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## Combined modality treatment in breast cancer

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## SUMMARY, CONCLUSIONS AND FUTURE DIRECTIONS

In spite of the promising results of mass screening programs to increase the number of early breast cancer patients, breast cancer still remains the leading cause of death in women in their fifth decade of life in most developed countries.

While adjuvant chemotherapy regimens have improved the life expectancy of early breast cancer patients, the side effects of these regimens remain an incurable problem.

As the disease free 10 years survival drops to almost zero in patients with more than three involved lymph nodes, there is an urgent need for new treatments to improve the efficacy of adjuvant treatment for this category of patients.

The hope of an effective treatment for these patients is not only based on the use of new drugs, but also on optimizing and intensifying the use of drugs that are already available. *Also of great importance is the improved understanding of the way in which anti-cancer drugs affect the tumour and normal tissue dynamics. In that respect problems of drug resistance and treatment related toxicity are of utmost importance and subject of this thesis. High-dose ablative chemotherapy with a tenfold higher dose compared to standard chemotherapy is nowadays feasible, because of the support of growth factors, autologous bone marrow transplantation (ABMT) and/or peripheral stem cell transplantation (PSCT). The treatment related morbidity and the impact on local control and long-term survival of the ablative chemotherapy regimens in patients with locally advanced and metastatic breast cancer has also been described in this thesis.*

In Chapter 2 a review has been given how to circumvent the problem of drug resistance, when using high-dose chemotherapy regimens followed by the support of growth factors and/or peripheral stem cell reinfusion. It was observed, that in the period after ablative chemotherapy there was an improved haematological recovery and a reduced duration of fever and hospitalisation by the addition of peripheral blood stem cells compared

to autologous bone marrow and growth factor support alone.

Also attention has been paid to the prediction of the presence of tumour cells not only in bone marrow but also in peripheral blood.

The new approach to protect tissue against chemotherapeutic drugs by transferring drug resistance genes into tumour cells, needs this resistance gene to be expressed. It has been emphasized that the use of drug resistant genes, by creating competent tumour cells, of drug resistant genes into tumour cells can be avoided, the use of drug resistant genes for the circumvention of chemotherapy-induced toxicity may be useful in the future. Furthermore, indications for high-dose chemotherapy in patients with solid tumours such as germ cell carcinomas, breast cancer, ovarian cancer and tumours of young adults like Ewing sarcoma has been discussed with special attention for this type of treatment in breast cancer patients.

Not only the results of high-dose chemotherapy in breast cancer patients with metastatic disease has been described, but also the results of high-dose chemotherapy in the adjuvant setting in patients with extensive disease in the axilla. The results did show not only an improvement of the disease free survival to 78% at a median observation of 50 months, but also an increase of radiopneumonitis up to 50%.

In Chapter 3 an induction chemotherapy regimen followed by a dose intensification with autologous bone marrow reinfusion has been reported in patients with locally advanced stage IIIb or disseminated stage IV breast cancer.

In 56 pre- or perimenopausal women with stage IIIb - stage IV breast cancer it was attempted to reach a state of complete response by a remission induction regimen containing prednisone, 5-fluorouracil, methotrexate, doxorubicin and vincristine. If successful, patients received an intensification regimen, consisting of cyclophosphamide 7 g/m<sup>2</sup> and etoposide 1.5 g/m<sup>2</sup> with autologous bone marrow reinfusion.

## SUMMARY, CONCLUSIONS AND FUTURE DIRECTIONS

In spite of the promising results of mass screening programs to increase the number of early breast cancer patients, breast cancer still remains the leading cause of death in women in their fifth decade of life in most developed countries.

While adjuvant chemotherapy regimens have improved the life expectancy for patients with early breast cancer, locally advanced (stage IIIb) and metastatic (stage IV) breast cancer remain an incurable disease.

As the disease free 10 years survival drops to almost zero in patients with more than three involved lymph nodes, there is an urgent need for new treatments to improve the efficacy of adjuvant treatment for this category of patients.

The hope of an effective treatment for these patients is not only based on the use of new drugs, but also on optimizing and intensifying the use of drugs that are already available. Also of great importance is the improved understanding of the way in which anti cancer drugs affect the tumour and normal tissue dynamics. In that respect problems of drug resistance and treatment related toxicity are of utmost importance and subject of this thesis. High-dose ablative chemotherapy with a tenfold higher dose compared to standard chemotherapy is nowadays feasible, because of the support of growth factors, autologous bone marrow transplantation (ABMT) and/or peripheral stem cell transplantation (PSCT). The treatment related morbidity and the impact on local control and long-term survival of the ablative chemotherapy regimens in patients with locally advanced and metastatic breast cancer has also been described in this thesis.

In **Chapter 2** a review has been given how to circumvent the problem of drug resistance, when using high-dose chemotherapy regimens followed by the support of growth factors and/or peripheral stem cell reinfusion. It was observed, that in the period after ablative chemotherapy there was an improved haematological recovery and a reduced duration of fever and hospitalisation by the addition of peripheral blood stem cells compared

to autologous bone marrow and growth factor support alone.

Also attention has been paid to the problem of the presence of tumour cells not only in bone marrow but also in peripheral blood. The new approach to protect tissue against chemotherapeutic drugs by transferring drug resistant genes into tissue that needs this resistance for its protection has been emphasized. If contamination with replication competent retrovirus and the transfer of drug resistant genes into tumour cells can be avoided, the use of drug resistant genes for the circumvention of chemotherapy-induced toxicity may be useful in the future.

Furthermore, indications for high-dose chemotherapy in patients with solid tumours such as germ cell carcinomas, breast cancer, ovarian cancer and tumours of young adults like Ewing sarcoma has been discussed with special attention for this type of treatment in breast cancer patients.

Not only the results of high-dose chemotherapy in breast cancer patients with metastatic disease has been described, but also the results of high-dose chemotherapy in the adjuvant setting in patients with extensive disease in the axilla. The results did show not only an improvement of the disease free survival to 78% at a median observation of 50 months, but also an increase of radiopneumonitis up to 50%.

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In 56 pre- or perimenopausal women with stage IIIb - stage IV breast cancer it was attempted to reach a state of complete response by a remission induction regimen containing prednisone, 5-fluorouracil, methotrexate, doxorubicin and vincristine.

If successful, patients received an intensification regimen, consisting of cyclophosphamide 7 g/m<sup>2</sup> and etoposide 1.5 g/m<sup>2</sup> with autologous bone marrow reinfusion.

Thirty-two patients who had no evidence of disease after induction chemotherapy received autologous bone marrow reinfusion after the dose intensification regimen. After a median observation of 4 years 11/19 patients with stage IIIb breast cancer were free of disease. In the stage IV group, only a relatively long time to progression of 15 months was observed.

It was concluded, that this approach prolonged disease free survival in stage IIIb breast cancer patients, but does probably not influence the survival in stage IV patients.

In **Chapter 4** the long term results of a phase II study consisting of induction chemotherapy followed by dose intensification supported with autologous bone marrow reinfusion in pre- or perimenopausal patients with stage IV or stage IIIb breast cancer has been reported.

Twelve patients with stage IIIb and 17 patients with stage IV breast cancer received a dose intensification chemotherapy regimen followed by autologous bone marrow reinfusion after complete response with induction chemotherapy.

Intensification consisted of cyclophosphamide 7 g/m<sup>2</sup> and etoposide 1.5 g/m<sup>2</sup> in 24 patients and thiotepa 800 mg/m<sup>2</sup> and mitoxantrone 50-75 mg/m<sup>2</sup> in 5 patients.

The median observation time was 7 years. The median survival of the patients with stage IIIb was 80 months. Thirty-three percent of the patients had a disease free survival of more than 5 years.

For patients with stage IV the median survival was 38 months.

Although the results especially in the group of patients with stage IIIb are promising, definite conclusions have to await comparative studies, that have been initiated.

In **Chapter 5** the outcome of cardiac toxicity studies in 27 stage IIIb and stage IV pre- and perimenopausal breast cancer patients, who were more than one year after induction chemotherapy followed by ablative chemotherapy with autologous bone marrow rescue combined with radiotherapy, has been evaluated. The majority of the patients (24) received a cumulative dose of 300 mg/m<sup>2</sup> doxorubicin,

while 3 patients received a cumulative dose of epirubicin 480 mg/m<sup>2</sup>.

Twenty patients received a mitoxantrone based ablative regimen. Seventeen of 20 patients with stage IIIb disease received 50-66 Gray (Gy) locoregional radiotherapy after ablative chemotherapy.

Cardiac evaluation consisted of a clinical functional classification according to the New York Heart Association (NYHA) standard with 12-lead electrocardiogram (ECG) and left ventricular ejection fraction (LVEF) by ECG-gated radio nuclide angiography with a LVEF of < 55% as the lower cut-off value. Only 1 patient who had a double transplant with a 4 year interval developed heart failure two weeks after the second transplant. Her LVEF dropped from 58% to 13%.

The other 26 patients had no clinical signs or symptoms of cardiac toxicity (NYHA classification 1).

These results are hampered by a limited follow-up and a small number of events. For this reason the impact of subclinical cardiac toxicity on the long term is not clear and needs continued evaluation.

In **Chapter 6** the pulmonary function after ablative chemotherapy with autologous bone marrow rescue and loco regional radiotherapy in 17 pre- and perimenopausal patients with advanced (stage IIIb) breast cancer has been reported.

Pulmonary toxicity was retrospectively analysed not only by evaluation of pulmonary signs and symptoms before, during and after the completion of therapy, but also the analysis of chest X-rays taken before chemotherapy, before radiotherapy and at 3 and 6 months after radiotherapy and thereafter once a year.

Pulmonary function tests include spirometry and single breath diffusing capacity. Functional data are described as percentages of predicted values, based on individual height and age. Pulmonary function parameters were considered abnormal when below 80% of the predicted value.

Clinical symptoms were graded according to Rothwell in mild (grade 1) requiring no treatment and marked (grade 2) requiring treatment.

The incidence of (1) and (2) in our study after radiotherapy or with completion of the course of therapy. Findings are supportive of functional tests and quality of life. In this limited series of 17 patients (median 43 months) a significant compromise in pulmonary function was not observed. An unexpected high incidence of interstitial pneumonitis. It is strongly suggested that this is caused by the intensity of the therapy regimen.

In **Chapter 7** the results of a study respectively pulmonary function tests or conventionally used radiotherapy and radiotherapy in patients with more than 5 years follow-up.

Between 1994 and 1997 10 stage II and IIIb breast cancer patients were randomized to cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) or cycles of 5-fluorouracil, epirubicin and cyclophosphamide, thiotepa (FECT) with haemopoietic growth factor support. All patients received radiotherapy. The impact of the

### Remarks and future directions

In patients with advanced and disseminated breast cancer, the use of autologous bone marrow rescue supported by autologous bone marrow support (ABMT) combined with transplantation combined with radiotherapy has been the subject of the last decade. As a result of the intensive chemotherapy regimen with a regional complication rate. Still too little is known about the sequelae like early pulmonary toxicity. Although preliminary life analysis as well as breast cancer follow-up pro-

The incidence of clinical symptoms (grade 1 and 2) in our study was 53% occurring during radiotherapy or within 2 months after completion of the course of radiotherapy. These findings are supported by the outcome of the functional tests and the chest X-ray analysis. In this limited series of 17 relatively young patients (median 43 years) without pretreatment compromised lung function, there is an unexpected high incidence of radiation pneumonitis. It is strongly suggested that this is caused by the intensification of the chemotherapy regimen.

In Chapter 7 the purpose is to analyse prospectively pulmonary function after ablative or conventionally dosed adjuvant chemotherapy and radiotherapy in breast cancer patients with more than three lymph nodes involved.

Between 1994 and 1998, 62 patients with stage II and III breast cancer were studied. Patients were randomised to receive either I: five cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) or group II: four cycles of FEC and high dose chemotherapy (cyclophosphamide, thiotepa and carboplatin (CTC) with haematopoietic stem cell rescue. All patients received locoregional radiotherapy. The impact of both schemes and

radiotherapy on the pulmonary status (clinical symptoms, chest X-ray and tests) was analysed.

The main results were: one patient died from pulmonary toxicity and 12 developed pneumonitis in the high dose group versus 10 patients with pneumonitis in the control group (n.s.). One year after the radiotherapy 6 patients in the high-dose group and 1 in the standard dose group had significant X-ray pathology ( $p < 0.005$ ). FEC chemotherapy led to a 6% reduction in the transfer-factor for carbonmonoxide ( $T_{L,CO}$ ) and 15% reduction in the diffusing capacity of the alveolocapillary membrane ( $D_m$ ). Radiotherapy in the high-dose chemotherapy group led to a decrease of 16.3% and 27.3%, respectively. In the control group this was 8.2% and 12.9% ( $p < 0.002$ ). After 12 months the excess toxicity in the high-dose group had disappeared. The conclusion of this study is that high-dose chemotherapy adds to the changes brought about by radiotherapy especially as far as the membrane factor in the pulmonary function is concerned. This additional effect is, however, reversible. The incidence of significant X-ray pathology of the lungs is higher in the high-dose group, but clinical symptomatology is the same.

### Remarks and future perspectives

In patients with locally advanced (stage IIIb) and disseminated (stage IV) breast cancer patients, the use of high-dose chemotherapy supported by autologous bone marrow transplant (ABMT) and/or peripheral stem cell transplantation (PSCT) with growth factors combined with locoregional radiotherapy has been the subject of extensive research over the last decade.

As a result of the improved support ablative chemotherapy is nowadays a feasible treatment with a reduced number of haematological complications.

Still too little is known about treatment related sequelae like early and late cardiac and/or pulmonary toxicity and the quality of life, although preliminary data from the quality of life analysis as part of a randomised adjuvant breast cancer study show that after a half year follow-up period there was no difference

between patients who received or did not receive high-dose chemotherapy and more over both groups did not differ from healthy individuals in that respect.

A goal for the future will be to determine subgroups of patients, that might benefit from dose intensification regimens and to limit treatment related toxicity to an acceptable level.

Rapid technological progress concerning detection of tumour cells in the peripheral blood, the easier access to peripheral stem cell technology, the potential use of drug resistant genes for tissue protection and conformal radiotherapy techniques to further reduce the irradiated volumes of the heart and the lung may allow further extension of this treatment. In the future new anti cancer drugs like paclitaxel and topoisomerase I inhibitors might also become useful in high-dose chemotherapy regimens.