Patient selection for high-dose chemotherapy in stage II and IV breast cancer
Schrama, J.G.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 9.

Summary
Chapter 9

Summary

Every year, over 11,000 women are diagnosed with breast cancer in the Netherlands. The majority of these patients will achieve long term survival (curation) by surgery, usually in combination with radiotherapy, systemic chemotherapy and/or hormonal therapy. When distant metastases occur, the disease is considered incurable. Breast cancer is a chemotherapy sensitive-disease and high-dose chemotherapy (HD-CT) has been employed as a strategy to achieve cure or long-term survival in patients with advanced disease. Although the results of the first randomized studies in advanced breast cancer have shown that the majority of patients have been treated with this therapy without achieving long-term survival, there are indications that a limited subgroup of patients with advanced disease can benefit of this approach. The toxicity of high-dose chemotherapy has decreased appreciably in the past few years, mainly due to the use of growth-factors, peripheral blood progenitor cells (PBPC) and better supportive care, but it clearly continues to be a toxic treatment modality. Consequently, it is crucial to identify predictive factors which make it possible to select the patients that will benefit from HD-CT. Several studies have reported prognostic and predictive factors for benefit of HD-CT in metastatic breast cancer patients. Most studies agree that limited disease, good clinical condition, younger age and responsiveness to conventional-dose chemotherapy are favourable factors. Analyses of data of the European Bone Marrow Transplantation (EBMT) registry of patients treated between 1990-1999 with HD-CT followed by autologous haematopoietic stem cell transplantation for breast cancer showed a 5-years progression-free survival (PFS) of 18% and an overall survival (OS) of 27% in the whole cohort and a 5-years PFS of 29% for women transplanted in complete remission.

In this thesis, the clinical course and potential predictive factors for response are examined in patients receiving HD-CT for advanced or locally advanced breast cancer in the Netherlands Cancer Institute.

In chapter 1, an overview of the available literature and a description of the principles of high-dose chemotherapy are given.

The literature on dose intensive chemotherapy in locally advanced breast cancer is reviewed in chapter 2. Dose intense chemotherapy prior to surgical treatment is effective in down-staging the tumour in order to make breast conserving surgery possible, even for larger tumour sizes. Although multimodality therapy has improved survival in patients with locally advanced breast cancer, many tumours relapse and since many patients still have microscopic disease at time of macroscopic remission, new therapeutic approaches focus on additional treatment of micrometastases.

Chapter 3 describes an update of the survival and an evaluation of the relation between outcome and pathology findings in a randomized phase II trial in patients with operable breast cancer with extensive lymph node involvement. In this study 97 patients received three FE$_{120}$C courses (5-fluorouracil 500 mg/m$^2$, epirubicin 120 mg/m$^2$, cyclophosphamide 500 mg/m$^2$) followed by surgery, and 81 patients were randomized to receive either a fourth FE$_{120}$C course.
alone or a fourth FEC course followed by a single course of HD-CT with autologous PBPC. After a median follow-up of almost 7 years, there was no difference in overall or disease-free survival, although less relapses occurred after high-dose therapy. Several prognostic factors were analyzed (age, clinical T-stage, pathological T-stage after chemotherapy, the number of positive axillary lymph nodes, oestrogen (ER) and progesterone receptor (PR), Her-2/neu, p53, histological grade, clinical response, and pathological response). Only the number of positive axillary lymph nodes (following induction chemotherapy) and clinical T-stage before chemotherapy were significant prognostic factors for OS. The same factors and the ER were borderline significant prognostic factors for PFS.

In chapter 4, the results are described of a phase II study of three consecutive courses of high-dose chemotherapy, 'tiny CTC' (tCTC, containing two thirds of the dosage of a standard CTC course: cyclophosphamide, thiotepa and carboplatin) in advanced breast cancer. In this study, 41 patients with metastatic breast cancer were enrolled to determine efficacy and toxicity of the following treatment sequence: two courses of FE_{120}C, the second of which was followed by PBPC harvesting, and subsequently three courses of tCTC. Thirty-three of the 41 patients received a total of 86 ‘tiny CTC’ courses. The major toxicity, besides myelotoxicity, consisted of hemorrhagic cystitis (six patients), prolonged gastrointestinal toxicity (three patients) and veno-occlusive disease of the liver (two patients). There was one therapy-related death of unknown cause. Twenty (49%) patients achieved a complete, nine (22%) a partial response and three patients stable disease (7%) after the high-dose treatment. At 4 years, the PFS and OS for the whole patient group were 23 and 30%. The results were better in the FEC-responsive patient-group, with median PFS and OS of 32 and 36% respectively. In the patient-group with a PFS longer than 18 months, all patients had limited disease (defined as metastatic disease in only one or two sites) and fewer patients had bone or liver metastases compared to the overall patient group (33 vs. 51%).

This study showed that three courses of tCTC are feasible, with acceptable toxicity and the potential to achieve complete or partial remission and even long-term PFS in a subgroup of patients with limited metastatic disease, which had responded to conventional dose induction chemotherapy.

In chapter 5, our findings are evaluated in relation to a study of Porrata et al., who reported a retrospective analysis of the absolute lymphocyte count (ALC) in 29 patients treated with HD-CT followed by PBPC for metastatic breast cancer. These investigators found that an ALC of equal or more than 500 cells/µl on day 15 post PBPC predicted a significantly better overall (OS) and disease-free survival (DFS). We retrospectively studied a quite similar group of 41 patients with hormone-refractory metastatic breast cancer treated in the phase II study described in chapter 3. We also analyzed lymphocyte counts before the start of the chemotherapy, because we could not exclude that patients with a lower lymphocyte count at day 15 already had a lower lymphocyte count to begin with. Thirty-three of the 41 patients received HD-CT. There was no significant difference between the survival curves of the patients with an ALC below or over 500 cells/µl at day 15 post PBPC. We also analyzed the
association with outcome of (i) the ALC count before start of induction chemotherapy, (ii) before HD-CT and (iii) at day 29 post PBPC. No significant relation was seen. Our study was small, however, and may lack the statistical power to detect smaller differences, if these should indeed exist.

Because of recent developments in hormonal and cytotoxic treatment, there are increasing possibilities for palliative treatment in patients with metastatic breast cancer. Most patients do relapse after HD-CT and if palliative chemotherapy was less effective and/or more toxic after HD-CT, this would reduce the treatment possibilities and this could therefore reduce the survival rate and the quality-of-life. The toxicity of the full dose high-dose chemotherapy CTC regimen is described in chapter 6. CTC has been shown to be able to improve the PFS when added to standard adjuvant therapy in patients with high-risk breast cancer and therefore the regimen has been selected for several high-dose chemotherapy studies in and outside the Netherlands. In this study we describe the immediate and long-term toxicity of the first 100 CTC courses (cyclophosphamide 6000 mg/m2, thiotepa 480 mg/m2, carboplatin 1600 mg/m2 followed by PBPC) in the Netherlands Cancer Institute. Most patients had high risk (n=86) or metastatic (n=4) breast cancer, eight patients had a germ cell tumour, one had a medulloblastoma and one an aesthesioneuroblastoma. Unsurprisingly, the main toxicity was bone marrow suppression. Most patients had PBPC transplantation followed by granulocyte-colony stimulating factor (GCS-F) and the median times to a neutrophil count of over 500x10^6/l and to platelet transfusion independence were 10 days (range 8-25) and 13 days (range 8-60), respectively. The therapy-related death rate was 1%. Neutropenic fever, bleeding episodes and gastro-intestinal toxicity were the most frequent toxicities. Six patients had reversible cardiac toxicity and seven patients had a pulmonary event (six patients had a pneumonia and one patient pulmonary embolism). We conclude that treatment with the high-dose CTC regimen is associated with moderate and reversible toxicity, which is acceptable in comparison with that of several other regimens employed for this purpose.

The most frequent late complication of the radiotherapy after HD-CT was radiation pneumonitis, reversible in all patients after treatment with prednisone. In the follow-up, five second malignancies (two melanomas, one squamous cell carcinoma, one basal cell carcinoma (all in the skin) and one mixed müllerian tumour of the ovary) were seen. Two patients were diagnosed with myelodysplasia, (in retrospect, one of these patients already had this disease before HD-CT).

Antitumour immunity may play a role in controlling minimal residual disease. It is therefore important to study cellular immunity after HD-CT, as a protracted recovery of the immunity could lead to a defective control of minimal residual disease.

In chapter 7, an analysis is presented of all patients treated with chemotherapy for recurrence or progression of breast cancer after HD-CT. We studied 148 patients who had received HD-CT for primary or metastatic breast cancer. In this patient-group, 79 patients had a relapse or progressive disease and 41 of these patients were treated with palliative chemotherapy. The most commonly used regimens were CMF (cyclophosphamide, methotrexate, 5-fluorouracil)
Summary

An doublet regimen. Both regimens were associated with acceptable toxicity. The highest response rate was seen for docetaxel (69%), but CMF also had a reasonable objective response rate of 23%. We conclude that palliative chemotherapy after HD-CT for metastatic breast cancer is both effective and safe.

In chapter 8 we studied the relation between amplification and overexpression of HER-2 and Topo-isomerase II alpha (Topo2A) and response to chemotherapy and survival in stage IV (metastatic) breast cancer. HER-2 is a transmembrane tyrosine-kinase receptor and its overexpression is the result of HER-2 amplification. There is strong evidence that the HER-2 amplification in tumours results in a worse prognosis, but a dose-dependent favourable response to anthracyclines has also been documented. The assumption is that this relative anthracyclin sensitivity is mediated by co-amplification of the Topo 2a gene together with the HER-2 gene, a result of their proximity on chromosome 17. Topo 2a is a key enzyme in DNA-replication and a well-documented target for anthracyclines. Several studies have already shown that HER-2 amplification is a negative predictor for the response to high-dose alkylating chemotherapy. We analyzed the HER-2 and Topo 2a overexpression with immunohistochemistry (IHC) and the amplification with Chromogenic In Situ Hybridization (CISH) in tumours of 59 patients treated with HD-CT for stage IV breast cancer. As suggested in the literature, all tumours that were HER-2 3+ by IHC also showed amplification with CISH. Only five tumours harboured excess copies of the Topo 2a gene and all of these also showed Her-2/neu amplification. We did not find Topo 2a amplification in any of the HER-2 negative tumours, supporting the co-expression hypothesis. No obvious correlation was seen between Topo 2a and HER-2 overexpression or amplification and the outcome in terms of PFS or OS. There was also no clear relation with the response to the induction anthracyclin therapy. We conclude that the previously suggested inverse relationship between HER-2 amplification and treatment outcome is not sufficiently strong to be detected in this small retrospective study.

Many papers have been written this last decade about the controversy of HD-CT in breast cancer. At this time, it is clear that high-dose chemotherapy in metastatic breast cancer is not as effective as hoped a decade ago. The prognosis of metastatic breast cancer remains poor. The data from seven randomized studies on HD-CT in advanced breast cancer have been published. Overall survival was analyzed in only four, because the other studies had a cross-over design. In these four studies, overall survival was similar for HD-CT and standard-dose therapy, but progression-free survival was improved in six of the seven trials. All studies were small, and lacked the statistical power to detect small but important differences in overall survival. Consequently, for a meaningful evaluation the meta-analyses have to be awaited. As metastatic breast cancer is still incurable, delay of progression is important in metastatic disease.

Breast cancer is a heterogenic disease and although it is clear that not all patients benefit, it is well possible that a subgroup of patients do benefit of dose intensive therapy. Recent data have shown that younger age and HER-2 negativity are favourable factors for HD-CT in the
adjuvant setting. The studies in this thesis suggest that HD-CT can induce long-term PFS in a subgroup of patients: the patients with limited disease responsive to (induction) chemotherapy. HD-CT can clearly be used for reducing the tumour load in these selected patients, but new treatment modalities must be developed to achieve control of the resulting minimal residual disease. It is also possible that high-dose chemotherapy is only likely to succeed in cure in patients with so-called ‘oligometastatic disease’, which refers to patients with metastatic disease in whom all macroscopic lesions can either be resected or irradiated. In this situation, the chemotherapy only needs to eradicate microscopic disease, a task which has been shown to be achievable in at least a part of the patients in the adjuvant setting.

In conclusion, it is too early to reject the concept of HD-CT in metastatic breast cancer as the outcome of metastatic breast cancer is poor and it is possible that a selected subgroup of patients benefits of dose intensive chemotherapy. The problem to delineate this subgroup continues to be a major challenge in the curative treatment of breast cancer.