SUMMARY AND CONCLUSIONS

The prevalent solid tumors in the western world can not be cured once the tumor has outgrown beyond the stage of surgical resectability. Neither conventional chemotherapy nor immunotherapy or hormonal manipulation can rescue patients with disseminated cancer of the breast, lung, colon or advanced stage ovarian cancer. Cytotoxic drugs can however reduce tumor volume when given in a standard dose. For various tumor types the experimental base for the supposition that high-dose chemotherapy might give better results, or even lead to cure is considerable. In the clinical situation the curative possibilities of intensive chemotherapy combined with autologous or allogeneic bone marrow transplantation have been proven in hematological malignancies.

In the chapters of this thesis we have outlined the experience of intensive chemotherapy and autologous bone marrow transplantation (ABMT) in adult patients with various solid tumor types treated in our oncology department.

In Chapter 1 the criteria for the use of ABMT have been formulated. Also the procedures of bone marrow collection, cryopreservation and reinfusion are described. Special attention is paid to the fact that bone marrow harvesting was performed with local anesthesia with lidocain and analgesia with meperidine/diazepam on an outpatient basis and that general anesthesia is not necessary. Complications and patient acceptance of the harvesting procedure were evaluated.

We advocate the use of irradiated allogeneic blood products during the bone marrow harvesting procedure and in the ABMT period because of the risk of graft-versus-host-disease.

The overwhelming problem of the clinical management of ABMT patients lies in the supportive care that they require. In this thesis this problem has been analysed to some extent, especially nutritional support, bleeding prophylaxis, incidence and effects of herpes virus infection and infection prophylaxis were subjects of investigation.

Chapter 2 deals with the nutritional problems of ABMT patients. Despite intensive counseling of dieticians, nurses and doctors, these patients were found to eat insufficiently, while their metabolic needs were increased. This resulted in an unacceptable weight loss of almost 10%. Therefore, we conducted a prospective randomized study of the efficacy of hyperalimentation. Hyperalimentation consisted of 3400 non-protein Kcalories and 25 grams of nitrogen (equivalent to 148 grams of protein) per day and was given either as total parenteral nutrition or as half enteral and half parenteral nutrition. We concluded that both regimens were effective in maintaining body weight and nitrogen balance. We noticed that in balance studies the administration of blood products should not be omitted because they account for substantial additional intake of nitrogen.
Probably due to vomiting and diarrhea the daily requirements of copper and zinc in ABMT patients were increased. The patients fed by a combination of parenteral plus enteral nutrition suffered less days with diarrhea and got better supplementation with calcium, copper, magnesium and zinc than the patients fed by total parenteral nutrition. Hyperalimentation caused a significant increase in creatinine clearance. This phenomenon required an increase in the dosage of all drugs with renal elimination (including antibiotics) administered to patients during the hyperalimentation period.

In addition to the balance studies, serial measurements of serum albumin, transferrin and prealbumin were performed during the ABMT period. In general these visceral proteins are considered useful as nutritional markers. Serum levels were decreased on day 7, 14 and 21, compared to the initial level on day 0. We found evidence that non-nutritional factors influence the course of the serum levels of these proteins. Such factors may consist of dilution due to the intravenously administered volume, transcapillary leakage of small proteins and altered protein metabolism due to cytotoxic drugs.

Chapter 3 deals with bleeding prophylaxis. Severe thrombocytopenia exists during a 15-20 days period starting approximately one week after the beginning of intensive chemotherapy.

Allogeneic thrombocytes are most often used for bleeding prevention. However, autologous platelets eliminate the risk of transfusion related viral disease, graft-versus-host-disease and immune reactions. We studied the feasibility of bleeding prophylaxis using autologous platelets cryopreserved prior to intensive chemotherapy. In nearly half of the 43 patients the thrombocytopenic period could be bridged with four donations of their own platelets. In the other half of the patients either more than 4 transfusions were required, or inaccessible veins or insufficient time for platelet aphereses precluded the sole use of autologous thrombocytes.

No bleeding episodes occurred following the administration of prophylactic autologous platelet transfusions, so that respect they were as active as fresh single donor allogeneic platelets. The one hour increment for allogeneic thrombocytes twice was as high as for autologous thrombocytes, but the interval between transfusions in days was the same. So most probably autologous platelets possess a longer in vivo life span than allogeneic platelets.

The washing step for removal of the cryoprotectant of the autologous platelets can be omitted without adversely affecting this bleeding prophylaxis capacity and also without introducing immediate or late complications due to intravenous administration of the cryoprotectant (5% dimethyl sulfoxide).

The major problem in the immediate posttransplant period is created by infectious complications. From the experience with allogeneic bone marrow transplantation it became apparent that cytomegalovirus infection is a common cause of posttransplant morbidity and mortality. In contrast, in our experience with autologous bone marrow transplantation, cytomegalovirus disease occurred despite the fact that the transplant procedure included chemotherapy.

The incidence and severity of HSV disease were higher than in allogeneic bone marrow transplantation, despite the fact that patients were HSV seronegative. HSV disease was seen in more than one third of patients. This is surprising because we expected HSV disease to be a self-limited, and most likely symptomatic, disease.

In Chapter 5 it was discussed that intensive, selective decontamination of the gastrointestinal tract, performed with parenteral treatment, is an effective means of preventing gram-negative and gram-positive bacteria in the decolonization of patients. However, a shift has taken place recently to use of antifungal agents and antibiotics to prevent fungal and bacterial infections. We found that a shift in the pathogen profile from bacteria to fungi could be seen. Although viral infections are recognized as being a major threat, infectious complications are being overshadowed by infections with bacteria and fungi. In our experience, about 50% of the infections were caused by gram-negative or gram-positive bacteria, and 25% by fungi. The remaining 25% were caused by HSV infection.

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transplantation, cytomegalovirus infection is a seldom observed clinical complication despite the fact that the virus is latent in half of the patients at the start of intensive chemotherapy.

The incidence and effects of another herpes virus are described in Chapter 4. We noticed that this virus, the herpes simplex virus (HSV) is reactivated in more than 60% of HSV seropositive patients approximately seven days after bone marrow reinfusion. This is surprising because recipients of bone marrow transplantation are immuno-compromised. Half of the patients with culture-proven HSV infection showed a significant rise in complement-fixing antibody titer. Primary HSV infections did not occur. Patients with a HSV infection had significantly more days with fever than those without HSV infection. We found no difference in speed of hematological recovery between these two groups of patients as suggested by other investigators.

Although viral infections cause morbidity in ABMT patients, the more serious threats are caused by bacterial and fungal infections during the period with profound granulocytopenia. Both the length and the depth of this granulocytopenia determine the infection risk. The majority of these infections is caused by gram-negative microorganisms originating from the gastro-intestinal tract.

In Chapter 5 infection prevention by elimination of these micro-organisms by selective decontamination of the gut was studied in ABMT patients. Three regimens were evaluated consisting of polymyxin B combined with oral neomycin, or combined with parenteral temocillin or with oral cotrimoxazole. All three regimens were effective in decolonization of the gut and in preventing gram-negative bacterial infections. However, a shift has taken place towards gram-positive infections, especially towards viridans streptococci and coagulase negative staphylococci. For the moment the problem how to prevent effectively gram-positive bacterial and fungal infections remains unsolved. In that respect more gain may be expected from the use of hematopoetic growth factors to shorten the granulocytopenic period than from prophylaxis with local and/or systemic antibiotics.

Whether the concept of high-dose chemotherapy is an effective approach in the treatment of disseminated solid tumors is investigated in Chapters 6, 7 and 8. Most of the experience was gained in previously treated patients who had relapsing or refractory tumors. Occasionally this treatment modality was the initial therapy in hopeless cases. The total cure rate or at least long-term disease free survival is in over 50 patients in these situations approximately 10%. Although this result is not negligible, it should be balanced against the toxicity of the treatment, especially against the chance of treatment related death. In Chapter 6 the results of high-dose chemotherapy with cyclophosphamide and etoposide followed by ABMT in patients with disseminated testicular cancer are described. In general non-seminomateus germ cell tumors are chemosensitive and with remission-induction chemotherapy a durable complete remission rate of 70% is reached. The patients treated in our study had failed remission-induction treatment and showed bad prognostic signs (big tumor load, very high levels of tumor marker(s)).
Only two out of eleven patients achieved a complete remission. It was concluded that 2 courses of maximally tolerable doses of chemotherapy offer insufficient prospect to long-term disease free survival. Nevertheless the cure rate of 20% is uncommon compared to any other regimen in this stage of disease.

More promising results were obtained with high-dose chemotherapy and ABMT in eleven patients with advanced epithelial ovarian cancer, refractory to prior chemotherapy and debulking surgery (Chapter 7). Six complete remissions were achieved in patients with residual tumor smaller than 2 cm. Two of these patients have now a disease free survival of 4+ respectively 6+ years. The experience with the treatment of patients with locally advanced or disseminated breast cancer described in Chapter 8 also supports the concept that high-dose chemotherapy may have a curative potential but that it should be applied in patients with limited tumor load. These 18 patients with breast cancer were treated with the intensification regimen after they were rendered disease free by 6 prior courses of remission-induction chemotherapy with adriamycin, 5-fluorouracil, methotrexate, vincristine and prednisone. To date, 24 patients with breast cancer have been treated that way with presently disease free survival in 13 patients.

To extend the scope of intensive treatment in solid tumors, new treatment combinations have to be defined. Two new cytostatic agents of interest for study in intensive chemotherapy regimens are mitoxantrone, an antracenedione derivative and carboplatin, a cisplatin analogue. Pharmacokinetic studies of new drugs are important to investigate the optimal moment for bone marrow reinfusion, because marrow stem cells should not be exposed to cytotoxic drug concentrations. The pharmacokinetic behavior of mitoxantrone and of carboplatin is described in respectively Chapter 9 and 10. We conducted a phase I trial with escalating doses of mitoxantrone plus cyclophosphamide. This combination was not feasible because of unexpected haemorrhagic cystitis. Therefore cyclophosphamide was replaced by melphalan. The maximally tolerable dose of mitoxantrone in combination with high-dose melphalan appeared to be 60 mg/m². Dose-limiting toxicity was mucositis of the oropharyngeal region.

High-dose carboplatin (750 mg/m²) was given as part of an ablative regimen to patients with testicular or ovarian cancer, who had been pretreated with cisplatin and who had a subnormal renal function. Carboplatin is less nephrotoxic than cisplatin because it has less (cell) protein binding and because the renal elimination of the drug is by glomerular filtration and in contrast to cisplatin not by tubular secretion. Nevertheless we observed one patient with impaired renal function who developed frank renal failure and signs of tubular damage during carboplatin treatment.

We conclude that high-dose chemotherapy with autologous bone marrow rescue offers response rates in various solid tumors as ovarian cancer, breast cancer and testicular cancer that are superior to the best available results with conventional therapy in comparable patient groups and has curative potential.
Breast cancer and ovarian cancer and possibly testicular cancer should be studied further as indications for this treatment strategy. We will continue the study with the cyclophosphamide plus etoposide regimen in breast cancer. For ovarian cancer a new regimen has been developed as described in this thesis, consisting of mitoxantrone and melphalan.

In the future, the applicability of carboplatin should deserve serious consideration. The renal function in patients previously treated with cisplatin should however be an area of concern.

Improvement on the current results of high-dose chemotherapy followed by ABMT can probably be reached by using it as a consolidation at the time of limited tumor load, by the use of new active drugs in ablative regimens and by application of post-intensification radiotherapy or appropriately timed surgery. Also the clinical benefits of the use of hematopoetic growth factors should be investigated because reduction of the period of severe granulocytopenia may lead to decreased morbidity and mortality.

These further improvements are critically dependent on clinical research facilities for this form of developmental medicine.