Since its clinical introduction cisplatin has had a major impact on the improvement of cancer treatment. Because of its curative potential in a selected number of tumor types cisplatin has become one of the most widely used anticancer drugs. As outlined in the introduction of this thesis treatment with cisplatin is accompanied by two major clinical problems, pronounced treatment associated toxicity and the development of resistance for this drug. These factors have stimulated the improvement of the knowledge and understanding of the therapeutic and toxic effects of currently used cisplatin containing regimens. On the other hand the search for alternative platinum compounds with a better therapeutic index was initiated, as were investigations for ways to ameliorate associated toxicity. In this thesis several of these aspects of platinum based chemotherapy for patients with cancer are described.

Earlier studies revealed that renal function is reduced in malnourished non-cancer patients. In **chapter 2** we investigated whether the nutritional status had an effect on renal function in 46 patients with disseminated non-seminomatous testicular cancer treated with combination chemotherapy including cisplatin. The renal function was expressed as glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and filtration fraction (FF). Nutritional assessment of the patients was performed by means of three nutritional parameters: weight for height index (WHI), creatinine height index (CHI), and serum albumin concentration (Salb). The patients were divided into two groups; group 1, patients with a sufficient nutritional status (n = 30), and group 2, patients with an insufficient nutritional status (n = 16). Before treatment no correlation was found between the individual nutritional parameters and GFR, ERPF and FF respectively. The median GFR, ERPF and FF of both group 1 and group 2 did not differ significantly. Although renal function of the total group of patients was reduced as a result of cisplatin, this reduction was not influenced by the individual nutritional parameters and not higher in the group with an initially insufficient nutritional status. It was concluded that in this study nutritional status and renal function of patients with disseminated testicular cancer are not related.

Chemotherapy for patients with seminoma has generally been reserved for the patient who presents with advanced disease, or for the patient who relapses following primary radiotherapy. The general treatment philosophy has been to treat these patients with combination chemotherapy in a fashion similar to those with metastatic non-seminomatous testicular cancer. Since salvage chemotherapy with etoposide and cisplatin has shown to be effective in some patients failing induction chemotherapy with cisplatin, vinblastine, and bleomycin, one may conclude that these combination regimens are not completely cross-resistant. In order to improve response rates and survival we have treated patients with advanced seminoma with an alternating regimen of cisplatin, vinblastine, bleomycin (PVB) and bleomycin, etoposide, cisplatin (BEP). In **chapter 3** the results of this regimen are described. Thirty-three patients with advanced seminoma were treated with 4

courses of alternating chemotherapy PVB/BEP. Patients were classified as Stage IIC (n=8), IID (n=8), III (n=13) and IV (n=4), eight patients had prior radiotherapy. Thirty patients were evaluable for response and 33 for toxicity. During chemotherapy three patients died. Thirteen patients (43%) had a complete response, 17 (57%) had a clinical partial response (residual radiographic mass). At a median follow-up of 28 months (range 16-88), three patients relapsed, 6-8 months from entry. After completion of therapy there were two deaths, one due to bleomycin-pneumonitis and one not tumor or treatment related. Twenty-six of 33 (79%) patients achieved a continuously disease free status. Leukocytopenia and thrombocytopenia of WHO grade 3/4 occurred in respectively 32/33 (97%) and 20/33 (61%) of the patients. We conclude that this alternating regimen of PVB and BEP has a curative potential in this patient group and that this schedule yields comparable response rates with non alternating schedules. The high incidence of serious adverse events however, makes this regimen a toxic one. A less toxic combination regimen is presently under investigation in advanced seminoma patients.

The majority of the patients with disseminated testicular cancer can be cured with cisplatin-containing chemotherapy. As a consequence, the incidence of delayed side effects of this treatment has become relevant. A number of reports appeared concerning the long-term side effects such as hypertension, renal function disturbance and vessel damage after chemotherapy for testicular cancer. Ischemic cardiovascular and cerebrovascular events have been seen after treatment with several cytostatic agents used in these patients. There might be an increased risk that cardiovascular disease can develop later on in the presence of additional risk factors. **Chapter 4** contains the results of a study with the objective to assess cardiovascular risk factors over time in patients who received chemotherapy for disseminated testicular cancer and were apparently cured. Fifty-seven patients (median age, 28 years; range, 16 to 43 years) who received cisplatin-containing chemotherapy were studied. Serum cholesterol and high-density lipoprotein (HDL) cholesterol levels, body mass index (BMI), blood pressure, kidney function, and hormonal status were monitored during follow-up after chemotherapy (median follow-up, 88 months; range, 56 to 143 months). The BMI and cholesterol values obtained 4 to 6 years after chemotherapy were compared with values from a sample of healthy, age-matched Dutch males; the cholesterol level was also compared with that of 31 patients treated with orchidectomy for stage I disease. The mean cholesterol level in patients at the start of chemotherapy was 3.96±0.98 mmol/L, and increased significantly 4 to 6 years later to 6.12±1.20 mmol/L; 49 of 57 patients had an elevated low-density lipoprotein (LDL) cholesterol, with a mean level of 4.47±1.05 mmol/L. Compared with a sample of healthy Dutch men, the chemotherapy group had an elevated cholesterol level. At 4 to 6 years, the mean HDL cholesterol was 0.76±0.18 mmol/L and was lower compared with that of the healthy Dutch men. The mean BMI for all patients was 2.8 % higher than

expected 4 to 6 years after chemotherapy, but was not higher than expected 7 to 10 years after chemotherapy. We conclude that in addition to other known late side effects of chemotherapy in patients with testicular cancer, hypercholesterolemia and overweight might represent additional risk factors for cardiovascular disease in such patients, especially in those who are younger.

The significant morbidity of treatment with cisplatin encouraged the search for new platinum analogues with equal efficacy and a reduced toxicity profile. Carboplatin has emerged as the leading cisplatin analogue with reduced nephro- and neurotoxicity but more pronounced myelotoxicity when compared with the parent platinum compound cisplatin. Another platinum analogue zeniplatin was selected for clinical trials because of its mild myelosuppressive effects and presumed lack of nephrotoxicity in phase I trials. In **chapter 5** results are reported of a phase II study with zeniplatin in patients with advanced ovarian cancer, who have been pretreated with cis- or carboplatin based chemotherapy. Twenty five patients with residual or recurrent ovarian cancer were treated with zeniplatin 120 mg/m^2 (i.v.) once every 3 weeks for a maximum of 6 cycles. Twenty-three patients were evaluable for response. Myelotoxicity was mild, with grade 3 leucopenia in only 14 percent of treatment cycles, and no grade 4 leucopenia in fully dosed cycles. Thrombocytopenia was incidental. With standard antiemetics nausea and vomiting were moderate. Responses were achieved in four patients, one complete and three partial remissions. Seven patients had stable disease after six cycles of treatment and 12 patients had tumor progression. At a median follow-up of 12 months, the median progression free survival in responding patients was 11 months and the overall survival 81% (median survival not yet reached). The median overall survival of progressive patients amounted to 9 months, indicating the advanced stage of disease in most patients. Renal function was monitored by isotope clearance-studies. There was no significant change in ERPF or GFR in patients who completed six cycles of treatment. One patient with a marginal creatinine clearance at baseline suffered from sudden and severe renal failure during the first cycle. It was concluded that zeniplatin may be active in relapsing, platinum pretreated patients, and has no direct effects on renal function. Despite these findings, occasional nephrotoxicity may occur in patients with compromised kidney function, and thus limits the application of this new platinum analogue.

Although the toxicity profile of carboplatin is favorable compared with cisplatin, its antitumor activity does not differ significantly from the parent compound cisplatin, so cross-resistance between the two drugs can therefore be anticipated. This stimulated the identification of platinum compounds that show activity in tumors that are resistant to cisplatin, in order to improve the treatment results. In **chapters 6 and 7** we describe the first clinical experience with such a new platinum compound lobaplatin (D-19466). Preclinical data suggested that lobaplatin is not or only partial cross-resistant in a number of cisplatin resistant cancer cell lines. This lack of cross-resistance is combined with a mild rodent toxicity pro-

file. In **chapter 6** the results of a phase I trial with lobaplatin, administered as an iv bolus daily for 5 days every 4 weeks, are described. Twenty-seven patients with refractory solid tumors received 72 treatment courses. Thrombocytopenia was dose-limiting, its degree was related with the creatinine clearance (CRCL). For patients with a CRCL of 60-80 ml/min the maximum tolerated dose was 40 mg/m^2, for patients with a CRCL of 81-100 ml/min it was 70 mg/m^2, and for patients with a CRCL > 100 ml/min it was 85 mg/m^2. The percentual platelet nadir (percentage of day 1 platelet count) correlated with CRCL at different dose levels and could be described by: percentual platelet nadir = 0.76 x CRCL (ml/min) - {1.45 x dose (mg/m^2)} + 43.38. The potential utility of this equation was tested and found to produce a significant correlation between observed and predicted percentual platelet nadir. No renal function impairment was observed. Urinary excretion of platinum was estimated and revealed that 91.5 % (SE ± 7.9) of the platinum dose was excreted within 4 hours after the administration. The recommended dose of lobaplatin iv bolus daily for 5 days for phase II studies depends on renal function, namely 30 mg/m^2 at CRCL 60-80 ml/min; 55 mg/m^2 at CRCL 81-100 ml/min; 70 mg/m^2 at CRCL > 100 ml/min. Of interest were one complete response and one partial response in two patients with ovarian cancer (both pretreated with carboplatin and cisplatin). In **chapter 7** a phase I trial with lobaplatin in another regimen is reported. Lobaplatin was administered by 72 hours continuous intravenous infusion (CI), every 4 weeks. Eleven patients enroled in this study and received a total of 30 courses lobaplatin. Thrombocytopenia was dose-limiting toxicity it reached WHO grade III in 3 out of 6 patients at 45 mg/m^2/72h and, WHO grade IV in 2 out of 2 patients at 60 mg/m^2/72h. Leukopenia was mild, as was the nausea and vomiting. There were no signs of renal, neuro, or ototoxicity. The recommended phase II dose for this regimen is 45 mg/m^2/72h every 4 weeks. One patient with ovarian cancer, pretreated with three different platinum complexes, achieved a partial response. It is concluded that lobaplatin is a promising new platinum analogue with predictable hematological toxicity, no signs of renal toxicity, with anti-tumor activity in both regimens, and with clinical evidence that lobaplatin might be non-cross resistant with cisplatin and carboplatin. Further studies with lobaplatin are recommended.
Another way to improve treatment results is by dose intensification. The most important and usual dose limiting toxicity of combination chemotherapy is myelosuppression, which limits the treatment of large groups of patients with intensive chemotherapy without the use of supportive care measures. The recent availability of hematopoietic growth factors for clinical use enables us to study their ability to ameliorate chemotherapy induced bone-marrow depression. A carboplatin based chemotherapy regimen with myelosuppression as dose-limiting side effect seems to be suitable for combination with the administration of hematopoietic growth factors. In **chapter 8 and 9** details are given of a dose-finding study with a new hematopoietic growth factor Interleukin-3 (rhIL-3) after combination che-

motherapy and of the ability of rhIL-3 to influence hematopoietic recovery. rhIL-3 is a glycoprotein with an in vitro broad spectrum of activity on hematopoiesis. It stimulates the proliferation and differentiation of multipotent hematopoietic stem cells, as well as the committed progenitor cells of erythroid, granulocyte/macrophage, megakaryocyte, eosinophil, basophil, and mast cell lineages in vitro. Nineteen patients who had relapsed small cell lung cancer received rhIL-3 after their second course of chemotherapy which consisted of either cyclophosphamide, doxorubicin, and etoposide (CDE) every 3 weeks or vincristine, ifosfamide, mesna, and carboplatin (VIMP) every 4 weeks. Twenty-four hours after the last chemotherapy dose, rhIL-3 was administered subcutaneously (s.c.) once daily for 14 days on an outpatient basis. Escalating dosages (1 - 2 - 4 - 8 - 16 μg/kg/day) of rhIL-3 were tested. Hematologic effects were evaluated by comparing blood cell recovery after chemotherapy cycle 1 and cycle 2 plus rhIL-3. Adverse effects of rhIL-3 at dosages up to 8 μg/kg/day consisted mainly of low grade fever and flu-like symptoms. At 16 μg/kg rhIL-3 headache became dose limiting. Severe neutropenia after VIMP cycle 2 plus rhIL-3 was shorter in duration than after cycle 1 (3 vs 7 days). At rhIL-3 dose levels 8 and 16 μg/kg hematological effects in seven patients who were treated with VIMP showed a hastened recovery of leucocyte and neutrophil counts during cycle 2 compared with cycle 1 and increased monocyte and eosinophil counts in cycle 2 compared with cycle 1. rhIL-3 also increased reticulocyte, and platelet counts at dose level 8 μg/kg. No significant stimulation of basophils and lymphocytes was observed. Apart from hematologic effects, rhIL-3 also augments the release of cytokines such as tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6). This release of IL-6 was followed by a subsequent acute phase response. Of interest was also the finding that rhIL-3 lowered cholesterol levels. We conclude that rhIL-3 can be safely administered after chemotherapy on an outpatient basis. RhIL-3 is tolerated well at doses up to 8 μg/kg/day and is biological active in patients after myelosuppressive chemotherapy.

In this thesis some experience with the use of platinum based chemotherapy at the University Hospital Groningen is reported. Clinical studies described in this thesis may have in some way influenced the perspective in which platinum based chemotherapy can be viewed. The nutritional status of a patient with disseminated testicular cancer does not seem to influence renal function prior to cisplatin combination chemotherapy nor does it influence the renal function loss due to cisplatin treatment. The high incidence of toxicity associated with an alternating regimen of PVB and BEP in patients with advanced seminoma makes this regimen of limited value in this patient group. Further treatment improvements in patients with advanced seminoma should be made with the use of carboplatin based regimens. Patients cured with chemotherapy from disseminated testicular cancer have an increased incidence of cardiovascular risk factors. The majority of

these cured patients have a disturbed lipoprotein profile. Especially in younger patients this coincided with overweight. These risk factors in combination with other known late side effects of platinum containing chemotherapy may represent a threat for this group of cured cancer patients. The data indicate that at this point in time a close follow-up of long-term survivors with special attention for cardiovascular risk factors is warranted. Further investigation is necessary to identify underlying mechanisms of this phenomenon in order to develop possible intervention strategies.

Further improvement of the fate of patients with cancer, requiring treatment with chemotherapy, awaits new strategies. In the search for new cisplatin analogues with reduced toxicity and improved activity lobaplatin appears to be a promising drug. Lobaplatin showed activity in patients with platinum resistant tumors. In phase II and III studies this activity should be further defined. Since the toxicity of lobaplatin concerns primarily the bone marrow, with thrombocytopenia as dose limiting side effect, lobaplatin seems to be an ideal candidate for high-dose administration. The use of hematopoietic growth factors, perhaps in conjunction with peripheral stem-cell reinfusions, might felicitate the administration of high-dose chemotherapy. Interleukin-3 either alone or in combination with other, more lineage-specific growth factors such as granulocyte-colony stimulating factor or Interleukin-6, may disclose this concept of chemotherapy dose-intensification for larger groups of patients. An adequate control of short-term toxicity of intentional curative chemotherapy may become reality in the near future. An accurate follow-up however, of successfully treated patients, with suspicion for the occurrence of long-term side effects should become a second nature of medical oncologists.