New treatment modalities in ovarian cancer

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CHAPTER 1

In this chapter the theoretical basis of intraperitoneal (IP) therapy, practical implications such as obtaining access to the peritoneal cavity and clinical utility are discussed. Because ovarian cancer remains confined to the peritoneal cavity for most of its natural course, it was proposed in the early 70's that IP chemotherapy could be employed to increase the exposure of tumor cells to chemotherapeutic agents and thereby increase responses and survival. Since that time, we have learned some valuable lessons. Firstly, IP therapy in ovarian cancer is feasible with a variety of chemotherapeutic agents, although some agents have a limited utility due to either local toxicity or a rapid removal from the abdominal compartment. The latter is expressed by the peritoneal/plasma area under the curve (AUC) ratio. When high, this means that relatively more of the drug is present in the abdominal cavity. This in turn could in theory result in better efficacy and ultimately improved survival. The second lesson learned is that patients with minimal residual disease following initial cytoreductive surgery are the prime candidates for IP therapy. This is explained by the fact that most agents have only a limited ability to penetrate directly into tumor nodules. Thirdly, the intrinsic resistance of tumor cells has not been overcome by IP therapy despite the increased exposure. And fourth, although peritoneal levels of chemotherapeutic agents can be significantly higher than obtained intravenously (IV), with a peritoneal/plasma AUC ratio which can >1000-fold higher for some of the agents, the systemic effects of IP therapy are generally mild. The theoretical concept of IP therapy has been proven in recent phase III trials in patients with newly diagnosed ovarian cancer and minimal residual disease. Patients treated with IP cisplatin did significantly better in terms of survival and less systemic side effects. Finally in this chapter some of the future perspectives in IP therapy are briefly discussed. With the introduction of new classes of potent therapeutic agents the combination of choice as first-line treatment needs to be addressed. IP therapy could play a key role in the multidrug approach in ovarian cancer, due to its efficacy and mild systemic adverse effects as will be demonstrated in chapter 2. Furthermore, IP therapy offers a potential route of administration for non-cytotoxic agents such as gene therapy or monoclonal antibodies.

CHAPTER 2

IP chemotherapy as a means to increase dose-intensity in patients with ovarian cancer has been the focus of studies for decades as summarized in chapter 1. In chapter 2 the efficacy, tolerability and pharmacokinetics of IP paclitaxel combined with IV carboplatin and cyclophosphamide in patients with newly diagnosed ovarian cancer is reported. In this phase II trial 25 patients with ovarian cancer received IP paclitaxel (75 mg/m^2) on day 1 and 8 in combination with IV carboplatin (AUC =5) and cyclophosphamide (750 mg/m^2) on day 1 for 6 cycles every 4 weeks as front-line treatment. During the first treatment cycle IP and plasma samples for paclitaxel determination were collected.

The treatment was tolerated well. Adverse events consisted mainly of abdominal pain and hematological toxicities, but were both manageable. Neurotoxicity grade I/II was reported in 18% and was completely reversible in all patients. Myalgia occurred in 24% of the patients. After treatment 76% of the patients had no evidence of disease. The median progression free survival for the whole group was 22.7 months. Patients with residual disease after surgery (n=10) had a median progression free survival of 13 months, for the optimally debulked group (n=15) the actuarial progression free survival was 60% at 48 months.

Paclitaxel elimination from the peritoneal cavity followed first order kinetics with a mean half-life ($T_{1/2}$) of 25.7 hours. The plasma kinetics was best described by a one compartmental model. This regimen is effective and well-tolerated and allows a triple drug schedule without compromising dose-intensity. About 1000-fold higher AUC of paclitaxel was achieved IP compared with the systemic compartment. The absence of neurotoxicity and acute symptoms is in favor of IP administration of paclitaxel, while its efficacy is comparable to IV-based schedules.

CHAPTER 3

Topotecan is a potent inhibitor of DNA topoisomerase I in vitro and has shown promising activity in relapsed ovarian cancer. Topotecan inhibits topoisomerase I, an enzyme needed for replication of DNA, thus resulting in cell death. Topotecan is present in two forms dependent on pH, namely the active lactone, which is predominantly present at a pH <4, and the less active carboxy form. In theory, topotecan is an attractive agent for IP therapy, but data on its clinical utility if administered IP are limited. The feasibility and pharmacology of IP topotecan is reported in chapter 3. Fifteen patients with recurrent ovarian cancer were entered in this phase I trial. Patients were treated with escalating doses of topotecan IP (5-30 mg/m^2) administered every 3 weeks for up to 8 cycles. During the first treatment cycle IP and plasma samples were collected for pharmacological analysis.

Dose limiting toxicity was an acute reaction in one of three patients at the 30 mg/m^2 dose level. Mild abdominal pain was reported in six patients and was not related to the dose level tested. In IV schedules, the dose limiting toxicity of topotecan is mostly myelosuppression. In this study hematological toxicity was mild with grade IV leukopenia in one patient, while two patients experienced grade III thrombocytopenia.

Plasma levels of topotecan were determined during the first treatment cycle. Plasma peak levels were reached after 2.7 hours (range 1.2- 5.4 hours). Both the maximum concentration (C_{max}) and the AUC were dose dependent. The mean peritoneal/plasma AUC ratio for total topotecan was 54 ± 35, indicating a major pharmacokinetic advantage for IP topotecan. Plasma concentrations required for cytotoxicity were reached even at the lowest dose-levels. An interesting observation was the fact that the plasma AUC ratio of lactone and total topotecan increased with the topotecan dose from 16% to 55%, indicating not only an absolute increase but also a relative increase of active topotecan

levels. In these pretreated patients no complete clinical tumor responses were observed, but of the biochemically evaluable patients six out of thirteen patients had a partial response, which is evidence of clinical efficacy. This study shows the ability to administer IP topotecan at dose levels not feasible IV with only mild systemic adverse effects. IP topotecan could therefore be an interesting option for a multidrug approach as first-line treatment in ovarian cancer.

CHAPTER 4

Recombinant human interleukin-3 (rhIL-3) is a hematopoetic growth factor which has shown a stimulation of uncommitted blood cell progenitors in vitro. In clinical studies encouraging results were reported on its ability to ameliorate myelosuppression by accelerated bone marrow restoration. In chapter 4 the results of the first randomized clinical trial with rhIL-3 are reported. In this multicenter study 185 patients with advanced ovarian cancer receiving combination chemotherapy, carboplatin (AUC =4) and cyclophosphamide (750 mg/m^2) IV on day 1, every 3 weeks for 6 cycles were randomized to receive rhIL-3 (5 µg/kg) or a placebo every cycle as a once daily subcutaneous injection on days 3-12. The aim of the study was to determine whether rhIL-3 reduces bone marrow depression and improves adherence to a chemotherapeutic schedule in this set of patients. Although significant effects had been observed in phase I/II trials with rhIL-3, adherence to the chemotherapeutic regimen and the mean chemotherapy cycle length did not differ between the two groups. There was also no difference observed in tumor response rate and median survival at 24 months between the groups. The number of side effects observed - primarily allergic reactions, flu-like symptoms and fever - were higher in the rhIL-3 group. This led to 21 discontinuations in that group as compared to one in the placebo group. Compared with the placebo group, the rhIL-3 group had higher ($p<0.001$) platelet counts on day 1 of cycles 2 to 6. No difference, however, was observed in the number of patients with nadir WHO grade IV thrombocytopenia or in the number of platelet transfusions. Leukocyte counts between the two groups differed only in the first 2 cycles. The leukocyte nadir occurred earlier in the rhIL-3 group, on day 12, as compared to day 15 in the placebo group ($p=0.006$). Leukocytes and neutrophils were only significantly higher in the rhIL-3 group on day 1 of cycle 2. Thus, although rhIL-3 had stimulatory hematopoietic effects it resulted neither in a reduction of platelet transfusions nor in an improvement of adherence to the chemotherapeutic schedule. There were more side effects observed in the rhIL-3 group than in the placebo group. Because of its limited effects and its toxicity profile, the use of rhIL-3 at a dose of 5 µg/kg/day is therefore not of clinical benefit in this chemotherapeutic regimen.

CHAPTER 5

Since their introduction, hematopoietic growth factors, such as granulocyte-macrophage colony stimulating factor (GM-CSF), have found a role, particularly in the field of oncology. GM-CSF has been shown to stimulate the proliferation and maturation of myeloid cells in the marrow and blood. When GM-CSF is administered at daily doses of 5-10 µg/kg subcutaneously to patients, who have received cytotoxic therapy which induces significant leucopenia, the white blood cell nadir is not altered but the duration of leucopenia is shortened. GM-CSF is also used for hematopoietic stem cell mobilization and subsequent harvesting for high-dose chemotherapy with hematopoietic stem cell transplantation. Chapter 5 focuses on questions about its use in the different settings. Firstly, in the management of drug-induced neutropenic fever, a potential serious complication of chemotherapy. With the available data, the use of GM-CSF routinely as an adjunct to antibiotic therapy in this setting is not recommended. However, it is not precluded that a subgroup of patients may benefit from the application of GM-CSF. Secondly, CSFs may play a role in the use of dose-intense chemotherapy as well as autologous stem cell transplantation. They have shown to shorten the duration of neutropenia and reduce infections in patients undergoing high dose chemotherapy with stem cell reinfusion. CSFs might be used as an adjunct to allogenic and autologous stem cell transplantation, both for mobilization and to enhance hematopoietic recovery following stem cell reinfusion. Finally, an economic model is described to assess the potential savings from a clinical application of CSFs in different settings.

CHAPTER 6

Measuring responses in patients with ovarian cancer is a difficult task. Most patients have disease that cannot be adequately monitored with computed tomography, MRI or ultrasound. In the palliative setting patients are therefore often treated until clinical progression, without performing standardized tumor measurements at strict intervals. Monitoring of CA-125 serum levels is an attractive alternative in ovarian cancer, because it is elevated in most patients with advanced disease and its course is well correlated with tumor growth or regression. An other way to evaluate responses is the calculation of the rate of change of CA-125 serum levels over time. This method can be used to calculate a CA-125 doubling time or half-life, and enables a biochemical response definition which is dependent on the time between measurements and less on absolute values.

In chapter 6 the effect of oral etoposide as palliative chemotherapy on CA-125 serum levels was evaluated using this principle to assess efficacy in 17 patients with recurrent ovarian cancer. A prolonged schedule of low dose daily oral etoposide has proven to be an effective second-line treatment, also in patients with platinum resistance. In this study, CA-125 levels after 4 courses were compared to baseline (CA-125 ratio). The rate of change of CA-125 (s = slope of the exponential regression curve) during the first 4 courses was compared to s over a similar period before treatment.

Although the biochemical response rate was modest (12.5%), a decrease of s was observed in 14/16 patients (p = 0.02). The mean change of s represented an increase of mean doubling time from 52 to 693 days. No patients were withdrawn because of toxicity. General malaise, nausea, diarrhea and anemia were the most important side-effects. At the given dose schedule, oral etoposide shows activity in advanced ovarian cancer if the rate of change of CA-125 is used as a measure of activity.

CHAPTER 7

With the presence of hormone receptors in a high percentage of ovarian cancer, hormonal therapy is an interesting option in the treatment of ovarian cancer. In mice, endogenous gonadotropins, which stimulate the theca granulosa cells under physiological conditions, play a role in the carcinogenesis of epithelial ovarian cancer. Injecting mice with a luteinising hormone releasing hormone (LHRH) analog showed suppression of the development of ovarian tumors. Tamoxifen proved effective in a stem cell assay in about 40% of the ovarian cancer cell lines tested, but the clinical efficacy of this antiestrogen is reported to be from 0 to 25%. In chapter 7 the results are reported of 25 patients with recurrent, chemotherapy resistant ovarian cancer who were treated with goserelin (LHRH-analog) and tamoxifen until clinical or serological (serum CA-125 levels) evidence of progression. Patients received a combination of goserelin 3.6 mg subcutaneous once every four weeks and oral tamoxifen 20 mg daily. Suppression of gonadotropin and prolactin levels in this group were compared with a second group of ten patients treated with decapeptyl for the same indication. The combination of tamoxifen with goserelin was well tolerated. The median progression free survival amounted to five (range 2-96+) months and overall survival to eight (range 3-96+) months. One of the responding patients is still alive without progression at 10 years. The median levels of LH and FSH were markedly suppressed during treatment with this combination, to respectively 2.6% and 3.7% of baseline values. During treatment with decapeptyl the LH levels were suppressed to a similar extent, but the resulting FSH levels were significantly higher. These results confirm that combination hormonal therapy in patients with relapsed chemotherapy resistant ovarian cancer cannot be recommended as standard therapy, but may result in long term survival in individual patients with little or no side-effects.

FUTURE PERSPECTIVES

Finally, some future perspectives of new therapy options are discussed in a nutshell.