Summary and conclusions

The natural process of cell growth, differentiation and apoptotic death is regulated by a variety of peptide cell regulators. Produced by different cells, these cytokines work in an autocrine and paracrine way in the process of physiological growth, inflammatory states and malignancy. Recombinant DNA technology has made several cytokines available for clinical use. In medical oncology the recombinant cytokines have gained interest for their capability to mediate the regression of cancer and to reduce the myelosuppressive side effects of chemotherapy.

The present thesis deals with the clinical aspects of the use of cytokines as biological response modifiers in the treatment of cancer. In chapter 1 a review is given of the literature on the role of two recombinant human cytokines, interleukin-2 and interferon-alfa in the treatment of patients with disseminated solid tumors. IL-2 plays a central role in the induction of the immune response and this cytokine is able to induce tumor responses in approximately 20% of patients with renal cell cancer or metastatic melanoma. Therapy with IL-2 is however associated with substantial toxicity which is dependent on dose, schedule and route of administration. High dose intravenous application of this drug requires patient selection and intensive monitoring, while subcutaneous administration can be conducted as outpatient treatment. No apparent dose-response relationship is observed for IL-2, although different mechanism may be responsible for the in vivo observed antitumor activity at various doses. The addition of adoptively transferred activated cells has not consistently shown to improve the activity of IL-2 mediated immunotherapy.

Unlike IL-2, Interferon-α has a direct growth inhibiting and modulating effect on tumor cells. IFN is active in several hematological diseases. Its role in the treatment of solid tumors is limited to Kaposi’s sarcoma, renal cell carcinoma and melanoma although the synergistic effects with the cytostatic 5-fluorouracil are encouraging. The reversibility of the side effects of IFN, in contrast to those of many cytotoxic agents, makes it a worthwhile drug. A dose of 5 to 10 MU subcutaneously or intramuscular, at least three times a week has been found to be optimal.

Chapters 2 and 3 describe the efficacy and toxicity of sc administration of IL-2 in patients with RCC. Renal cell cancer is a tumor of tubular origin that is resistant to standard treatment modalities at the stage of metastatic disease. IL-2 has shown to be active in this disease and it is an accepted drug for the treatment of metastatic RCC in Europe and the USA. We found the subcutaneous route of administration to be associated with less severe toxicity than the standard intravenous administration, while antitumor activity was maintained in patients with RCC. Among 46 assessable patients with RCC we observed nine responses, for a response rate of 20% (9% to 34%, 95% confidence interval). Two patients had complete responses that lasted 29 and 35+ months. Toxicity of sc administered IL-2 consisted of local
inflammation and induration at the injection sites, fever, chills, nausea/vomiting, diarrhoea and mild hypotension. Subcutaneous IL-2 is active in patients with renal cell cancer and the toxicity profile enables treatment of patients with compromised organ function due to concomitant disease.

With the improvement of the tolerability of IL-2, the resistance to this form of treatment in the majority of patients emerges as even more of a challenge. The mode of action of IL-2 mediated antitumor responses in vivo are not understood. IL-2 is thought to act indirectly by stimulating and activating the cellular host defence mechanisms. Resistance to IL-2 treatment could therefore be the result of tumor dependent factors or alternatively be the result of factors related to the effector-cells. Several investigators have indicated an important role of cytotoxic T-lymphocytes in IL-2 mediated antitumor activity. Chapter 4 studies the addition of a monoclonal antibody (mAb) OKT3, targeting the CD3-part of the T-cell antigen-receptor, to the sc IL-2 treatment in an attempt to improve T-cell activation. While immunosuppressive at high doses, this mAb is a potent mitogen at low doses. In a phase I dose escalating setting we found a maximal tolerable dose of 400 µg OKT3 with neurotoxicity as dose-limiting factor. No increase of activated lymphocyte populations was observed in the range of 50 to 400 µg when compared with IL-2 monotherapy although the antibody was detectable on lymphocytes in vivo.

The observation of mixed responses, made in our patients on several occasions, suggests clonal differences in metastases as a cause for IL-2 unresponsiveness. Due to heterogeneity of the tumor, some cells seem to escape recognition by the immune system. In chapter 5 we studied the use of a bispecific monoclonal antibody to improve cell-cell interaction between activated effector-cells and tumor-cells in patients with renal cell carcinoma. In a phase I trial the bispecific monoclonal antibody BIS-1, targeting both CD3 and a 40 kD carcinoma-associated glycoprotein EGP-2, was combined with sc interleukin-2 treatment. This BsMab was toxic producing chills, peripheral vasoconstriction and dyspnea, with maximum tolerated dose of 5 µg/kg when given as a slow infusion. We showed that the BsMab binds to CD3 positive cells, with the development of BsMab-redirocted tumor cytotoxicity in an ex vivo assay. T-cells and monocytes disappeared from the peripheral blood after infusion of the BsMab and elevated serum levels of TNF-α and IFN-γ were detected.

In chapter 6 two case histories are described on the outpatient therapy with sc IL-2 in patients with advanced renal cell carcinoma who were on hemodialysis. It was shown that sc IL-2 induced immunological changes, similar to those observed after iv IL-2 therapy indicating in vivo induction of peripheral blood lymfokine activated killer cell (LAK) activity. We conclude that this treatment has a mild toxicity and can be given to patients with major organ dysfunction who are on hemodialysis.

Correspondence concerning two aspects of IL-2 related side effects are described in chapter 7. Combination of drugs can be useful to improve activity, but it also makes it
difficult to ascribe observed toxicities to one specific drug. The single-agent treatment with IL-2 could give additional information on this issue. While a high frequency of bacterial infection was observed with iv IL-2, and also in one study with combination of sc IL-2 and IFN treatment, the frequency of clinical significant infections during single-agent sc IL-2 treatment was low and did not indicate the requirement of prophylactic antibiotics in this setting. Neurotoxicity of IL-2 is dose and schedule related. In our experience with sc IL-2 neurotoxicity was rare and in most cases neurotoxicity was related to metastases in central nervous system localizations.

Chapters 8 and 9 describe two studies with recombinant IFN alfa-2a in combination with chemotherapy. In chapter 8, interferon is added to a combination of oral leucovorin and 5-FU to improve antitumor activity against colorectal cancer. This threefold combination was shown previously to be active with responses in 53% of 28 patients with colorectal cancer, but remission duration was disappointing with a median remission duration of 4.7 months. A clinical update of the regimen and the role of maintenance therapy in this setting is given in this chapter. In 50 assessable patients a response rate of 58% (43% to 72%, 95% confidence interval) was observed. The remission duration was improved in the patient cohort receiving maintenance therapy every 6 weeks compared to the cohort who received only the induction treatment, with median remission durations of 4.7 and 9.4 months, respectively. Overall survival of all patients was 17.2 months.

For patients with metastatic melanoma no treatment is available that has a substantial influence on their prognosis. Dacarbazine (DTIC) is one of few chemotherapeutic drugs that is marginally active. As a single-agent DTIC induces responses in 17% of patients. When combined with IFN, response rates up to 35% can be reached. Acute vomiting and myelosuppression, however are dose limiting toxicities of this drug at a standard dose of 800 mg/m² every 3 weeks. For several solid tumors, including melanomas, it has been shown that dose-intensity is an important factor for the efficacy of chemotherapy. With the availability of two new drugs that are capable of reducing chemotherapy induced side effects it might be possible to intensify the dose to improve therapeutic activity. Chapter 9 describes a study with dose escalation of dacarbazine in combination with interferon alfa-2a under support of the recombinant human hematopoietic growth factor G-CSF and the 5HT₁-receptor antagonistic antiemetic ondansetron in patients with metastatic melanoma. Individual DTIC-dose could be escalated up to 1500 mg/m² with thrombocytopenia and leucopenia as dose limiting factors. There was a marginal interference of IFN with the stimulation effect of G-CSF on leucocytes. Nausea and vomiting was controllable with the use of ondansetron in most patients. Among twenty assessable patient, four partial responses were observed. Dose escalation of DTIC did not appear to improve therapeutic activity.
Conclusions and perspectives

The use of recombinant cytokines as biological response modifiers in clinical medicine is established although the action mechanisms are only poorly understood. In clinical oncology immunotherapy has only a small role in selective tumors for which no alternative treatments are available. Despite the lack of clinical breakthroughs, the recombinant cytokines remain an important new modality in the treatment of cancer. Biological therapy is based on the capability of the immune system to recognize ‘self’ from ‘non-self’ by determinants on the cell membrane. Also the cytotoxic effects of immune effector cells take place at the level of the cell membrane, in contrast to most cytotoxic drugs that are targeting nuclear DNA. As it is not dependent on cell division or the penetration of drugs to the DNA, immunotherapy might be capable of eliminating those cells that escape chemotherapy because they are not dividing at the time of therapy. When used in combination, chemotherapy might alter epitopes on the cell membrane of tumor cells and thus make these cells more recognizable for the immune system. Recent studies with combinations of platinum containing chemotherapy and immunotherapy in patients with melanoma have been encouraging. Furthermore, it is speculated that in minimal residual disease at least for some patients the tumor is controlled by an interaction between tumor and the immune system. The reversibility of most side effects of immunotherapy, unlike those of chemotherapy, makes it a worthwhile alternative in the treatment in some forms of cancer. Since many aspects of immunotherapy remain investigational, this form of treatment should be conducted in the setting of clinical trial protocols.