investigate the areas of pharmaceutical information which are most valuable to patients. The care models could then be standardised for these groups which would support the broad application in the practice settings. These approaches seem to be particularly reasonable when considering the future developments in health care systems as mentioned in the introduction. Pharmaceutical care is a concept which is comparable to other approaches as DMPs and other integrated care models. To develop it in a sustainable manner and make it attractive to third party payers further effort has to be made in order to standardise the process.

Patients are the consumers of pharmaceutical care for whom the models have to be customised. Nevertheless the other parties should also be kept in mind when reflecting upon the results of this work. Although not measured in a scientific sense experiences were made regarding the cooperation with the participating physicians. The often undeveloped relationship among pharmacists and physicians in Germany is often considered a main obstacle in the realisation of pharmaceutical care. Correlative prejudices were by all means present at the beginning of the study. Through intensive discussions these prepossessions were removed after only a short time and yielded a constructive cooperation. As mentioned above this experience was not quantified in the frame of this work. Future projects could focus on this aspect in order to find out more about physicians perceptions of the value of a cooperation with pharmacists in the area of oncology.

Last but not least the pharmacists themselves play a role in the development of pharmaceutical care. In the present project there were very controlled conditions. The main focus was to survey the concept of pharmaceutical care. Not to underestimate is the attitude the majority of pharmacists has towards pharmaceutical care. Within the pharmacy profession obstacles have to be overcome, too. Angaran realised already at the beginning of the 1990s that it is an arduous and slow process to improve quality and change a profession. It requires a long lasting commitment to the previously mentioned goals to realise a change (1991). The profession has to identify the obstacles and develop strategies to successfully overcome them (McDonough et al., 1998). These can for example be pharmacists' attitudes, a lack of advanced practice skills or interprofessional obstacles. Referring to an article in the Harvard Business Review Tice addressed the question whether pharmaceutical care has the potential of being a 'disruptive innovation' in health care (2002). He challenged the pharmacy profession to create systems which guarantee that society could rely upon the pharmacy profession for their expertise in managing drug therapy problems and achieving desired therapeutic goals.

5.3 Monitoring of carboplatin

The results of this feasibility study support the formerly described observations of inaccuracies in dosage when estimations of the creatinine clearance are being used. Principle conclusions cannot be drawn due to the small number of observed patients (four patients with twelve observed cycles). However, the results suggest a tendency towards an under-dosage of patients treated with carboplatin when the Calvert equation is being used in combination with the Cockcroft-Gault equation for the estimation of creatinine clearance.

A systematic error in the application of the equations by the physicians who determined the dose is very unlikely as the four patients were treated in three different settings with changing staff. One aspect that should be mentioned however, is that different infusion techniques were applied. In some cases an infusion pump was used while in other cases the normal infusion based on gravity was applied. With the latter, a rest of the infusion solution often remains in the tube. Depending on the length of the tube and the volume of the solution it is conceivable that the AUC of the

administered drug might be reduced. However, this phenomenon cannot explain the extent of under-dosing observed. The limited sampling method of Sørensen et al. that was used in this study had been validated by other groups and showed good precision and little bias (van Warmerdam et al., 1994; Huitema et al., 2000b). These groups tested the one-sample method. The two-sample method used in this study presented in the original paper had even better values for precision and was unbiased (Sørensen et al., 1993). The required conditions were met. An exact sample timing was achieved which was followed by an immediate sample preparation. The analytical method was validated and QC samples proved precise and unbiased measurements.

These results raise the question of alternative dosage strategies. A number of publications address the question of whether the commonly used dosage methods lead to the desired drug exposure in an individual patient. Van Warmerdam et al. performed a pharmacokinetic study to evaluate the Calvert equation estimating the creatinine clearance based on either the 24-h urine collection or the Cockcroft-Gault equation as well as the Chatelut equation. They found an approximate underexposure of 10% for the Calvert equation used in combination with the Cockcroft-Gault equation whereas the combination with the 24-h urine collection led to an overexposure of approximately 10%. According to van Warmerdam et al. the Chatelut equation seemed to be the least biased one (1996). Panday and colleagues compared the modified Calvert equation in combination with the Jelliffe equation or the Cockcroft-Gault equation as well as the Chatelut equation. Their results showed a poor precision for all three dosage strategies which all led to an underexposure of carboplatin In comparison the Chatelut equation predicted the AUC closest to the actually achieved AUC (Panday et al., 1998). The group concluded that the original Calvert equation, though inconvenient, still should remain the ‘gold standard’. Huitema and colleagues used a population pharmacokinetic data set to evaluate the commonly used methods. The modified Calvert equation based on the creatinine clearance estimated by the Jelliffe, Cockcroft-Gault or Wright equation and also the Chatelut equation resulted in poor precision and the Jelliffe equation especially provided a biased prediction. They tested the one-sample method from Sørensen et al. which turned out to be slightly biased but precise (Huitema et al., 2000). These results are in accordance with many studies that evaluated these equations. The modified Calvert equation which uses estimations for the GFR based on Jelliffe or Cockcroft and Gault

leads to underexposure of carboplatin. The Chatelut equation seems to predict the AUC more precisely, compared to the original Calvert equation and is applicable to clinical practice (Ozols, 1995; Calvert et al., 1995; Langer et al., 1995; Izquierdo et al., 1997; Donahue et al., 2001).

However, there are also some studies which found contrasting results. Okamoto et al., for example, compared the Chatelut equation with the modified Calvert equation using the 24-h urine collection or the Cockcroft-Gault equation to estimate the GFR. They found that both variations of the modified Calvert equation were superior to the Chatelut equation in terms of accuracy and precision (Okamoto et al., 1998).

Investigations on the pharmacokinetics and pharmacodynamics of carboplatin have led to the proposal of other methods of tailoring dosage to individual patients, particularly in clinical studies. Calvert already proposed in 1994 that TDM should be used to ensure an optimal exposure to the desired AUC of carboplatin for the patient. From his point of view a limited sampling method would expedit the TDM and therefore be more practical. To find a way to integrate TDM for carboplatin into clinical practice a variety of limited sampling methods were developed (van Warmerdam et al., 1994; Miyazaki et al., 1997; Panday et al., 1999; Chatelut et al., 2000). In this study the limited sampling method of Sørensen et al. was used. Compared to other methods the limited sampling according to Sørensen et al. seemed applicable as the sampling times were reasonably close together (0.25h and 2.75h post infusion). This allowed integration into clinical practice without significant patient burden, keeping in mind that the advantage of the applied chemotherapy regimen (paclitaxel/carboplatin) is its application in outpatient settings. In order to improve the precision the two-sample method was chosen. This method proved to be unbiased (MPE% ± SD, -2.2% ± 2.1%) and precise (RMSE%, 9.4%) (Sorensen et al., 1993). Patients tolerated the blood sampling well, although they did not have an immediate personal benefit from the intervention. It also integrated without difficulty into the usual clinical routine. Limited sampling models such as this rely on accurate sampling times so this might sometimes be a limitation in everyday clinical practice (van Warmerdam et al., 1994; Miyazaki et al., 1997; Panday et al., 1999; Chatelut et al., 2000).

Huitema and colleagues introduced an advanced method to predict carboplatin exposure. They developed and validated a sparse data Bayesian method for the estimation of carboplatin exposure (Huitema et al., 2000a). An open two-compartment model with first-order elimination from the central compartment underlies this method. The data was fitted with the NONMEM population pharmacokinetic programme. The advantage of their model is the independence of exact infusion and sampling times. The method allows an unbiased and precise prediction of the carboplatin exposure of high-dose chemotherapy regimens.

Calvert and Egorin just recently published an editorial on the evaluation of carboplatin dosing equations (Calvert and Egorin, 2002a). They conclude that all predictive dosage methods lack precision. They support the results of the studies discussed above, especially that the use of the Cockcroft-Gault equation and the Jelliffe equation lead to immense under-exposure of carboplatin. They deem the Chatelut equation as being more precise in the prediction of carboplatin clearance and more useful for everyday clinical practice. Calvert and Egorin (2002) judged the various limited sampling methods as accurate methods to predict carboplatin exposure, but think that due to the necessity of rapid measurements their use might be limited to special circumstances such as paediatric practice or high-dose regimens. They point out that future investigations should focus on deriving more convenient methods for estimating renal function than the ^{51}Cr-EDTA method, and on developing precise methods for achieving a target AUC. Future studies should also focus on validating equation-based dosing in combination therapies where there may be pharmacokinetic or -dynamic interactions. Duffull and Robinson additionally point out that any discussion about precise and unbiased dosing is idle as long as relationships between AUC and outcome are not clearly defined (Duffull and Robinson, 1997).

The relationship between AUC and haematological toxicity has been described in a few studies (Egorin et al., 1984; Jakobsen et al., 1997). Jodrell et al. showed that the risk of developing a grade 3 thrombocytopenia increased rapidly at AUC values above 5-6 mg·min/mL (Jodrell et al., 1992). The documentation of the haematological toxicity in this study is too fragmentary to derive conclusions, but the available data suggests that the dosage of the antineoplastic agents never reached levels that would cause dose-limiting toxicities. Either the potential protective effect of paclitaxel or the

fact that all patients were under-exposed to carboplatin could have contributed to this (Kearns et al., 1995; Kearns and Egorin, 1997). The principles of antineoplastic therapies that the maximum tolerated dose that has proved to be effective should be given to the patient, was not met in this observed patient collective.

The inaccuracy of the individual dosage is only the end of the chain of deficiencies in the complexities of carboplatin dosing. Many of the clinical studies conducted to find the optimal dose of carboplatin for the treatment of epithelial ovarian cancer are based on estimations rather than on pharmacokinetically guided dosage (du Bois et al., 1997; Neijt et al., 2000; Ozols et al., 2003). Therefore it can be assumed that the described dosage inaccuracies already apply for the studies. The conclusions drawn from those studies based on observed outcome parameters are most probably scattered due to variability in the actual AUC and biased due to systemati differences between actual and target AUC of the study population. Additionally, among studies and even within some studies the dosage methods vary (Neijt et al., 2000). This leads to additional variability and questionable results. Thus, knowledge about the inaccuracies of many of the commonly used dosage methods alone does not seem to solve the problem. The exact relationship between the carboplatin AUC and the antitumour effect remains to be established. Duffull and Robinson discuss in their review the problem of insufficient AUC-response data. Retrospective studies suggest a response plateau at AUC 5-7 mg·min/mL. Newer studies consider the possibility of response enhancement when increasing the AUC up to 12 mg·min/mL (Duffull and Robinson, 1997). Therefore, large-scale PK/PD studies are necessary to investigate this issue. In order to achieve interpretable data it is mandatory to not only calculate the AUC with the variable estimations but to determine the achieved AUC as accurately as possible utilising pharmacokinetic methods.

Overall, patients are under-treated with carboplatin, not due to intolerable side effects, but due to suboptimally used dosage strategies. It can therefore be suggested that the common practice should be reconsidered and every effort should be made to minimise interpatient variability. In practice the available options are not yet fully utilised. From what most studies and reviews conclude, the original Calvert equation remains the gold standard in predicting the carboplatin exposure. Chatelut provided a suitable and more practical alternative. This feasibility study showed that a limited

sampling method to support an optimal individual dosing is well tolerated by patients and can be integrated into the daily clinical routine. A combination of an estimation method with a pharmacokinetically guided dosage on the basis of a limited sampling model seems to be a reasonable approach. Here either limited sampling models or Bayesian approaches can be considered. These efforts are only exploited to an optimum if also the AUC-response relationship is characteriseded in pharmacokinetically guided clinical studies.

[6] Summary

6 Summary

Pharmaceutical care in oncology aims at reducing treatment-related toxicity and improve patients' quality of life. The objective of this pilot study was to develop a specific pharmaceutical care model for breast and ovarian cancer including patient counselling, optimisation of supportive medication and the implementation of a therapeutic algorithm for antiemetic prophylaxis. Additionally, it is the objective of this pilot study to assess the value and feasibility of therapeutic drug monitoring in outpatient settings for patients treated with antineoplastic agents, in particular carboplatin and its contribution to pharmaceutical care.

Patients with breast or ovarian cancer treated with chemotherapy for the first time were included. The feasibility and outcome of this pharmaceutical care model was investigated using a prospective, multi-centred, sequential control group design.

Quality of life (QoL) served as the primary endpoint. Patient satisfaction with the information on cancer treatment and the response to the antiemetic treatment were evaluated as secondary endpoints.

The results regarding the health-related quality of life were difficult to interprete. Looking at the complete treatment period the global health status/QoL decreased in the control group in the median relatively to the baseline by 14% compared to only 6% in the intervention group by ($p = 0.563$, Mann-Whitney U-test). The quality of life could not be improved but stabilised in comparison to the control group. For certain symptom scales an improvement could be achieved (e.g. pain, constipation) which was not statistically significant.

The global satisfaction with information on cancer treatment was significantly improved throughout the study (CG: median = 3.94, IG: median = 4.41, $p = 0.014$, Mann-Whitney U-test). Two of the 4 subscales also improved significantly. The patients' perception of pharmacists much improved throughout the study. Only 15% of the patients in the control group described the pharmacist as one of their most important sources of information compared to 68.4% in the intervention group. This increase was statistically significant ($p = 0.001$, Mann-Whitney U-test).

The strongest criterion to assess the success of the prevention of nausea and emesis is the complete response (CR) to the antiemetic treatment. Looking at the full treatment period for the intervention group an increase in the number of cycles with CR in emesis could be achieved ($p = 0.155$). The incidence of nausea could not be improved by the intervention.

The monitoring of carboplatin confirmed results of previous earlier publications on this topic. In the median the achieved AUC differed from the target AUC by 21.7%. The doses necessary to achieve the target AUC would have needed to be in the mean 31.1% (SD 13.65%) higher than the actual dose given.

This pilot study can be rated as an inital contribution to the development of pharmaceutical care models in oncology. Patients with breast and ovarian cancer seem to benefit from pharmaceutical care as demonstrated by improved clinical and subjective outcomes. The pharmaceutical care model was feasible and integrated in the daily routine. It was well accepted by patients and health care providers.

The results of the TDM show a necessity to reconsider the individual dosing strategies for carboplatin in combination with paclitaxel. It proved to be feasible in the outpatient setting and was tolerated by the patients.

In future pharmaceutical care research in oncology further effort should be made to develop improved outcome parameters which are capable of reflecting the impact of pharmaceutical care and allow conclusions on the quality of care. Additionally it should focus on additional aspects such as further patient needs, pharmacoeconomic aspects and standardisation for the integration into disease management programmes.

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Appendix

Appendix A **Patient satisfaction with information on cancer treatment**

Tab. A- 1 Alpha-if-item deleted values of the pre-test

Appendix B **Tumour classification and staging**

Tab. B-1 TNM classification of breast cancer

Tab. B-2 Stages of ovarian cancer according to TNM and FIGO

Appendix C **Levels of evidence and grades of recommendation**

Tab. C-1 Levels of evidence

Tab. C-2 Grades of recommendation

Appendix D **Standard operating procedures**

Appendix E **Patient information material**

Appendix F **Informed consent**

Appendix G **Privacy statement**

Appendix H **Coding system of drug-related problems: PI-Doc®**

Tab. H-1 Main groups of drug-related problems

Tab. H-2 Main groups of drug-related interventions

Appendix I **Care material**

Patient information on expected side effects

Appendix J **Questionnaires**

EORTC QLQ-C30 (v. 3.0)

Nausea and emesis questionnaire including patient information

Patient satisfaction questionnaire (PS-CaTE)

Appendix K **Documentation**

Patient profile I and II

Medication file

Medication profile

Care plan

Appendix L **Platinum analysis**

Tab. L-1 Instrumentation and operating conditions

Tab. L-2 Chemicals and Reagents

Tab. L-3 Validation of the FAAS method

Appendix M **Monitoring of carboplatin**

Tab. M-1 Platinum concentrations and resulting AUCs

Tab. M-2 Serum creatinine and GFR-estimation

Tab. M-3 NCI Common toxicity criteria

Appendix A

Patient satisfaction with information on cancer treatment

Tab. A- 2 Alpha-if-item deleted values of the pre-test

	Alpha-if-item deleted
I am satisfied with the information I have been given about my cancer treatment.	0.92
I am satisfied with the information I have been given about possible side effects of my treatment.	0.92
I am satisfied with the information I have been given on what to do if side effects happen.	0.91
I am satisfied with the answers to my questions about vitamins, herbs, and complementary therapies.	0.91
I am satisfied with the explanations about possible interactions between my prescribed cancer treatment and other treatments I amusing or thinking about using.	0.92
I am satisfied with the way treatment information is presented to me. It is clear and easy to understand.	0.92
I am satisfied that I get enough opportunity to ask questions about my cancer treatment.	0.91
I am satisfied that I get enough opportunity to ask questions about how to manage side effects.	0.91
I am satisfied that I get enough opportunity to ask questions about the use of vitamins, herbs, and complementary therapies.	0.91
I am satisfied with the available information resources such as the handouts and staff.	0.92
Overall, I am satisfied with the manner in which the information is provided. It is friendly, respectful and non-judgemental.	0.92
I am satisfied that I am able to make informed choices about my cancer treatment.	0.92
I am satisfied that I am able to make informed choices about how to manage side effects.	0.92
I am satisfied that I am able to make informed choices about vitamins, herbs, and complementary therapies.	0.92

Appendix B

Tumour classification and staging

Tab. B-1 TNM classification of breast cancer

TNM		Diagnostic findings
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma in situ
T1		Tumour is 2cm or less in greatest dimension
	T1a	0.5 cm or less in greatest dimension
	T1b	0.5-1cm in greatest dimension
	T1c	1-2cm in greatest dimension
T2		2-5cm in greatest dimension
T3		More than 5cm in greatest dimension
T4		Tumour of any size with direct extension to chest wall or skin
	T4a	Extension to chest wall
	T4b	Edema or ulceration of the skin
	T4c	Both 4a and 4b
	T4d	Inflammatory carcinoma
N	Nx	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis to ipsilateral axillary nodes
	pN1a	Only micrometastasis (<0.2cm)
	pN1b	Metastasis to lymph nodes any larger than 0.2cm
	N2	Metastasis to ipsilateral axillary nodes fixed to one another or to other structures
	N3	Metastasis to ipsilateral internal mammary lymph nodes
MX		Distant metastasis cannot be assessed
M0		No evidence of distant metastasis
M1		Distant metastasis are present

Tab. B-2 Stages of ovarian cancer according to TNM and FIGO

TNM		FIGO		Diagnostic findings
T1		I		Tumour is limited to one or both ovaries
	T1a		Ia	Tumour is limited to one ovary. The capsule, or outer wall of the tumour, is intact, there is no tumour on the ovarian surface, and there are no cancer cells in ascites (abdominal fluid build-up) or peritoneal lavage ("washings" from the abdominal cavity).
	T1b		Ib	Tumour is limited to both ovaries. The capsule is intact, there is no tumour on the ovarian surface, and there are no cancer cells in ascites or peritoneal lavage.
	T1c		Ic	Tumour is limited to one or both ovaries with any of the following: ruptured capsule (burst outer wall of the tumour), tumour on ovarian surface, or cancer cells in the ascites or peritoneal lavage.
T2		II		Tumour involves one or both ovaries with spread into the pelvis.
	T2a		IIa	Tumour has spread and/or attaches to the uterus and/or fallopian tubes. There are no cancer cells in ascites or peritoneal lavage.
	T2b		IIb	Tumour has spread to other pelvic tissues. There are no cancer cells in ascites or peritoneal lavage.
	T2c		IIc	Tumour has spread to pelvic tissues, with cancer cells in ascites or peritoneal lavage.
T3		III		Tumour involves one or both ovaries, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to regional (nearby) lymph node(s).
	T3a		IIIa	Microscopic peritoneal metastasis beyond the pelvis.
	T3b		IIIb	Macroscopic (visible to the naked eye) peritoneal metastasis beyond the pelvis, 2 cm or less in greatest dimension.
	T3c		IIIc	Peritoneal metastasis beyond the pelvis, more than 2 cm in greatest dimension.
N	Nx			Regional lymph nodes not judgable
	N0			Regional lymph nodes contain no metastasis.
	N1			Evidence of lymph node metastasis.
M1		IV		Distant metastasis are present

Appendix C

Levels of evidence and grades of recommendation

Tab. C-1 Levels of evidence (Gralla et al., 1999)

Level	Type of Evidence
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies. Randomised trials have low false-positive and low false-negative errors (high power).
II	Evidence is obtained from at least one well designed experimental study. Randomised trials have high false-positive and/or –negative errors (low power).
III	Evidence is obtained from well-designed, quasi-experimental studies such as non-randomised, controlled, single group, pre-post, cohort, time or matched case-control series.
IV	Evidence is from well designed, non-experimental studies, such as comparative and correlational descriptive and case studies.
V	Evidence is from case reports and clinical examples.

Tab. C-2 Grades of recommendation (Gralla et al., 1999)

A	There is evidence of type I or consistent findeings from multiple studies of types II, III, IV.
B	There is evidence of types II, III and IV and findings are generally consistent.
C	There is evidence of types II, III and IV, but findings are inconsistent.
D	There is little or no systematic empirical evidence.

Appendix D

Standard operating procedures

Standard Operating Procedure – SOP 01
Aufnahme der Patientinnen in das Projekt
Der Prüfarzt, der die Rekrutierung der Patientinnen für das Projekt *"Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie"* vornimmt, sollte die im folgenden dargestellten Aspekte beachten.
Die Patientinnen, die in das Projekt einbezogen werden, müssen folgenden Kriterien gerecht werden:
Einschlusskriterien:

1. Ärztliche Diagnose eines Mamma- oder Ovarialkarzinoms
2. Erstmalige Behandlung mit Zytostatika
3. Alter von 18 bis 65 Jahren
4. Schriftliche Einwilligung der Patientin
5. Kenntnis der deutschen Sprache

Ausschlusskriterien:
Erkrankungen, die es ausschließen, dass die Patientin die Aufklärung zu Art und Inhalt der Studie versteht und die ausschließen, dass die Fragebögen richtig verstanden werden und eigenständig ausgefüllt werden können. (z.B. Morbus Alzheimer)

Die Patientin muss, gemäß der „Good Clinical Practice for Trials on Medicinal Products in the European Community" (Note for Guidance (11.07.1990):III/3976/88-EN, Anlage 2), mündlich und schriftlich informiert werden. Die Information muss angemessen, vollständig und gut verständlich sein und die Patientin über die Studie, ihre Ziele, den voraussichtlichen Nutzen, die voraussichtlichen Risiken und Unannehmlichkeiten, sowie die Patientin über ihre Rechte und Verantwortlichkeiten in Kenntnis setzen.

Für die Patientin sind, abhängig vom Primärtumor und dem Zeitpunkt der Rekrutierung, Informationsmaterialien vorbereitet, die ihr während des Informationsgespräches ausgehändigt werden. Jede Patientin wird die Information zu den **Hintergründen und Zielen des Projektes** erhalten.

To be continued on the following page

Zusätzlich bekommen die Patientinnen Informationen entsprechend dem Primärtumor und der Gruppenzugehörigkeit:

I.Mamma-Karzinom

a) Kontrollgruppe	Patienteninformation-„Brustkrebs-Kontrolle“
b) Interventionsgruppe	Patienteninformation-„Brustkrebs-Intervention“

II.Ovarial-Karzinom

a) Kontrollgruppe	Patienteninformation-„Eierstockkrebs-Kontrolle“
b) Interventionsgruppe	Patienteninformation-„Eierstockkrebs-Intervention“

Die Informationsmaterialien sind dem beigefügten Datenträger im Prüfarztordner zu entnehmen.
Der Patientin ist bis zur Entscheidung über die Teilnahme am Projekt angemessen Zeit einzuräumen (etwa bis zum folgenden Arzttermin).
Die Einwilligungserklärung (ebenfalls vom Datenträger zu entnehmen) muss sowohl
vom Prüfarzt mit aktuellem Datum versehen und eigenhändig unterzeichnet werden, als auch von der Patientin.

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Standard Operating Procedure – SOP 02
Erhebung allgemeiner Patientendaten mit Hilfe des Prüfbogens

Um die Ergebnisse der Untersuchung angemessen darstellen zu können, ist es wichtig, dass eine vollständige Zusammenfassung der Information über die an der Studie teilnehmende Person verfügbar ist. Dies wird durch die Verwendung eines Prüfbogens gemäß „Good Clinical Practice for Trials on Medicinal Products in the European Community“ (Note for Guidance (11.07.1990):III/3976/88-EN, Anlage 2) erreicht, der die Ziele des Prüfplans berücksichtigt.

Für jede in die Studie aufgenommene Patientin werden alle auf dem Prüfbogen vermerkten Daten eingetragen.
Ein Exemplar des Prüfbogens verbleibt beim behandelnden Prüfarzt, eine weitere Kopie wird an den betreuenden Apotheker weitergeleitet.
Änderungen, die sich über den Behandlungszeitraum ergeben, werden im Prüfbogen vermerkt und an alle mitverantwortlichen Personen weitergeleitet.
Eine Liste der Adressen aller an der Studie mitwirkenden Personen befindet sich im Prüfungsordner.

Eine Dokumentenvorlage des Prüfbogens ist dem Datenträger des Prüfungsordners zu entnehmen.

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Standard Operating Procedure – SOP 03
Ärztliche Dokumentation

Das Projekt *"Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie"* erfordert über den gesamten Prüfungszeitraum eine fortlaufende Dokumentation seitens der beteiligten Ärzte.

Dokumentiert werden müssen:
- die verabreichte Therapie (Chemotherapie und Begleittherapie)
- der anschließend an die Therapie erhobene Befindungszustand der Patientin mit Hilfe der Common Toxicity Criteria des NCI, Version 2.0 Publish Date: April 30, 1999
- die Ausgabetermine der Fragebögen

Um eine einheitliche Dokumentation gewährleisten zu können, stehen Dokumentationsbögen zur Verfügung.

Die Dokumentenvorlagen der jeweiligen Exemplare (siehe Anhang) sind dem Datenträger im Prüfungsordner zu entnehmen.
Nach Bearbeitung der jeweiligen Dokumentationsbögen ist eine Kopie an den betreuenden Apotheker weiterzuleiten. Das Original verbleibt im Prüfungsordner.

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Standard Operating Procedure – SOP 04
Ausgabe und Rückfluss des EORTC QLQ-C30 Fragebogens

Im Rahmen des Projektes *"Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie"* werden Daten zur Lebensqualität der Patientinnen erhoben.
Dies geschieht mit Hilfe des EORTC QLQ-C30 Fragebogens (Version 3.0).
Der Fragebogen soll zu drei Zeitpunkten von der Patientin ausgefüllt werden.

- Vor Beginn der zytostatischen Therapie
- Nach der 1. Hälfte der Zyklen
- Nach Abschluss der Therapie

Die Ausgabe der Fragebögen erfolgt am Anfang der Studie. Der Prüfarzt wird gebeten, der Patientin einen Ordner mit drei unausgefüllten, durch-nummerierten Fragebögen und den dazugehörigen frankierten und adressierten Rückumschlägen auszuhändigen. Der Fragebogen soll erläutert und mögliche Fragen der Patientin beantwortet werden. Die Ausgabe sollte auf dem Dokumentationsbogen für Fragebögen festgehalten werden.
Der Arzt soll die Patientin bitten, den ersten Fragebogen noch am Tag der Ausgabe zu Hause auszufüllen und in einen der Rückumschläge zu stecken und an die Universität Bonn zu schicken. Die Aufforderung die weiteren Fragebögen auszufüllen, wird der Patientin telefonisch, bzw. postalisch durch den betreuenden Apotheker mitgeteilt. Die Fragebögen sollen jeweils etwa eine Woche nach dem jeweiligen Zyklus ausgefüllt werden.
Eine Kopie des Fragebogens wird dem Prüfarzt von der Universität Bonn zugesendet.
Die Fragebögen gehen gesammelt bei der Universität Bonn ein und werden dort mit Hilfe des Scoring Manuals ausgewertet.

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Standard Operating Procedure – SOP 05
Ausgabe und Rückfluss des Fragebogens zu Nausea und Emesis

Im Rahmen des Projektes *"Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie"* werden Daten zu Übelkeit und Erbrechen der Patientinnen erhoben.

Dies geschieht mit Hilfe eines Fragebogens, der die beiden Parameter über einen Zeitraum von 5 Tagen nach der Therapie abfragt.
Der Fragebogen soll nach jedem Therapiezyklus von der Patientin ausgefüllt werden.
Die Ausgabe der Fragebögen erfolgt am Therapietag durch den Prüfarzt. Der Fragebogen soll erklärt werden und möglich Fragen der Patientin beantwortet werden. Mit jedem Fragebogen wird gleichzeitig ein frankierter und adressierter Rückumschlag ausgegeben, in dem die ausgefüllten Bögen an die Universität Bonn zurückgesendet werden sollen. Vor der Ausgabe sind die Details der Patientin und die Medikation vom Prüfarzt in den Fragebogen einzutragen. Die Ausgabe sollte auf dem Dokumentationsbogen für Fragebögen festgehalten werden.
Der Arzt soll die Patientin bitten noch am Tag der Ausgabe mit dem Ausfüllen des Fragebogens zuhause zu beginnen, ihn nach 5 Tagen in den Rückumschlag zu stecken und an die Universität Bonn zu schicken.
Eine Kopie des Fragebogens wird dem Prüfarzt von der Universität Bonn zugesendet.
Die Fragebögen gehen gesammelt bei der Universität Bonn ein und werden dort mit Hilfe des Scoring Manuals ausgewertet.

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Standard Operating Procedure – SOP 06
Ausgabe und Rückfluss des Fragebogens zur Patientenzufriedenheit

Im Rahmen des Projektes *"Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie"* werden Daten zur Zufriedenheit der Patientinnen mit der Information bezüglich ihrer Krebserkrankung erhoben.

Dies geschieht mit Hilfe eines Fragebogens, der verschiedene Bereiche abfragt.
- Krebsbehandlung
- Mögliche Nebenwirkungen und deren Management
- Alternativtherapien
- Informationsquellen

Der Fragebogen soll nach Beendigung aller Zyklen von der Patientin ausgefüllt werden.
Die Ausgabe der Fragebögen erfolgt durch den betreuenden Apotheker. Der Fragebogen soll erklärt werden und mögliche Fragen der Patientin beantwortet werden. Mit dem Fragebogen wird gleichzeitig ein frankierter und adressierter Rückumschlag ausgegeben, in dem der ausgefüllte Fragebogen an die Universität Bonn zurückgesendet werden soll.

Eine Kopie des Fragebogens wird dem Prüfarzt von der Universität Bonn zugesendet.
Die Fragebögen gehen gesammelt bei der Universität Bonn ein und werden dort mit Hilfe des Scoring Manuals ausgewertet.

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Standard Operating Procedure – SOP 07
Therapeutisches Drug Monitoring – TDM
Schema zur Entnahme der Blutproben

Im Rahmen des Projektes *"Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie"* wird für die an Ovarial-Karzinom leidenden Patientinnen, die mit einer Kombination aus Paclitaxel und Carboplatin behandelt werden, ein Therapeutisches Drug Monitoring durchgeführt. Dazu ist die Entnahme zweier außerroutinemäßiger Blutproben notwendig.

Die Proben müssen in PVC-freie heparinisierte Monovetten® aufgezogen werden. Die Monovetten® werden bereits beschriftet an die Praxis geliefert. Das Probenvolumen sollte 10 mL nicht unterschreiten.

Folgende Probenentnahmezeiten sind wichtig und möglichst einzuhalten:

1. Probe	15 min. nach Beendigung der Carboplatin-Infusion
2. Probe	2h 45 min. nach Beendigung der Carboplatin-Infusion

Unmittelbar nach den Probennahmen sind diese im vorliegenden Dokumentationsbogen festzuhalten. Der Dokumentationsbogen wird mit den Proben zusammen an die Universität Bonn geliefert. Innerhalb einer Stunde nach der Entnahme muss die Probenaufarbeitung (siehe SOP 08) abgeschlossen sein.

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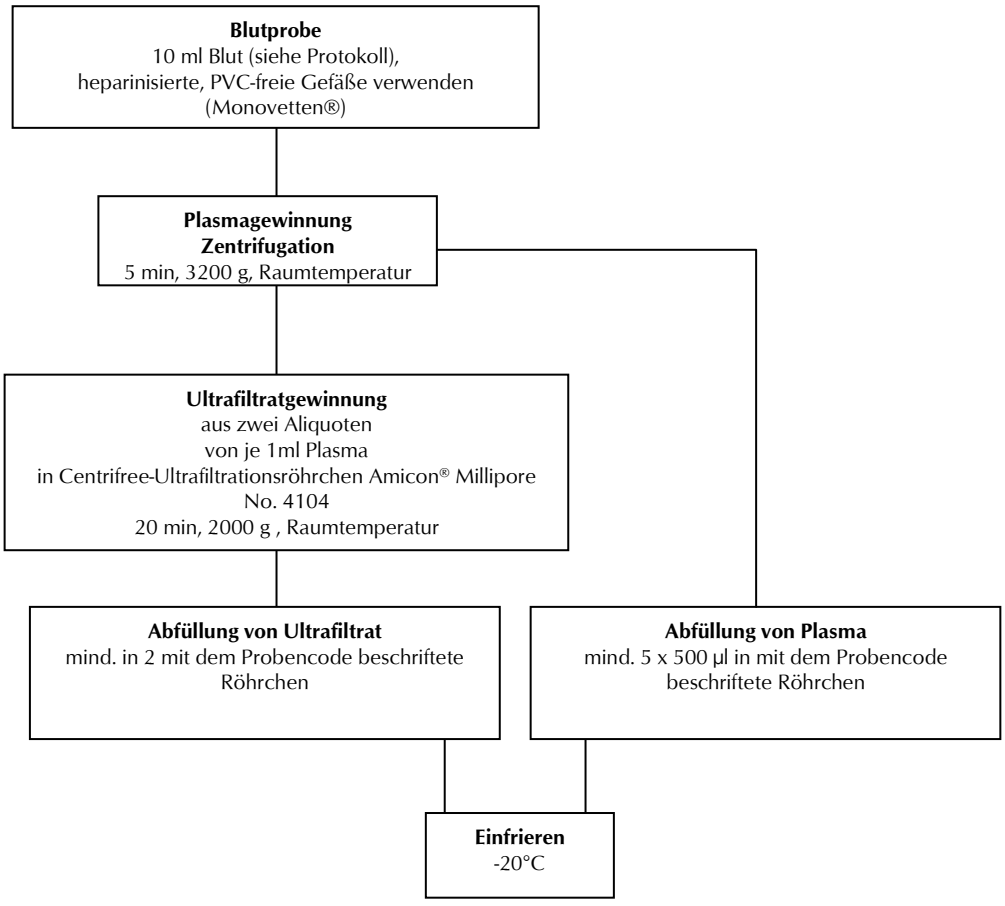
Standard Operating Procedure – SOP 08
Therapeutisches Drug Monitoring – TDM
Probenaufarbeitung

Im Rahmen des Projektes *"Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie"* wird für die an Ovarial-Karzinom leidenden Patientinnen, die mit einer Kombination aus Paclitaxel und Carboplatin behandelt werden, ein Therapeutisches Drug Monitoring durchgeführt. Die für diesen Zweck entnommenen Blutproben müssen nach einem vorgegeben Schema aufgearbeitet werden.

<u>Probenaufarbeitungsprotokoll</u>



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Die Entnahmezeitpunkte richten sich nach den Zeitpunkten der Beendigung der jeweils letzten Infusion. Diese sind genau zu dokumentieren.
Blut soll aus dem, der Injektionsstelle gegenüberliegenden Arm entnommen werden.

Eine Kontamination mit der Infusionslösung muss ausgeschlossen werden.
Alle Arbeitsschritte müssen innerhalb einer Stunde abgeschlossen sein.
Die Vorgänge sollten genau dokumentiert werden und das Formular mit den Proben mitgeliefert werden. (siehe SOP 07)

Unterschrift des leitenden Prüfarztes	Unterschrift des Projektleiters	Unterschrift des Wiss. Mitarbeiters
_____	_____	_____
Ort, Datum	Ort, Datum	Ort, Datum
Dr. med. Jan Dünnebacke	Prof. Dr. Ulrich Jaehde	Andrea Liekweg

Rheinische Friedrich-Wilhelms-Universität Bonn
Pharmazeutisches Institut
Klinische Pharmazie
Prof. Dr. U. Jaehde

Appendix E

Patient information material

Was Sie über diese Studie wissen sollten!

Patientinneninformation

Pilotstudie
zur Pharmazeutischen Betreuung
onkologischer Patienten vor, während und nach ambulanter Chemotherapie

Prospektive, kontrollierte, multizentrische Studie
zu Durchführbarkeit und Nutzen
Pharmazeutischer Betreuung
von Tumorpatienten einschließlich
des Therapeutischen Drug Monitorings ausgewählter
Zytostatika.

Pharmazeutisches Institut
Klinische Pharmazie
Prof. Dr. Ulrich Jaehde

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Sehr geehrte Patientin,
Sie sind dabei eine Chemotherapie zu beginnen. Sie sind im Moment sicher besorgt über das, was nun auf Sie zukommen mag. In der kommenden Zeit wird sich ein Team aus Ärzten, Pflegenden und anderen besorgten Menschen um Sie kümmern, um Ihre Behandlung möglichst gut und belastungsarm zu gestalten.
Wir möchten in dieser Studie herausfinden, ob es sinnvoll ist Chemotherapiepatientinnen rund um ihre Therapie zusätzlich durch einen Apotheker zu betreuen und zu informieren; ob diese neue Form der Unterstützung den Patientinnen wirklich nützt, oder sie eher belastet.
Um dies herauszufinden sind wir auf Ihre Hilfe angewiesen.
In dem Ihnen vorliegenden Informationsmaterial wird Ihnen die geplante Studie genau vorgestellt. Es wird beschrieben, welche Überlegungen zur Planung der Studie geführt haben, wie die Studie ablaufen soll und was eine Teilnahme für Sie als Patientin ganz praktisch bedeuten würde.
Nehmen Sie sich für das Lesen ruhig viel Zeit. Legen Sie die Unterlagen zwischendurch beiseite, um darüber nachzudenken. Machen Sie sich überall im Heft Notizen zu den Dingen, die Sie gerne noch mit uns klären würden.
Sollte Ihnen während des Lesens irgend etwas unklar erscheinen oder Fragen aufwerfen, so scheuen Sie sich nicht, Ihren behandelnden Arzt, oder die verantwortliche Apothekerin Andrea Liekweg anzusprechen.

Vielen Dank für Ihr Interesse und Ihre Mühe und viel Erfolg bei Ihrer Behandlung!

Dr. med. Jan Dünnebacke
(Leitender Prüfarzt)

Andrea Liekweg
(Studien-Apothekerin)

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1. Hintergründe und Ziele des Projektes

Diese Studie ist ein Projekt der Arbeitsgruppe „Klinische Pharmazie“ der Universität Bonn. Pharmazie ist das Fach, welches Apotheker für ihren Beruf ausbildet. Klinische Pharmazie ist ein relativ neues Gebiet innerhalb der Pharmazie. Durch die Entwicklung des Gesundheitssystems haben sich neue Anforderungen an den Apothekerberuf ergeben. Die Rolle des Patienten und auch seine Bedürfnisse haben sich gewandelt. Das Fach Klinische Pharmazie soll daher dazu beitragen, die Ausbildung und Berufsausübung der Apotheker verstärkt im Dienste der Patienten auszurichten. In diesem Zusammenhang werden Untersuchungen durchgeführt, anhand derer der Nutzen und die Durchführbarkeit patienten-orientierter Leistungen des Apothekers unter Beweis gestellt werden sollen.

In Deutschland sind heute ca. 45.000 zugelassene Arzneimittel am Markt erhältlich. Mit der wachsenden Zahl an Medikamenten gehen verschiedene Probleme einher. Zum einen wird es immer schwieriger, das Angebot zu überblicken und alle Neuerungen kritisch zu bewerten, zum anderen steigt die Gefahr, Medikamente zu kombinieren, die sich in ihrer Wirkung gegenseitig beeinflussen, was möglicherweise zu unerwünschten Wirkungen führen kann.

Diese Entwicklung macht es notwendig, dass alle an einer Therapie Beteiligten, also sowohl Sie als Patientin, wie auch die Ärzte und Apotheker, möglichst gut zusammenarbeiten, um eine optimale Therapie zu erreichen.

Die Hauptaufgabe des Apothekers besteht darin, Sie rund um Ihre Arzneimitteltherapie zu informieren und zu beraten. gerade in einer Dauertherapie ist es wichtig, dass der Patient durch den Apotheker begleitet wird und möglicherweise aufkommende Fragen und Probleme zu den Medikamenten direkt beantwortet und beseitigt werden können.

Die Realität der gegenwärtigen Apothekenpraxis sieht jedoch häufig anders aus. Patienten erwerben die vom Arzt verordneten, oder selbst gewählten freiverkäuflichen Arzneimittel in der Apotheke und erhalten zu den Medikamenten Einnahme- oder Anwendungshinweise. Danach besteht jedoch oft wochenlang kein Kontakt mehr zum behandelnden Arzt oder Apotheker.

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Um dieser Aufgabe gerecht zu werden, wurde das Konzept der **Pharmazeutischen Betreuung** entwickelt. Durch eine fortlaufende Betreuung soll der Apotheker eine sinnvolle und sichere Arzneimitteltherapie für Sie als Patientin gewährleisten.

Da die Idee der Pharmazeutischen Betreuung noch recht jung ist, werden derzeit zahlreiche Studien durchgeführt, die Durchführbarkeit und Nutzen dieser erweiterten Apotheker-Dienstleistung für verschiedene Patientengruppen ermitteln sollen.

Für Krebspatienten hat es bislang in dieser Form noch keine Untersuchung gegeben, obwohl gerade diese Patientengruppe besonders betreuungsbedürftig ist.

Ziel dieser Untersuchung ist es:

- die Qualität und Sicherheit der Arzneimitteltherapie zu erhöhen
- die Zusammenarbeit von Arzt, Patient und Apotheker zu verbessern
- die Patientenbetreuung in Apotheken weiter zu entwickeln
- die Lebensqualität der Krebspatientinnen zu steigern
- durch Analyse der Konzentrationen der Arzneistoffe im Blut Informationen zur optimalen individuellen Dosierung zu erhalten

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Was bedeutet das konkret für Sie als Krebspatientin?

In Ihrem Fall ist eine Chemotherapie - nach dem heutigen Stand der wissenschaftlichen Erkenntnisse - Teil einer optimalen Behandlung Ihrer Erkrankung. Üblicherweise wird die Chemotherapie mit einer Kombination verschiedener Arzneimittel durchgeführt. Die für Sie vorgeschlagene Therapie sieht die Gabe von Paclitaxel (Taxol®) in Verbindung mit Carboplatin (Carboplat®) vor. Diese Therapie zeichnet sich, wie die Erfahrungen gezeigt haben, durch eine gute Wirksamkeit aus.

Es ist schwierig, die Wirkung der Krebsbehandlung auf die Krebszellen allein zu beschränken. Das hat zur Folge, dass auch gesunde Zellen geschädigt werden, was zu unangenehmen Nebenwirkungen führen kann.

Das Ausmaß der Nebenwirkungen bei der einzelnen Patientin bei gleich bleibender Wirksamkeit der Behandlung zu senken, ist das Ziel dieser Studie. Das bedeutet, dass Apotheker sich mehr als bisher üblich in die Gestaltung und Durchführung der Therapie einbringen und durch ihr Wissen Ihnen als Patientin einen weiteren Nutzen bringen sollen.

Wenn im Zusammenhang mit dieser Studie von Therapieverbesserung gesprochen wird, so ist damit vor allem die so genannte „Supportivtherapie“ gemeint. „Supportiv“ bedeutet im eigentlichen Sinne „unterstützend“. Auf die Therapie einer Krebserkrankung bezogen sind damit alle Behandlungsmaßnahmen gemeint, die zur Vorbeugung und/oder Therapie von unerwünschten Wirkungen (z. B. Übelkeit und Erbrechen) eingesetzt werden, die mit der eigentlichen Therapie der Krebserkrankung einhergehen können. Auf diese unterstützenden Therapien soll besonderes Augenmerk gerichtet werden.

Es soll an dieser Stelle ausdrücklich darauf hingewiesen werden, dass es sich bei der geplanten Studie zwar um eine klinische Prüfung handelt, jedoch **keine** neuen, noch nicht erprobten Arzneimittel zum Einsatz kommen.

Des weiteren möchten wir Sie darauf aufmerksam machen, dass sich die betreuende Apothekerin zwar mit Ihrer Arzneimitteltherapie befasst und diese gemeinsam mit Ihnen und den behandelnden Ärzten zu optimieren sucht, es aber keine Rolle spielt, woher Sie Ihre Arzneimittel beziehen. Sie können also auch während der Teilnahme an dieser Studie, so wie Sie es gewohnt sind, weiter bei den von Ihnen bevorzugten Apotheken die Arzneimittel beziehen.

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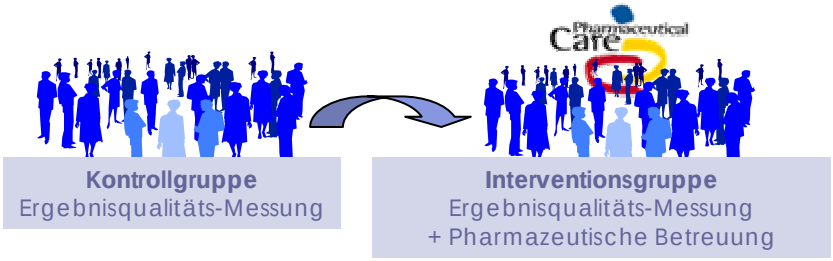
2. Konzept der Studie

a) Studiendesign

Der Ausdruck „Studiendesign“ beschreibt, welche Untersuchungs-Methode der Studie zugrunde liegt und auf welche Weise die Ergebnisse zustande kommen sollen.

Diese Studie basiert auf dem sogenannten *„ sequenzierten Kontrollgruppen-Design“*.



Dieser Ausdruck bedeutet, wie auch aus der oben gezeigten Grafik hervorgeht, dass zunächst nur eine Gruppe Patientinnen in die Studie aufgenommen wird, bei der die Therapie wie bisher üblich durchgeführt wird. Die Patientinnen dieser *„Kontrollgruppe“* werden gebeten, bestimmte Fragebögen zu festgelegten Zeitpunkten auszufüllen. Außerdem werden alle möglicherweise auftretenden Nebenwirkungen von den Ärzten in speziell für die Studie erarbeiteten Dokumentationsbögen festgehalten. Dieses Verfahren ist notwendig, um Vergleichswerte zu erhalten, die es später ermöglichen, Veränderungen, die durch die neu eingesetzte Betreuungsmaßnahme eingetreten sein könnten, zu messen.

Sobald diese Vergleichswerte vorliegen, wird die nächste Gruppe Patientinnen in die Studie aufgenommen. Diese Patientinnen gehören der *„Interventionsgruppe“* an. Diese Patientinnen werden zusätzliche durch die Studienapothekerin betreut. Eine genaue Beschreibung des Betreuungs-ablaufes finden Sie unter Punkt 3. dieses Heftes. Auch diese Patientinnen werden gebeten, die gleichen Fragebögen zu den gleichen Zeitpunkten im Laufe ihrer Therapie auszufüllen, wie vorher die Patientinnen in der Kontrollgruppe.

Auch bei Patientinnen der Interventionsgruppe werden von den behandelnden Ärzten alle möglicherweise auftretenden Nebenwirkungen genau aufgezeichnet. Abschließend werden die Ergebnisse der Fragebögen und Aufzeichnungen beider Gruppen verglichen. Dieser Vergleich wird dann zeigen, ob die zusätzliche Betreuung durch einen Apotheker für Krebspatientinnen einen Nutzen hat, oder nicht.

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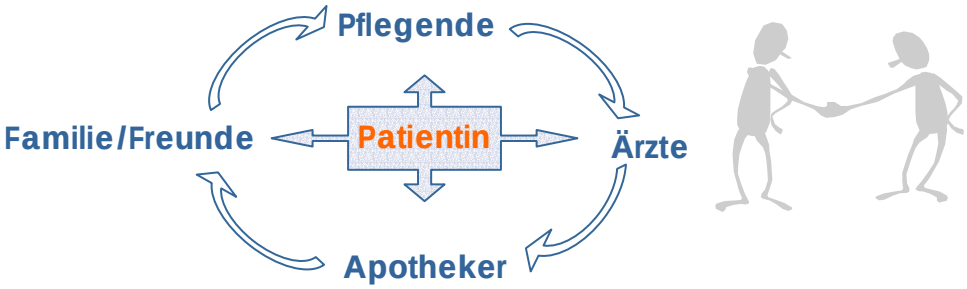
b) Kommunikation

Rund um die Therapie Ihrer Erkrankung sind viele Menschen in sehr unterschiedlichen Funktionen darum bemüht, Ihnen die bestmögliche Versorgung zukommen zu lassen. Im Zusammenhang mit dieser Studie sind es mehr Personen als in der allgemeinen Praxis üblich. Es wird daher angestrebt, alle an Ihrem Betreuungsprozess Beteiligten in ein Kommunikationsnetzwerk einzubinden (siehe Grafik). Dadurch soll gewährleistet werden, dass keine wichtigen Informationen verloren gehen, die für Ihre Behandlung von Bedeutung sein könnten.



3. Ablauf der Studie

Die Betreuung findet im Rahmen Ihrer Chemotherapie statt.
Die Studien-Apothekerin steht zur Beantwortung aller aufkommenden Arzneimittel-bezogenen Fragen zur Verfügung und wird versuchen, die Therapie in Abstimmung mit dem Arzt und Ihnen als Patientin zu verbessern.
Eine fortlaufende Dokumentation der aktuellen Medikation ist erforderlich, um einen Überblick zu bekommen, wie die Arzneimittel vertragen werden.
Die Daten werden ständig verarbeitet und ausgewertet, so dass eine bestmögliche Therapiegestaltung erfolgen kann.
Der Nutzen der durchgeführten Betreuung soll durch einen Vergleich mit der bisherigen Betreuungssituation gezeigt werden. Hierzu soll die Qualität der durchgeführten Betreuung mit verschiedenen Fragebögen zu Lebensqualität, Arzneimittelnebenwirkungen und Patienten-Zufriedenheit überprüft werden .
Die Pharmazeutische Betreuung im Rahmen dieser Studie wird von einer Apothekerin durchgeführt, die als wissenschaftliche Mitarbeiterin an der Universität Bonn tätig ist. Der Kontakt zu ihr wird über Ihren behandelnden Arzt hergestellt, der Sie auch über die Möglichkeit informiert hat, an dieser Studie teilzunehmen.

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a) Studienverlaufsplan

Die Betreuung soll sich dadurch auszeichnen, dass sie Ihren individuellen Bedürfnissen gerecht wird. Einen Eindruck, wie Sie sich den Ablauf dieser Studie in etwa vorstellen können, soll der folgende Studienverlaufsplan vermitteln.

Im **Aufklärungsgespräch** werden Sie von der betreuenden Apothekerin über die Ziele und Hintergründe der geplanten Studie informiert.

- ◊ In diesem Gespräch sollte Ihnen vermittelt werden, was Sie von der Studie erwarten können und was als Patientin auf Sie zukommt.
- ◊ Sie erhalten Informationsmaterial zur Studie, welches Sie zu Hause in Ruhe lesen können, bevor Sie eine Entscheidung über Ihre Teilnahme treffen.

Im Verlauf dieses Gespräches haben Sie die Gelegenheit, Fragen zu stellen und sich Dinge erläutern zu lassen, die Ihnen unklar erscheinen.

Im **folgenden Gespräch** können Sie Ihre Entscheidung mitteilen, ob Sie bereit sind, an der Studie teilzunehmen, oder lieber davon absehen möchten. Zuvor besteht die Möglichkeit, weitere Fragen zu klären.
Falls Sie bereit sind, an der Studie teilzunehmen

- ◊ werden Sie gebeten, Ihr Einverständnis zur Teilnahme an der Studie schriftlich zu bestätigen.
- ◊ werden Sie gebeten Ihr Einverständnis zur Speicherung Ihrer persönlichen Daten schriftlich zu bestätigen.
- ◊ werden Ihnen die Studienunterlagen (z.B. Fragebögen) ausgehändigt und vollständig erläutert sowie Ihre Fragen diesbezüglich beantwortet.

⇒ Die Patientinnen der Kontrollgruppe werden von diesem Gespräch an hauptsächlich telefonisch mit der Studien-Apothekerin in Kontakt stehen, wenn es zum Beispiel um das Ausfüllen der Fragebögen geht. Außerdem werden auch von ihnen bestimmte personenbezogene Daten erhoben (z. B. Alter usw.)

⇒ Für die Patientinnen der Interventionsgruppe verläuft der Betreuungsplan etwa wie folgt:

- ◊ Zunächst wird ein Termin und der Ort für das erste Betreuungsgespräch vereinbart.

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Das **erste Betreuungsgespräch** sollte vor dem ersten Therapiezyklus stattfinden. Wenn dies nicht möglich sein sollte, wird ein anderer passender Termin gesucht. Während des Gespräches ist geplant

- ◊ Ihre persönlichen Daten, die für die Betreuung sinnvoll sind (z.B. Alter u.ä.) aufzunehmen.
- ◊ eine Übersicht über die Arzneimittel, die Sie regelmäßig einnehmen, zu erstellen.
- ◊ Fragen zur Arzneimitteltherapie zu klären.
- ◊ Ihre persönlichen Ziele und Hoffnungen verbunden mit der Arzneimitteltherapie zu erörtern und daraus gemeinsam einen Plan zu erstellen.

Für die jeweils verabredeten Termine wird Ihnen ein Terminplan mitgegeben.

Die **folgenden Betreuungsgespräche** sollten möglichst mindestens ein Mal zwischen den Therapiezyklen stattfinden. Während dieser Gespräche werden

- ◊ in der Zwischenzeit aufgekommene Fragen zur Arzneimitteltherapie geklärt.
- ◊ Probleme und Wünsche im Zusammenhang mit der Arzneimitteltherapie gemeinsam erörtert.
- ◊ Ziele gesteckt, um Ihren Bedürfnissen bestmöglich gerecht zu werden.
- ◊ Sie über zusätzliche Maßnahmen informiert, die Sie zur Vermeidung von Nebenwirkungen, die möglicherweise eintreten können, ergreifen können (z.B. gegen Übelkeit und Erbrechen).

Die Betreuung im Rahmen der Studie endet nach dem letzten Zyklus der derzeit verordneten Chemotherapie.

b) Ergebnisqualitätsmessungen

Die im folgenden vorgestellten Fragebögen stellen die „Messinstrumente“ dar, mit denen ermittelt werden soll, ob die Pharmazeutische Betreuung in diesen Punkten eine Verbesserung herbeiführen kann. Die Fragebögen sind so konzipiert, dass Sie von den Patientinnen selbständig ausgefüllt werden können.

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i. Fragebogen zur Messung der Lebensqualität

Man stellt immer wieder fest, dass die Lebensqualität der Patientinnen für den Therapieverlauf von entscheidender Bedeutung ist. Um einen Eindruck zu bekommen, inwieweit die Therapie Einfluss auf die Lebensqualität hat, soll zu dieser Fragestellung ein Fragebogen ausgefüllt werden. Dieser Fragebogen wurde speziell für Krebspatienten entwickelt. Während der Studienphase wird der Fragebogen zu drei Zeitpunkten ausgefüllt.

ii. Fragebogen zur Messung von Übelkeit und Erbrechen

Da die Nebenwirkungen bei jeder Patientin unterschiedlich sein können und auch anders empfunden werden, soll mit Hilfe eines Fragebogens zu Übelkeit und Erbrechen ermittelt werden, wie gut in jedem einzelnen Fall die Maßnahmen zur Vermeidung dieser Nebenwirkungen greifen. Dieser Fragebogen soll nach jedem Zyklus über 5 Tage (wie eine Art Tagebuch) geführt werden. Dadurch soll erfasst werden, ob sowohl das akute Erbrechen (innerhalb der ersten 24 Stunden nach Beginn eines Therapiezyklus), als auch das verzögerte Erbrechen (Tag 2 bis 5 nach Beginn eines Therapiezyklus) zufriedenstellend behandelt wird. Die Einträge erfolgen strichlistenartig, so dass kein allzu großer Zeitaufwand zu befürchten ist.

iii. Fragebogen zur Messung der Patientenzufriedenheit mit der Information zu ihrer Behandlung

Nicht zuletzt ist auch Ihre Zufriedenheit ein Ziel der Studie. Es ist das Anliegen der Apotheker, die Betreuung möglichst nach Ihren Bedürfnissen zu gestalten. Um die Qualität der Betreuung festzustellen, soll nach Beendigung der Studie die Patientenzufriedenheit ermittelt werden. Hierbei wird ein besonderes Augenmerk auf die Information gelegt, die Sie zu Ihrer Behandlung erhalten. Anhand der ermittelten Ergebnisse können Strategien entwickelt werden, wie Patienten gemäß Ihrer individuellen Bedürfnisse informiert werden sollten. Dieser Fragebogen wird nur einmal, am Ende der Behandlung, ausgefüllt.

iv. Verlaufsplan–Ergebnisqualitätsmessungen

Der Verlaufsplan gibt Ihnen eine Übersicht über die verschiedenen Ergebnisqualitätsmessungen über den gesamten Zeitraum der Studie.

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c) Therapeutisches Drug Monitoring

Der Ausdruck „Therapeutisches Drug Monitoring“ kommt aus dem Englischen und wird für eine Methode verwendet, bei der die Arzneistoff-Konzentrationen im Blut des Patienten zu festgelegten Zeitpunkten bestimmt werden. Häufig können aus diesen Werten Rückschlüsse auf den Werdegang des Arzneistoffs im individuellen Patienten gezogen werden, was bei der Anpassung der Arzneistoff-Dosis hilfreich sein kann.

Im Rahmen dieser Studie soll patientenindividuell überprüft werden, ob zwischen den im Blut der einzelnen Patientin auftretenden Konzentrationen Arzneistoff und den eintretenden Nebenwirkungen ein Zusammenhang besteht. Diese Information soll helfen in Zukunft die individuelle Dosierung der untersuchten Arzneistoffe zu optimieren.

Für diese Untersuchung ist es erforderlich, zusätzlich zu den Routineuntersuchungen 2 weitere Blutproben von je maximal 10 ml zu entnehmen, aus denen die Konzentrationen der Arzneistoffe (Paclitaxel und Carboplatin) bestimmt werden.

Um aussagefähige Messwerte zu erhalten, ist es notwendig, die Proben aus einer von der Injektionsstelle verschiedenen Stelle zu entnehmen.

Die Zeitpunkte der Entnahme liegen im Fall der ersten Probe direkt im Anschluss an die Beendigung der Infusionen, während die zweite Probe etwa 3 Stunden nach der ersten Probe entnommen wird.

Die Blutproben werden in der Praxis ihres Onkologen, oder in der Ambulanz des Krankenhauses entnommen, in der Sie betreut und behandelt werden.

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4. Schutz der Patientin

Die Teilnahme an dieser Studie birgt für Sie keine zusätzliche Risiken.

Sie haben selbstverständlich das Recht, jederzeit und ohne Angabe von Gründen von der Teilnahme an der Studie zurückzutreten. Es entstehen Ihnen dadurch keine Nachteile in Ihrer Behandlung.

a) Patienteneinverständnis

Wenn Sie dieses Informationsmaterial eingehend gelesen haben und die Ihnen aufgekommenen Fragen beantwortet wurden, können Sie frei über die Teilnahme an der Studie entscheiden. Ihre Teilnahme bestätigen Sie schriftlich mit einer so genannten Patienten-Einverständniserklärung.

b) Datenschutz

Die Information, die Sie bisher über diese Studie erhalten haben, lässt schon vermuten, dass eine Vielzahl von Daten über Ihre Person im Zusammenhang mit dieser Studie erfasst werden sollen. Das geschieht allerdings erst, wenn Ihr schriftliches Einverständnis dazu vorliegt.

Zum einen sollen bestimmte, für die Betreuung notwendige Daten aus Ihrer vom Arzt geführten Patientenakte übertragen werden (z.B. Laborwerte u. ä.). Dann sollen hilfreiche Informationen, die gemeinsam mit Ihnen im Gespräch erörtert werden, gespeichert werden (z.B. Schwierigkeiten oder Unsicherheiten mit der Arzneimitteltherapie). Außerdem sollen Daten gespeichert werden, die neben Ihrer Betreuung speziell zur Auswertung der Studie benötigt werden. Das sind zum Beispiel die Ergebnisse der Fragebögen.

Alle Informationen, die zu Ihrer Person erfasst werden sollen, werden in einer Computergestützten Datenbank gespeichert. Diese Datenbank wurde speziell für diese Studie entwickelt und unterstützt die Apothekerin bei Ihrer Aufgabe Sie umfassend zu betreuen. Die Ergebnisse der Studie sollen mit einem Statistikprogramm (SPSS®) ausgewertet werden. Dadurch soll auch in Zahlen dargestellt werden können, ob die Betreuung durch Apotheker einen Nutzen gezeigt hat.

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Die im Zusammenhang mit dieser Studie erhobenen Daten unterliegen den Bestimmungen des Datenschutzes und werden ausschließlich zum Zweck der Durchführung der Studie erhoben und ausgewertet. Das bedeutet, dass Sie der Verwendung Ihrer Daten für Studienzwecke zustimmen müssen, bevor mit der Dokumentation begonnen wird.

Außerdem ist gewährleistet, dass aus Veröffentlichungen der in der Studie erhobenen Daten Ihr Name nicht hervorgeht. Die **Ergebnisse der Studie** werden anonymisiert veröffentlicht und stehen Ihnen dann selbstverständlich auf Anfrage zur Verfügung.

Nach dem Landesdatenschutzgesetz ist die Durchführung einer solchen Studie jedoch nur zulässig, wenn Sie sich mit der Aufzeichnung Ihrer Krankheitsdaten und deren Weitergabe an die zentrale Auswertungsstelle einverstanden erklären. Die zentrale Anlaufstelle dieser Studie ist die Abteilung Klinische Pharmazie an der Universität Bonn. Dort werden alle für Ihre Betreuung und für die abschließende Auswertung der Studie notwendigen Daten zusammenlaufen.

c) Versicherungsschutz

Für die Studie besteht eine Patientenversicherung bei Gerling Industrie Service GmbH West, Düsseldorf unter der Versicherungs-Nummer 70-005539942-2. Um den Versicherungsschutz nicht zu gefährden, darf eine andere medizinische Behandlung nur mit dem Einverständnis des Prüfarztes durchgeführt werden. Eine Gesundheitsschädigung, die als Folge der Therapie eingetreten sein könnte, sollten Sie unverzüglich Ihrem Arzt melden.

Sollten Sie nach der Lektüre dieser Informationen weitere Fragen haben, wenden Sie sich bitte jederzeit an Ihren behandelnden Arzt, oder Ihre betreuende Apothekerin.

Sollten Sie nach der Lektüre dieser Informationen weitere Fragen haben, wenden Sie sich bitte jederzeit an Ihren behandelnden Arzt, oder Ihre betreuende Apothekerin.

Appendix F

Informed consent

Pharmazeutische Betreuung onkologischer Patienten vor, während und nach ambulanter Chemotherapie Patienten-Einverständniserklärung

Hiermit erkläre ich, _____, an der oben genannten Studie teilzunehmen.

Ich bestätige, dass ich von Dr. med._____ und der/dem Apotheker(in) _____ in Anwesenheit des Zeugen _____ über diese Studie aufgeklärt wurde. Mir wurde ausreichend Zeit für die Entscheidung über die Teilnahme an der Studie eingeräumt.

Ich bin bereit, die an mich ausgegebenen Fragebögen zu "Lebensqualität", "Übelkeit und Erbrechen" und „Patientenzufriedenheit“ ordnungsgemäß auszufüllen und die Beratungstermine mit der Prüfapothekerin wahrzunehmen.

Ich bin damit einverstanden, dass mir jeweils am Tag der Chemotherapie zwei zusätzliche Blutproben entnommen werden.

Ich wurde darüber aufgeklärt, dass ich die Teilnahme an dieser Untersuchung ablehnen kann und dass mir aus der Ablehnung keine Nachteile für die weitere Therapie entstehen.

Ich habe ein Exemplar des Aufklärungsbogens und dieser Einwilligungserklärung erhalten. Die Aufklärung über die Studie war mir in allen Punkten verständlich.

_____ , den	_____	_____
Ort	Datum	Unterschrift der Patientin
_____	_____	_____
Unterschrift des Arztes	Unterschrift des Apothekers	Unterschrift des Zeugen

Rheinische Friedrich-Wilhelms-Universität Bonn
Pharmazeutisches Institut, Klinische Pharmazie
Prof. Dr. Ulrich Jaehde

Appendix G

Privacy statement

Pharmazeutische Betreuung onkologischer Patienten

vor, während und nach ambulanter Chemotherapie

Datenschutz-Erklärung

Ich, _____, erkläre mich damit einverstanden, dass meine im Rahmen des Projektes erhobenen Krankheitsdaten (Studiendaten) aufgezeichnet und zur Überprüfung an die Studienzentrale zur Auswertung weitergegeben werden. Ich bin damit einverstanden, dass vom Projektleiter bevollmächtigte Personen meine originalen Krankenakten sowie die originalen Studiendaten beim Prüfarzt einsehen.

Ich erkläre außerdem, dass ich mit der im Rahmen der Studie erfolgenden Aufzeichnungen von Krankheitsdaten/Studiendaten und ihrer anonymisierten Weitergabe zur Überprüfung an die zuständige Überwachungsbehörde und, soweit es sich um personenbezogene Daten handelt, mit deren Einsichtnahme durch zur Verschwiegenheit verpflichtete Beauftragte oder der Behörden einverstanden bin. Hierbei wird §4, Abs. 3 des Landesdatenschutzgesetzes berücksichtigt.

_____ , den _____ _____

Ort Datum Unterschrift der Patientin

Rheinische Friedrich-Wilhelms-Universität Bonn
Pharmazeutisches Institut, Klinische Pharmazie
Prof. Dr. Ulrich Jaehde

Appendix H

Coding system of drug-related problems: PI-Doc®, Version September 2000

Tab. H-1 Main groups of drug-related problems (Schaefer, 2002)

A	Inappropriate drug choice
A1	Unsuitable drug for indication
A2	Physiological contraindication not considered
A3	Contraindication by other disease not considered
A4	Unintended use of two drugs with the same active substance
A5	Unintended use of two drugs from the same therapeutic group
A6	Missing or wrong application aids
A7	Wrong strength
A8	Unsuitable preparation
A9	Unsuitable package size
A10	Wrong spelling of the brand name on unreadable prescription
A11	Drug out of the market
C	Inappropriate drug use by the patient/compliance
C1	Insufficient knowledge about the application of the drug
C2	Handling problems
C3	Patient uses drug without an indication
C4	Patient does not use a recommended drug (primary non-compliance)
C5	Self-reliant change of the recommended dose by the patient
C6	Unsuitable period of use
C7	Unsuitable time of application
C8	No or insufficient drug monitoring, where necessary
D	Inappropriate dosage
D1	Patient does not know his or her dosage
D2	No strength given, when more than one available
D3	Overdosage
D4	Underdosage
D5	Unsuitable dosage intervals

to be continued on the next page

E	Drug–drug interaction
E1	Reference to an interaction by literature
E2	Symptoms of an interaction
E3	Patient's fear of an interaction
F	Adverse drug reaction
F1	Patient's fear of adverse drug reactions
F2	Symptoms of an adverse drug reaction
F3	Medication stopped due to unacceptable adverse drug reaction
G	Other problems
Patient-related	
GP1	Limited knowledge about the nature of the disease
GP2	Non-specific fear of drug use in general
GP3	Dissatisfaction with current treatment
GP4	Unsuitable lifestyle of the patient
GP5	Patient does not want to change his or her medication
GP6	Patient does not receive a drug although an indication exists
Physician-related	
GA1	Missing or incomplete information about drug use by the prescribing physician
Communication-related	
GC1	Text of the package insert is too difficult to understand
GC2	Information supplied by other health care professionals misinterpreted
GC3	Language problems
Technical and/or logistical	
GT1	Prescription for the wrong patient
GT2	Problems with the sickness funds (refunding)
GT3	Incomplete prescription
GT4	Special distribution activities to get certain medicines
GT5	Damaged packages, devices or application aids

Tab. H-2 Main groups of drug-related interventions (Schaefer, 2002)

I	General interventions
I0	Checking factual databases, books etc.
I1	Interview and counselling
I1a	Interviewing and counselling of the patient
I1b	Interview and counselling of the patient's relatives
I1c	Educational programme for the patient
I2	Contacting the physician
I3	Referrals
I3a	Refer a patient to a general practitioner
I3b	Refer a patient to a specialist
I3c	Refer a patient to self-help groups
I3d	Recommending other health care professionals
I4	Filling out a medication box for the patient in the pharmacy
IA	Intervention: inappropriate drug choice
IA1	Selecting or recommending an appropriate drug for the indication
IA2	Clarification with regard to a physiological contraindication
IA3	Clarification with regard to a contraindication due to concomitant diseases
IA4	Clarification of use of two drugs with the same active substance
IA5	Clarification of use of two drugs of the same therapeutic group
IA6	Clarification with regard to missing or wrong application aids
IA7	Determination of the appropriate strength
IA8	Determination of the appropriate administrative form
IA9	Determination of the appropriate package size
IA10	Clarification of a wrong spelling or unreadable prescription
IA11	Clarification with regard to a prescribed drug which is out of the market

to be continued on the following page

IC	Intervention: inappropriate drug use by the patient/compliance
IC1	Advice for correct application
IC2	Demonstration of the correct application, practicing with the patient
IC3	Information about the risk of drug use without appropriate indication
IC4	Searching for the reasons for primary non-compliance and counselling
IC5	Searching for the reasons to change a recommended dosage by the patient and counselling
IC6	Advice with regard to optimal duration of use
IC7	Advice with regard to optimal time of application
IC8	Initiating drug monitoring, information for the physician
ID	Intervention: inappropriate dosage
ID1	Advice to the patient with regard to dosing
ID2	Clarification with regard to the correct strength
ID3	Clarification with regard to an overdosage
ID4:	Clarification with regard to an underdosage
ID5	Clarification with regard to suitable dosage intervals
IE	Intervention: drug interactions
IE1	Attempt to clarify the clinical relevance of a drug interaction
IE2	Observation of the symptoms of an interaction
IE3	Advice to the patient in fear of an interaction
IE4	Information about possible interactions and countermeasures
IF	Intervention: adverse drug reaction (ADR)
IF1	Counselling patients fearing adverse drug reactions
IF2	Documentation of symptoms of an adverse drug reaction
IF3	Suggesting a change in medication to the physician
IG	Intervention: other problems

to be continued on the following page

Patient-related	
IGP1	Information from the patient about the nature of a disease
IGP2	Reducing fears and prejudices of a drug therapy
IGP3	Searching for reasons for dissatisfaction with current treatment
IGP4	Advice to the patient with regard to a health-supporting life style
IGP5	Clarification of the difference between a former and a current drug
IGP6	Advice with regard to treatment opportunities of ailments/recommendation to see a physician
Physician-related	
IGA1	Information to the physician about changes of the drug assortment
Communication-related	
IGC1	Explanation of the package insert
IGC2	Evaluation of information from different sources
IGC3	Clarification of language problems
Technical and logistical problems	
IGT1	Clarifying whether the patient got the right prescription
IGT2	Clarification with the sickness fund
IGT3	Clarification with regard to an incomplete or unreadable prescription
IGT4	Measures taken to obtain certain drugs for the patient (esp. from abroad)
IGT5	Replacement of damaged packages, devices or application aids

Appendix I

Care material

Patient information on expected side effects

Chemotherapie und die Nebenwirkungen

Sehr geehrte Patientin,

im Rahmen Ihrer Behandlung bekommen Sie eine Chemotherapie. Anders als die Operation und die Strahlentherapie wirken die in der Chemotherapie eingesetzten Wirkstoffe im ganzen Körper (systemisch), da sie über das Blut verteilt werden. Die Wirkstoffe sind gegen möglicherweise im Körper verteilte Krebszellen gerichtet. Die Wirkstoffe können jedoch nicht zwischen kranken und gesunden Zellen unterscheiden, so dass auch gesunde Zellen betroffen sein können. Das führt zu unerwünschten Nebenwirkungen. Hiervon sind hauptsächlich die Zellen in Ihrem Körper betroffen, die sich häufig teilen und dadurch erneuern. Dazu gehören zum Beispiel Haarzellen, Schleimhautzellen des Mundes und des Magen-Darmtraktes, Hautzellen und auch Zellen des Knochenmarks, welches Ihr Blut bildet.
Wichtig für Sie zu wissen ist, dass nicht alle der beschriebenen Nebenwirkungen auch tatsächlich auftreten. Falls es jedoch dazu kommen sollte, ist es gut, wenn Sie bereits davon gehört haben und wissen, was Sie dagegen tun können.
Im Zweifel sprechen Sie Ihren betreuenden Arzt an und unterrichten ihn genau über die Nebenwirkung und die Maßnahmen, die Sie dagegen eingeleitet haben.

Die Wirkstoffe, die Sie in Ihrer Chemotherapie erhalten, heißen: Epirubicin
Cyclophosphamid

Die Wirkstoffe werden eigens für Sie dosiert und die Infusionslösung wird speziell für Sie hergestellt.

Mögliche Nebenwirkung	Vorbeugende Maßnahmen	Im Falle des Falles
Übelkeit und Erbrechen (Nausea und Emesis)	oVorbeugende Medikation wie verordnet einnehmen (nicht nur im Bedarfsfall!) oGenerell gilt: Essen Sie, worauf Sie Appetit haben!! oGroße Mahlzeiten vermeiden; 5-6 kleinere Mahlzeiten pro Tag essen oKalte Speisen werden häufig besser toleriert als warme, ebenso gekühlte Flüssigkeiten oAppetit durch säuerliche Bonbons, Speisen oder Getränke anreizen oAusreichend frische Luft oSchlaf, entspannende Musik oder Spaziergänge im Freien oSüße, fette, stark gewürzte und gebratene Speisen vermeiden oStarke Gerüche vermeiden	oViel frische Luft zuführen oAusruhen oBedarfsmedikation einnehmen oAusreichend trinken
Durchfall (Diarrhoe)	oBei Durchfallneigung Ernährung umstellen (auf z.B. Weißbrot, Kartoffeln, Bananen, Äpfel, Mais usw.) oVermeiden: Süßstoffe, Vollkornbrot, Kaffee, stark gewürzte Speisen, Fruchtsäfte, Obst (mit Ausnahmen s. o.), rohe Milch oMineralwässer mit geringem Sulfatgehalt (SO_4)trinken	oAusreichend trinken oUrsache mit dem Arzt klären, evtl. Medikamente (Loperamid) einnehmen oWeiches Toilettenpapier und feuchte Tücher verwenden
Verstopfung (Obstipation)	oAusreichend trinken! (Pflaumensaft, Tee, Wasser) oBewegung (z.B. Spazieren gehen) oJedem Reiz, zur Toilette zu gehen, nachgeben oBallaststoffreiche Ernährung (Vollkornbrot, Gemüse, Weizenkleie usw.)	oUrsache mit dem Arzt klären, evtl. Abführmittel einnehmen oViel trinken!
Entzündungen im Mundraum (Mukositis)	oZahnsanierung beim Zahnarzt oGründliche, schonende Mundhygiene oWeiche Zahnbürsten verwenden oAlkoholfreie Mundwässer verwenden oSpülung mit lauwarmem Salbeitee oZahnreinigende Kaugummis zur Speichelanregung kauen oAusreichend trinken oNikotin und Alkohol vermeiden oScharfe, heiße und sehr saure Speisen vermeiden	oBei Anzeichen einer Mundschleimhautentzündung rechtzeitig den Arzt informieren oMundhygiene entsprechend der Vorbeugung fortsetzen oVom Arzt verordnete entzündungshemmende und schmerzlindernde Spüllösungen und Pinselungen verwenden oWeiche Speisen bevorzugen oEiswürfel aus Ananassaft lutschen oZusätzliche Verletzungen vermeiden

Mögliche Nebenwirkung	Vorbeugende Maßnahmen	Im Falle des Falles
Haarausfall (Alopezie)	Haarausfall ist leider nicht durch vorbeugende Maßnahmen zu vermeiden oder zu lindern. Sorgen Sie vorsorglich für geeigneten Haarersatz oder Kopfbedeckung anderer Art, die Ihnen gefällt. Die Haare werden nach Beendigung der Therapie wieder zu wachsen beginnen.	oKopfhaut vor Kälte, Hitze und direkter Sonneneinstrahlung schützen oBei Verlust der Wimpern, das Auge vor intensivem Licht und Staub bewahren
Infektionen	oAusreichende Ruhephasen oUngekochtes Obst/Gemüse vermeiden oGründliche Körperhygiene oKontakt meiden zu: -Menschen mit ansteckenden Erkrankungen -Frisch geimpften Menschen	oBei Fieber > 38°C sofort den Arzt verständigen! oErkältungsanzeichen genau beobachten oBei längerer Heilungsdauer üblicher Erkrankungen den Arzt aufsuchen oVom Arzt verordnete Antibiotika regelmäßig und gemäß der Verordnung einnehmen
Blasenentzündung (Zystitis)	oViel trinken oDen Drang zur Blasenentleerung nicht unterdrücken. Wenn immer möglich Blase entleeren. oNikotin, Koffein, Alkohol und scharfe Gewürze vermeiden oMilchprodukte essen	oBei Schmerzen beim Wasser lassen und häufigem Harndrang den Arzt informieren oBei Krämpfen eventuell Wärmeanwendung durch Heizkissen oKeine Sitzbäder machen oSorgfältige Intimhygiene oSlipeinlagen verwenden
Müdigkeit und Erschöpfung (Fatigue)	oEntspannungsübungen oRuhephasen einplanen oAngemessene körperliche Bewegung (Spaziergänge im Freien) oKoffein und Alkohol vor dem Einschlafen vermeiden oAlltagspflichten auf andere übertragen (z.B. Familienmitglieder)	oBei länger anhaltender Erschöpfung und Müdigkeit, die auch durch ausreichende Ruhepausen nicht deutlich verringert wird, den Arzt informieren oVorbeugende Maßnahmen weiter verfolgen

Appendix J

Questionnaires

EORTC QLQ-C30 (v. 3.0)

German

EORTC QLQ-C30 (version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen" oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Bitte tragen Sie Ihre Initialen ein:

Ihr Geburtstag (Tag, Monat, Jahr):

Das heutige Datum (Tag, Monat, Jahr):

		Überhaupt nicht	**Wenig**	**Mäßig**	**Sehr**
1.	Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)	1	2	3	4
2.	Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3.	Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke ausser Haus zu gehen?	1	2	3	4
4.	Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5.	Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:		**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
6.	Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7.	Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8.	Waren Sie kurzatmig?	1	2	3	4
9.	Hatten Sie Schmerzen?	1	2	3	4
10.	Mussten Sie sich ausruhen?	1	2	3	4
11.	Hatten Sie Schlafstörungen?	1	2	3	4
12.	Fühlten Sie sich schwach?	1	2	3	4
13.	Hatten Sie Appetitmangel?	1	2	3	4
14.	War Ihnen übel?	1	2	3	4
15.	Haben Sie erbrochen?	1	2	3	4

to be continued on the following page

Continuation

German

Während der letzten Woche:		**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
16.	Hatten Sie Verstopfung?	1	2	3	4
17.	Hatten Sie Durchfall?	1	2	3	4
18.	Waren Sie müde?	1	2	3	4
19.	Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20.	Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21.	Fühlten Sie sich angespannt?	1	2	3	4
22.	Haben Sie sich Sorgen gemacht?	1	2	3	4
23.	Waren Sie reizbar?	1	2	3	4
24.	Fühlten Sie sich niedergeschlagen?	1	2	3	4
25.	Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26.	Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27.	Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28.	Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

Appendix

Nausea and emesis questionnaire including patient information

Rheinische-Friedrich-Wilhelms Universität Bonn
Pharmazeutisches Institut
Klinische Pharmazie
Prof. Dr. U. Jaehde

Sehr geehrte Patientin,

die Chemotherapie, die Sie bekommen wird häufig von Übelkeit und Erbrechen begleitet. Um diesen sehr unangenehmen Nebenwirkungen vorzubeugen, hat Ihnen Ihr behandelnder Arzt einige Medikamente verordnet, die, wenn sie in der vorgesehenen Art und Weise eingenommen werden, eine optimale Wirkung erzielen, damit Sie auch während Ihrer Therapie ein Leben mit Lebensqualität führen können.

Um einen Eindruck zu bekommen, wie gut die ausgewählte Therapie bei Ihnen Wirkung zeigt und ob es eventuell sinnvoll ist, Veränderungen vorzunehmen, bitten wir Sie, diesen Fragebogen sorgfältig auszufüllen.

1. Tragen Sie bitte in der Zeile „Erbrechen“ in Form einer Strichliste ein, wie oft Sie sich übergeben bzw. würgen mussten.
   (Einzelne Ereignisse liegen etwa 1 Minute auseinander. Wenn Sie länger als 5 Minuten kontinuierlich erbrechen und/oder würgen müssen, wird ab 5 Minuten ein neues Ereignis gezählt. Beispiel: 7 Minuten = 2 Ereignisse)
   Berücksichtigen Sie bitte die Uhrzeit, zu der das Ereignis eingetreten ist und machen Sie in der entsprechenden Spalte einen Strich.
1. In Folge der Chemotherapie muss es nicht zwingend zum Erbrechen kommen.
   In den ersten Tagen nach der Behandlung kann es allerdings gelegentlich zu Gefühlen von Übelkeit kommen.
   Die Stärke der Übelkeit kann unterschiedlich ausgeprägt sein.
   - **0** Ich empfinde keine Übelkeit
   - **1** Die empfundene Übelkeit ist nur **leicht** und beeinträchtigt mich nicht in meinem normalen Tagesablauf
   - **2** Die empfundene Übelkeit ist **mäßig** und beeinträchtigt mich in meinem normalen Tagesablauf.
   - **3** Die empfundene Übelkeit ist **schwer** und beeinträchtigt mich in meinem normalen Tagesablauf
   - **4** Die empfundene Übelkeit ist **schwer** und macht einen normalen Tagesablauf unmöglich.
3. Alle unmarkierten Felder werden als ereignisfrei gewertet.

Rheinische Friedrich-Wilhelms-Universität Bonn
Pharmazeutisches Institut
Klinische Pharmazie
Prof. Dr. U. Jaehde

Fragebogen zu Übelkeit und Erbrechen im Rahmen des Projektes „Pharmazeutische Betreuung onkologischer Patienten“

Name:_____ Geb. Datum:_____ Behandelnder Arzt:_____

Therapieschema:_____ Zyklus:_____ Antiemetische Therapie:_____

Tag 1 _____

Uhrzeit		morgens 7:00 – 10:00 Uhr	vormittags 10:00 – 12:00 Uhr	mittags 12:00 – 15:00 Uhr	nachmittags 15:00 – 18:00 Uhr	abends 18:00 – 22:00 Uhr	nachts 22:00 – 7:00 Uhr
Erbrechen							
	0						
	1						
Übelkeit	**2**						
	3						
	4						
Medikation							

Bitte beschreiben Sie Ihre Übelkeit kurz mit eigenen Worten:

_____

_____

Patient satisfaction questionnaire (PS-CaTE)

Rheinische-Friedrich-Wilhelms
Universität Bonn
Pharmazeutisches Institut
Klinische Pharmazie
Prof. Dr. U. Jaehde

Untersuchung der Patientenzufriedenheit mit der Information zur Krebsbehandlung

Sehr geehrte Patientin,

mit diesem Schreiben bitten wir Sie, an einer von uns initiierten interessanten Studie teilzunehmen. Wir versuchen herauszufinden, wie zufriedenstellend die Informationen waren, die Sie (und andere Betroffene) bis zum heutigen Tage über Ihre Krebsbehandlung erhalten haben.

Mit dieser Untersuchung wollen wir zum einen feststellen, inwieweit die Bereitstellung von Informationen Ihren Erwartungen entspricht und wo Sie noch verbessert werden könnte. Zum anderen können uns Ihre Auskünfte und Anregungen dazu dienen, künftig bessere, auf Sie als Patienten zugeschnittene Informationsbroschüren zu entwickeln.

Die vorliegende Untersuchung gliedert sich in drei Abschnitte. Abschnitt eins fragt Sie anhand vorgegebener Aussagen nach Ihrer Meinung zu den erhaltenen Informationen. Abschnitt zwei beschäftigt sich mit den von Ihnen genutzten Informationsquellen. Schließlich werden in Abschnitt drei noch allgemeine Daten abgefragt, die für die wissenschaftliche Auswertung wichtig sind.

Alle Daten werden anonymisiert ausgewertet, deswegen ist es wichtig, dass sie weder Namen noch Anschrift auf einem der Bögen vermerken. Wir versichern Ihnen, dass zu keiner Zeit Rückschlüsse von den Daten auf eine bestimmte Person möglich sind.

Wir würden uns sehr freuen, wenn Sie uns Ihre Kommentare und Vorschläge auf der letzten Seite mitteilten.

Wir bedanken uns schon im Voraus für Ihre Mithilfe und Ihre Mühe.

Mit freundlichen Grüßen

Ihre

Meike Eckhardt
(Diplomandin)

Andrea Liekweg
(Wissenschaftliche Mitarbeiterin)

Bei Rückfragen stehen wir Ihnen gerne zur Verfügung.

to be continued on the following page

Fragebogen zur Patientenzufriedenheit mit der Information zur Krebsbehandlung
Information zur Zufriedenheit

Bitte kreuzen Sie bei jeder der folgenden Aussagen eine Zahl an. Sie drückt aus, wie stark Sie mit der jeweiligen Aussage übereinstimmen oder nicht übereinstimmen.

Bitte teilen Sie uns Ihre Meinung über all die Information mit, die Sie bis zum **heutigen Tage** erhalten haben.

Datum:

	trifft auf keinen Fall zu	trifft eher nicht zu	unsicher	trifft zu	trifft voll zu
1) Mit der Information, die ich zu meiner Krebsbehandlung erhalten habe, bin ich zufrieden.	1	2	3	4	5
2) Mit der Information zu den möglichen Nebenwirkungen meiner Behandlung bin ich zufrieden.	1	2	3	4	5
3) Mit der Information darüber, was ich im Falle eintretender Nebenwirkungen machen soll, bin ich zufrieden.	1	2	3	4	5
4) Mit den Antworten auf meine Fragen bezüglich Vitaminen, pflanzlichen Präparaten und ergänzenden Therapien bin ich zufrieden. (Ergänzende Therapien schließen Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.)	1	2	3	4	5
5) Mit den Erklärungen zu möglichen Wechselwirkungen zwischen meiner verordneten Krebsbehandlung und anderen Medikamenten, die ich bereits einnehme oder gedenke einzunehmen, bin ich zufrieden.	1	2	3	4	5
6) Mit der Art und Weise, in welcher mir die Informationen über meine Krebsbehandlung vermittelt werden, bin ich zufrieden. Sie ist klar und einfach zu verstehen.	1	2	3	4	5
7) Ich habe ausreichend Gelegenheit bekommen, Fragen zu meiner Krebsbehandlung stellen zu können.	1	2	3	4	5
8) Ich habe ausreichend Gelegenheit bekommen, Fragen darüber zu stellen, wie ich mich im Falle auftretender Nebenwirkungen verhalten soll.	1	2	3	4	5
9) Ich habe ausreichend Gelegenheit bekommen, Fragen zu dem Gebrauch von Vitaminen, pflanzlichen Präparaten und ergänzenden Therapien stellen zu können.	1	2	3	4	5
10) Mit den Informationsquellen, die mir zur Verfügung stehen, also Patienteninformationen, Broschüren und Personal, bin ich zufrieden.	1	2	3	4	5
11) Alles in allem bin ich mit der Art und Weise in der ich informiert werde zufrieden. Man begegnet mir freundlich, respektvoll und unvoreingenommen.	1	2	3	4	5
12) Ich bin zufrieden damit, in der Lage zu sein, begründete Entscheidungen über meine Krebsbehandlung treffen zu können.	1	2	3	4	5
13) Ich bin zufrieden damit, in der Lage zu sein, begründete Entscheidungen zur Behandlung der eintretenden Nebenwirkungen treffen zu können.	1	2	3	4	5
14) Ich bin zufrieden damit, in der Lage zu sein, begründete Entscheidungen zum Gebrauch von Vitaminen, pflanzlichen Präparaten und ergänzenden Therapien treffen zu können.	1	2	3	4	5

to be continued on the following page

Dieser Teil des Fragebogens beschäftigt sich mit allgemeinen Daten.

1) Lebensalter in Jahren :

2) Geschlecht (Zutreffendes bitte ankreuzen)

- ❑ weiblich
- ❑ männlich

3) Familienstand (Zutreffendes bitte ankreuzen)

- ❑ verheiratet/ Lebensgemeinschaft
- ❑ ledig
- ❑ geschieden
- ❑ verwitwet

4) Aktuelle Wohnsituation (Zutreffendes bitte ankreuzen)

- ❑ allein lebend
- ❑ mit Familie/ Lebenspartner lebend
- ❑ in Institution lebend (z.B.: Altenheim/ Pflegeheim...)

5) Ausbildungsabschluss: (Zutreffendes bitte ankreuzen)

- ❑ Volkschulabschluss
- ❑ Hauptschulabschluss
- ❑ Mittlerer Reife (Fachhochschulreife)
- ❑ Gesellenprüfung
- ❑ Abitur (Hochschulreife)
- ❑ Meisterschule
- ❑ Fachhochschulabsolvent
- ❑ Hochschulabsolvent
- ❑ Höherer universitärer Abschluss (Doktor, Priv. Doz., Prof. ...)

6) Beruf: (Zutreffendes bitte ankreuzen)

- ❑ Hausfrau/ mann
- ❑ Schüler/in /Student/in
- ❑ Beamte/r
- ❑ Rentner/in
- ❑ Angestellte/r
- ❑ Selbständige/r
- ❑ Arbeiter/in
- ❑ Handwerker/in

7) Man hat bei mir folgende Krebsart festgestellt: _____

8) Ich weiß seit _____ von meiner Erkrankung.

9) Ich befinde mich wegen meiner Krankheit (Zutreffendes bitte ankreuzen)

- ❑ in stationärer Behandlung
- ❑ in ambulanter Behandlung bei einem niedergelassenen Onkologen
- ❑ in ambulanter Behandlung eines im Krankenhaus tätigem Onkologen

10) Ich bin in einer Selbsthilfegruppe aktiv (Zutreffendes bitte ankreuzen)

- ❑ ja
- ❑ nein

Wir sind jederzeit dankbar für weitere Kommentare und Vorschläge:

Vielen Dank für die Zeit, die Sie sich hiermit genommen haben.

Sie dient Ihnen und anderen Patientinnen und Patienten!

Bitte beantworten Sie hier kurz ein paar Fragen zu den von Ihnen verwendeten Informationsquellen.

1) Woher haben Sie bisher Information zu Krebsbehandlungen erhalten?
(bitte markieren Sie alle Möglichkeiten, die auf Sie zutreffen)

- ❑ Hausarzt/ Hausärztin
- ❑ Familienmitglied
- ❑ Freund/in
- ❑ Internet
- ❑ Bücher
- ❑ Heilpraktiker/in
- ❑ Sozialarbeiter/in
- ❑ Selbsthilfegruppe
- ❑ Krankenhausinterne Patientenbibliothek
- ❑ Ich habe keine Information erhalten
- ❑ Tageszeitung
- ❑ Fernsehen
- ❑ Krankenschwester
- ❑ Ernährungsberater/in
- ❑ Onkologe/in
- ❑ Apotheker/in
- ❑ Radiologe/in
- ❑ Chirurg/in
- ❑ Reformhaus

2) Was oder wer war bisher Ihre <u>wichtigste</u> Quelle für Informationen zu Ihrer Krebsbehandlung? (Zutreffendes bitte ankreuzen)

- ❑ Hausarzt/ Hausärztin
- ❑ Familienmitglied
- ❑ Freund/in
- ❑ Internet
- ❑ Bücher
- ❑ Heilpraktiker/in
- ❑ Sozialarbeiter/in
- ❑ Selbsthilfegruppe
- ❑ Krankenhausinterne Patientenbibliothek
- ❑ Ich habe keine Information erhalten
- ❑ Tageszeitung
- ❑ Fernsehen
- ❑ Krankenschwester
- ❑ Ernährungsberater/in
- ❑ Onkologe/in
- ❑ Apotheker/in
- ❑ Radiologe/in
- ❑ Chirurg/in
- ❑ Reformhaus

Appendix K

Documentation

Patient profile I

Rheinische Friedrich-Wilhelms- Universität Bonn
Pharmazeutisches Institut
Klinische Pharmazie
Prof. Dr. U. Jaehde

Patientenstammblatt

Name | **Geburtsdatum**

Straße | **Telefon (privat)**
PLZ / Ort | **Telefon (geschäftlich)**
Mobil
e-mail: @

Kontaktperson

Name | **Telefon (privat)**
Straße | **Telefon (geschäftlich)**
PLZ / Ort | **Mobil**
e-mail: @

Hausarzt

Name | **Telefon (geschäftlich)**
Straße | **Mobil**
PLZ / Ort | **e-mail:** @

Apotheke

Name | **Telefon (geschäftlich)**
Straße | **Mobil**
PLZ / Ort | **e-mail:** @

Sozialanamnese

Nationalität | **Familienstand**
Muttersprache | **Beruf**
Religionszugehörigkeit

Anamnese

Diagnose

Krebsart | **ICD 10** | **TNM-Klassifikation**

Grunderkrankungen

Familiäre Erkrankungen

Bekannte Allergien

Patient profile II

Basisdaten

Datum	Körpergröße	Körpergewicht	Körperoberfläche
	m	**kg**	**m^2**
	m	**kg**	**m^2**
	m	**kg**	**m^2**
	m	**kg**	**m^2**
	m	**kg**	**m^2**
	m	**kg**	**m^2**

Lebensgewohnheiten

Körperliche Ertüchtigung		Gesellschaftsdrogen	
		Rauchen	
Hobbies		Alkoholkonsum	
Haustiere		Kaffee-/ Teekonsum	

Art der Ernährung

Wie viele Hauptmahlzeiten isst der Patient pro Tag?	1	2	3

Lebensmittelauswahl	ja	nein
Milchprodukte (täglich)		
Hülsenfrüchte/Eier (wöchentlich)		
Fleisch, Fisch, Geflügel (täglich)		
Obst, Gemüse (zweimal täglich)		

Flüssigkeitszufuhr	< 3 Gläser/Tag	3 – 5 Gläser/Tag	> 5 Gläser/Tag

Medication file

Präparat	Wirkstoffe	Stärke	Dosierung	Indikation	Therapie-zeitraum	Packungs-größe	Reichdauer
Bemerkung							
Bemerkung							
Bemerkung							
Bemerkung							

Medication profile

Arzneimittel/Stärke	Dosierung																											Bemerkung

Care plan

Datum	S Subjektive Beschwerden	O Objektive Parameter	A Problemanalyse	P Empfehlung	Beobachtungsparameter

Appendix L

Platinum analysis

Tab. L-1 Instrumentation and operating conditions

Atomic absorption spectrometer	SpectrAA® Zeeman 220, Varian, Darmstadt, Germany
Graphite tube atomizer	GTA 100
Autosampler	PSD 100
Data evaluation	Software SpectrAA® 220 Version 2.20
Hollow cathode lamp	UltrAA® lamp, platinum UltrAA® lamp control module
Graphite tubes	Partition tubes coated
Sample vials	Polyethylen vials, 2 mL, conical
Wavelength	265.9 nm
Monochromator	0.5 nm slit width with reduced slit height
Lamp current	10 mA
Background correction	Zeeman
Injection volume	20 µl
Purelab Plus® pure water system	USF Reinstwassersysteme, Ransbach-Baumbach, Germany
VoluMate® Pipettes	Mettler-Toledo GmbH & Co, Gießen, Germany
Eppendorf® Pipettes	Eppendorf AG, Hamburg, Germany
Centrifuge Rotanta RP	Hettich GmbH & Co KG, Tuttlingen, Germany
Centrifuge Universal 30RF	Hettich GmbH & Co KG, Tuttlingen, Germany
Centrifuge Megafuge 1.0R	Heraeus GmbH & Co KG, Hanau, Germany

Tab. L-2 Chemicals and Reagents

Chemicals

Carboplatin	Sigma, Taufkirchen, Germany
Nitric acid 'Suprapur' 65 %	Merck, Darmstadt, Germany
Triton® X-100	Serva, Heidelberg, Germany
Purelab Plus®-water	USF Reinstwassersysteme, Ransbach Baumbach, Germany
Argon 4.6	Air Product, Hattingen, Germany

Solutions

Triton-X-solution 1%	2,5 mL Triton-X water ad 250 mL
Nitric acid 6.5%	100 mL Nitric acid 65 % water ad 1000 mL
Carboplatin stock solution [1 mg Pt/mL]	19.0 mg Carboplatin water ad 10.0 mL
Carboplatin work solution 1 [10 µg Pt/mL]	100 µl stock solution water ad 10.0 mL

Consumables

Cellstar® tubes (15 mL)	Greiner Labortechnik, Frickenhausen, Germany
PP- reaction tubes (1.5 mL)	Greiner Labortechnik, Frickenhausen, Germany
Pipette tips	Greiner Labortechnik, Frickenhausen, Germany
Graphite tubes (Partition tubes coated)	Varian, Darmstadt, Germany
Sample vials (Polyethylen vials, 2 mL, conical)	Varian, Darmstadt, Germany
S-Monovettes® 9 mL EDTA KE	Sarstedt, Nümbrecht, Germany
Centrifree® Millipore	Amicon, Bedford, MA, USA

Tab. L-3 Validation of the FAAS method

	Plasma		Ultrafiltrate	
LLOQ [ng/mL]	20		5	
Recovery [%]	Concentration [ng/mL]	Recovery [%]	Concentration [ng/mL]	Recovery [%]
	50	100.3	5	83.3
	200	97.1	20	87.3
	500	96.2	50	88.8
Linearity Calibration set	F value [< 34.12]	Correlation coefficient r [> 0.99]	F value [< 34.12]	Correlation coefficient r [> 0.99]
1	4.37	0.9987	4.37	0.9998
2	0.58	0.9996	3.09	0.9985
3	3.13	0.9993	1.94	0.9997
4	4.07	0.9997	0.08	0.9994
5	4.35	0.9995	24.38	0.9989
Accuracy RE [%]*	Between-day plasma		Between-day ultrafiltrate	
Calibrators	0.3 - 2.3		0.6 - 3.4	
PQC	0.5 - 0.7		0.5 - 10.7	
SQC	1.6 - 6.4		1.6 - 8.0	
Precision RSD [%]*				
Calibrators	0.9 - 5.8		1.2 - 7.1	
PQC	2.7 - 3.6		1.5 - 4.7	
SQC	5.8 - 7.8		1.6 - 4.9	

*Presented are the absolut values of the smallest and highest values of all performed measurements.

Tab. L-4 Accuracy assessment using QC samples

Plasma	Concentration [ng/mL]	Nominal concentration [ng/mL]	RE [%]
PQC 500	439.9	500.0	-12.0
PQC 500	464.1	500.0	-7.2
PQC 2500	2358.3	2500.0	-5.7
PQC 2500	2431.2	2500.0	-2.8
PQC 5000	4801.3	5000.0	-4,0
SQC 500	439.9	500.0	-12.0
SQC 2000	2144.6	2000.0	7.2
SQC 2000	2338.9	2000.0	16.9
SQC 4000	4271.9	4000.0	6.8
SQC 4000	4271.9	4000.0	6.8
SQC 20000	4407.9	4000.0	10.2
SQC 20000	4519.6	4000.0	13.0
Ultrafiltrate	Concentration [ng/mL]	Nominal concentration [ng/mL]	RE [%]
PQC 500	394.0	500.0	-21.2
PQC 500	447.2	500.0	-10.6
PQC 2500	2339.0	2500.0	-6.4
PQC 2500	2547.0	2500.0	1.9
PQC 5000	4951.7	5000.0	-1.0
SQC 500	514.9	500.0	3.0
SQC 2000	1705.2	2000.0	-14.7
SQC 2000	1850.3	2000.0	-7.5
SQC 4000	3582.5	4000.0	-10.4
SQC 4000	3640.5	4000.0	-9.0
SQC 20000	3480.9	4000.0	-13.0
SQC 20000	3480.9	4000.0	-13.0

Appendix M

Monitoring of carboplatin

Tab. M-1 Platinum concentrations and resulting AUCs

		Pt conc. [µg/mL]		Carboplatin conc. [µg/mL]		AUC [mg·min/mL]	
Code	Sample	Plasma	UF	Plasma	UF	Plasma	UF
KOM01	BKHZIP1	16.41	13.65	31.22	25.98	7.03	4.85
	BKHZIP2	6.22	3.72	11.84	7.08		
	BKHZIVP1	8.15	5.36	15.51	10.19	5.91	3.96
	BKHZIVP2	5.84	3.66	11.12	6.96		
	BKHZVIP1	9.02	7.27	17.17	13.83	3.89	2.82
	BKHZVIP2	3.09	1.91	5.87	3.64		
KOD01	MLKHZIP1	11.74	11.31	22.35	21.52	4.84	3.93
	MLKHZIP2	3.97	2.83	7.56	5.38		
	MLKHZIIIP1	17.11	15.40	32.56	29.30	5.29	4.64
	MLKHZIIIP2	3.85	3.22	7.33	6.14		
	MLKHZVIP1	11.09	9.71	21.10	18.48	4.32	3.08
	MLKHZVIP2	3.37	1.93	6.42	3.68		
KOK11	IKUKZIP1	10.07	8.62	19.16	16.41	4.97	4.09
	IKUKZIP2	4.36	3.40	8.30	6.48		
	IKUKZIIIP1	8.00	7.90	15.23	15.03	4.61	3.66
	IKUKZIIIP2	4.16	2.93	7.91	5.58		
	IKUKZVIP1	9.36	7.29	17.82	13.88	5.46	3.90
	IKUKZVIP2	5.09	3.33	9.69	6.33		
KOS01	KBNZIP1	13.08	9.52	24.89	18.11	5.13	3.83
	KBNZIP2	4.17	2.94	7.94	5.59		
	KBNZIIIP1	10.53	7.99	20.04	15.21	4.57	3.94
	KBNZIIIP2	3.78	3.28	7.19	6.24		
	KBNZVIP1	10.04	7.36	19.11	14.01	4.91	3.37
	KBNZVIP2	4.29	2.61	8.16	4.98		

Tab. M-2 Serum creatinine and GFR-estimation

	KOM01	KOD01	KOK11	KOS01
Serum creatinine pre-treatment [mg/dL]	0.6	0.56	1	0.81
GFR [mL/min] according to CG	108.61	127.31	57.00	61.02
GFR [mL/min] according to Jelliffe	109.20	128.76	52.09	62.68
Serum creatinine pre-cycle III [mg/dL]	n.s.	0.59	0.85	n.s.
GFR [mL/min] according to CG	n.s.	120.84	67.06	n.s.
GFR [mL/min] according to Jelliffe	n.s.	122.21	61.28	n.s.
Serum creatinine pre-cycle VI [mg/dL]	0.6	n.s.	0.86	n.s.
GFR [mL/min] according to CG	108.61	n.s.	66.28	n.s.
GFR [mL/min] according to Jelliffe	109.20	n.s.	60.57	n.s.
Normal ratio Serum creatinine [ng/mL]	0.49-0.9			

CG = Cockroft-Gault

Tab. M-3 NCI Common toxicity criteria

Grade	0	1	2	3	4
Platelets ($\cdot 10^9$/L)	WNL	<LLN - 75.0	≥50.0-<75.0	≥10.0-<50.0	<10.0
Leukocytes ($\cdot 10^9$/L)	WNL	<LLN - 3.0	≥2.0 - <3.0	≥1.0 - <2.0	<1.0

WNL = Within normal limits

LLN = Lower limit of normal

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30th European Symposium on Clinical Pharmacy, ESCP, Antwerpen, Belgien, 10.-13. Oktober, 2001

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8th Internationale Symposium Oncology Pharmacy Practice, Vancouver, ISOPP, Kanada,
7.-11. Mai 2002

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32nd European Symposium on Clinical Pharmacy, ESCP, Valencia, Spain, 29.10.-01.11.2003

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Provision of pharmaceutical care to breast and ovarian cancer patients: Focus on supportive care
Journal of Cancer Research and Clinical Oncology 130, Suppl., PO236 (2004)

Lectures

September 2004	'Anwendung antiemetischer Therapieleitlinien in der Praxis' with Martina Westfeld, Adexa-seminar 'Die Beratung des onkologischen Patienten', Bonn
April and June 2004	Lecturer and tutor for the 'Bonner Kolleg für klinische Pharmazie' on 'Research in pharmacy practice' and 'Seamless care'
February 2004	Organisation of the scientific symposium 'Interdisziplinäre Supportivtherapie des Mammakarzinoms' at the 26th German Cancer Conference, Berlin for the 'Arbeitskreis für Supportivmaßnahmen in der Onkologie' in cooperation with Prof. Dr. Petra Feyer
June 2003	Chair of the panel discussion 'Pharmaceutical care' with own contribution during the 15th International Symposium of the Multinational Association of Supportive Cancer Care (MASCC), Berlin
February 2003 – January 2004	'Pharmazeutische Betreuung von Brustkrebspatientinnen – ein Beitrag zum Disease Management' Workshop for the Federal Union of G erman Associations of Pharmacists in Würzburg, Hamburg, Bonn and for the Pharmaceutical Associations Westfalen-Lippe and Thüringen, and at the Norddeutschen-Zytostatika-Workshop, Hamburg
Since October 2001 regularly	'Supportivmaßnahmen in der Onkologie' (mit Michael Höckel) Further education „Onkologische Pharmazie", Chamber of Pharmacists, Hamburg
January 2002	„Supportivmaßnahmen in der Onkologie - Möglichkeiten der Zusammenarbeit von Arzt und Apotheker" (with Prof. Dr. Petra Feyer) Norddeutscher Zytostatika Workshop, Hamburg
June 2001	Seminar on therapeutic recommendations, Bavarian Pharmacists association, Munich
May 2001	'Interventionsmöglichkeiten des onkologisch tätigen Pharmazeuten in der Supportivtherapie' Workshop – Der onkologisch tätige Pharmazeut (Firma medac), Hamburg
March 2000-September 2001	„Arzneimittelinformation in England" Workshop on drug-information, Prof. Dr. Richard Süverkrüp, University of Bonn
Since September 1999	Student course on clinical pharmacy, Prof. Dr. Ulrich Jaehde, University of Bonn