Challenges in supportive care in cancer medicine
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SUMMARY

The scope of this thesis is relief of unnecessary suffering of sequelae of cancer and its chemotherapeutic treatment.

In chapter 2 an overview is given of shortcomings and perspectives of some prevalent issues in supportive and palliative care in cancer and cancer chemotherapy; some of which have deleterious effects on quality of life. Emphasis has been put on cancer induced cachexia, elderly patients with cancer, carcinoid tumors, and integrity of epithelial cell surfaces after chemotherapy.

In chapter 3 the effect of age on decisions affecting diagnosis and treatment of ovarian cancer are reviewed. Almost half of all ovarian cancers occur in women over 65 years old, and this age group often presents with more advanced disease. Diagnostic and therapeutic approaches to elderly women appear less intensive than in their younger counterparts. There are no objective data supporting such an under-management. On the contrary, every patient, irrespective of age, deserves accurate diagnostic procedures and an optimal treatment. The first choice of treatment for advanced ovarian cancer in elderly women is as in younger patients, adequate staging of the disease by laparotomy with maximal surgical debulking, followed by combination chemotherapy.

In chapter 4 a new in-vitro assay of chemotherapy induced mucositis is described. Until now all mucositis scoring systems were based on apparent changes of mucosa, subjective complaints and functional impairment. These scoring systems are subjective and consequently hamper adequate evaluation and comparison of preventive strategies. In this study including 11 patients receiving high-dose chemotherapy followed by reinfusion of peripheral hematopoietic blood stem cells (PBSC), prior to and twice weekly after high-dose chemotherapy mucosa was evaluated. Clinically, mucositis was scored according to the generally used WHO toxicity grading. The new, in-vitro assessments of the mucosa included an oral washing and a buccal smear. In the oral washing the percentage viable epithelial cells was determined by trypan blue dye exclusion and leukocytes were counted by fluorescence microscopy after incubation with acridine orange. Maturity of buccal cells was assessed by staining buccal smears for morphology according to Papanicolaou. Furthermore, blood leukocyte levels were determined. Eight healthy volunteers served as controls. In the controls the mean percentage of viable oral epithelial cells was stable, whereas in patients after high-dose chemotherapy an increase was observed, which was significant after day 7 compared to pretreatment. In addition, in the buccal smears a shift from mature to immature epithelial cells was noted. Oral leukocyte levels were closely correlated with the blood leukocyte counts. The WHO score followed the results of this new system with some delay. The observed increase of viable oral epithelial cells after chemotherapy is probably the result of a desquamation of the upper oral mucosa layer, with a shift from mature to more immature cells. These data can be quantitated and therefore this assay may be useful in studies aimed at prevention of mucositis.

The results of a phase-I study with recombinant Transforming-Growth-Factor β3 (TGF-β3; GCP 46614) mouthwashes aimed at mucositis prevention, in which the new assay was applied, are reported in chapter 5. The primary aim of this phase-I study was to establish the safety and tolerability of the TGF-β3 mouthwashes. Especially local effects of the drug were analyzed with assessment of mucositis with objective and subjective measurements. Eleven breast cancer patients receiving two different, mildly stomatotoxic chemotherapy regimens were included. TGF-β3 mouthwashes were given q.i.d. for four consecutive days starting one day before chemotherapy, and were well tolerated. The maximal TGF-β3 dose
in this study (100 µg/mL) considerably exceeds the maximal topical applied dose used in animals, which in turn exceeded the dose showing already preventive effects in animals. That, together with the fact that 100 µg/mL TGF-β3 appeared the maximal feasible dose with respect to pharmacological manufacturing, was the reason that in this phase-I study no attempts have been made to reach a maximal tolerable dose. Clinically, mucositis incidence and severity were as expected. The percentage of viable oral epithelial cells was stable in one patient group and in the other group an increase was observed. This difference might be explained by different levels of stomatotoxicity of chemotherapy schedules or from dissimilarity of time elapsed after previous courses of chemotherapy. The morphology of buccal cells showed a transient shift from mature to immature cells in the first week, possibly suggesting a preventive effect of TGF-β3. Neither systemic absorption of TGF-β3 nor development of TGF-β3-antibodies was observed. It was concluded that mouthwashes with TGF-β3 are well-tolerated and deserve further study in preventing chemotherapy induced mucositis.

Chapter 6 describes a randomized multicentre study evaluating efficacy, safety and tolerability of 2 and 5 mg tropisetron, administered intravenously on day 1 and orally days 2-6, in prevention of nausea and vomiting induced by low-dose cisplatin or non-cisplatin containing chemotherapy in 152 chemotherapy-naïve cancer patients. There was a better total control (no events) of acute vomiting (day 1) in the 5 mg (73%) than in the 2 mg group (55%), and of total or major control (1-2 events) of acute vomiting (84% and 59% respectively). Total control (≤ 15 min) of acute nausea was obtained in 51% of the 2 mg and in 70% of the 5 mg group, total or major control (>15 min - 4 h) of acute nausea in 73% and 91% respectively. No differences were observed for total control of delayed (days 2-6) nausea or vomiting and for the overall outcome of nausea. Less vomiting (days 1-6) occurred in the 5 mg than in the 2 mg group. Efficacy rates ranged widely between chemotherapy regimens, independent of the tropisetron dose groups. More headache was experienced in the 5 mg group. It was concluded that once daily 5 mg tropisetron is superior to 2 mg for prevention of acute vomiting and nausea induced by low-dose cisplatin or non-cisplatin chemotherapy regimens, but causes more headache.

In chapter 7 an example of combining clinical observations with laboratory techniques to test a hypothesis aimed at gaining insight in pathophysiological mechanisms is presented. Reinfusion of PBSC or bone marrow is often followed by flushing, dyspnea and chest tightness, nausea and diarrhea, and abdominal cramps. Especially the prompt flushing, combined with the observation that some of these side effects can be prevented by the selective 5-HT3 receptor antagonist ondansetron, led to the assumption that reinfusion of PBSC or bone marrow is coincided with infusion of free serotonin. Therefore, in 25 patients with various solid tumors, receiving a total of 30 reinfusions of PBSC and/or bone marrow after myeloblastic chemotherapy, parameters of serotonin metabolism were assessed before and after reinfusion. The serotonin content of platelets increased significantly after reinfusion, whereas the 24 h urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) and serotonin were not affected. In 17 patients, the serotonin levels in the bags containing PBSC were measured and, combined with the total reinfused volume, the amount of serotonin coinciding reinfusion could be calculated. The reinfusion occurred with a substantial serotonin load of about 1000 µmol, which induced an increase in total circulating serotonin pool of about 100%. We concluded that side effects coinciding reinfusion of PBSC or bone marrow can, at least partially, be attributed to concomitant reinfusion of serotonin, and therefore the use of 5-HT3 receptor antagonists as premedication for this procedure are justified.
The last part of the thesis focuses on symptom relief in carcinoid patients.

**Chapter 8** describes the effects of the 5-HT̓ antagonist ondansetron on gastric emptying and on upper gastrointestinal symptoms in carcinoid patients. Patients with a metastasized carcinoid often exhibit symptoms such as diarrhea and flushing, but in addition, they sometimes complain about upper gastrointestinal symptoms, especially nausea. Reduction of symptoms might be achieved by inhibition of the production or release of serotonin, as well as by reduction of its effects. Recently, new information became available about serotonin receptors and their function in the digestive tract. Furthermore, highly selective serotonin (5-HT̓) receptor antagonists such as ondansetron have been developed, which appeared effective in preventing chemotherapy induced nausea and vomiting. We studied the effect of ondansetron on gastric emptying measured by applied potential tomography and, if applicable, on upper gastrointestinal symptoms in eleven carcinoid patients. The mean gastric half emptying time, measured by applied potential tomography, increased after treatment with ondansetron, implicating a possible slower gastric emptying. Nausea was reported by 4 patients and improved in 3 of them during ondansetron, whereas diarrhea improved in all 6 patients reporting diarrhea. Flushing was not affected. As expected, no changes in serotonin in platelets and urinary excretion of 5-HIAA levels were observed, since ondansetron only blocks 5-HT̓ receptors, without influencing serotonin release. It was concluded that ondansetron can improve gastrointestinal symptoms in carcinoid patients and possibly slows gastric emptying.

In **chapter 9** the results of a multi-centre study are reported, evaluating the effect of the long-acting somatostatin analogue lanreotide prolonged release (PR) in patients with gastrointestinal neuroendocrine tumors, on hormone related symptomatology, tumor markers and tumor size and tolerability. In addition, this study is the first study in this patient category that addresses the effects of somatostatin analogue treatment on quality of life. In the past, somatostatin analogues such as octreotide appeared effective in amelioration of symptoms in these patients. A major disadvantage of octreotide is that it must be administered subcutaneously two or three times a day. Treatment with lanreotide PR can be administered by intramuscular injection every two weeks, and eliminates the multiple daily injections. The study included 55 patients with substantial daily symptoms, 48 with carcinoid tumors, 6 with gastrinomas and 1 with VIPoma. Symptomatic improvement was observed in 38% of evaluable patients with carcinoid tumor, in 67% of patients with gastrinoma, and the VIPoma patient. Tumor markers were evaluable in 45 patients. Normalization occurred in 2 patients (5%: 1 gastrinoma and the VIPoma), 19 patients (42%) exhibited a reduction, 19 patients (42%) exhibited no change and tumor markers rose in 5 patients (11%). Two of the 31 evaluable carcinoid patients showed a significant tumor reduction, 25 patients remained stable and 4 patients (3 carcinoid, 1 gastrinoma) experienced progression (>50%). Quality of life assessments after 1 month showed improvements in emotional and cognitive function as well as diminished fatigue, sleeping disorders and diarrhea. Eight out of 30 evaluable patients developed gallstones. We concluded that lanreotide PR is a well-tolerated somatostatin analogue with significant clinical, biochemical and anti-tumor effects, and a significant improvement of quality of life in patients with neuroendocrine tumors.

In **chapter 10** a case history is presented, which demonstrates that a metastasized carcinoid tumor is capable to induce an extraordinary symptom complex, due to the production and release of various hormones. In addition to conventional treatment for carcinoid disease, patients obviously can benefit of more selective drug treatment, which is based on the biochemical secretion profile of the tumor.