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How to fit the treatment to the breast cancer patient

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Summary, conclusions and further remarks

In the Netherlands, breast cancer is the most frequent type of cancer in women. It is characterized by a wide spectrum of clinical behavior and is accompanied by a large variation in patient characteristics. The large amount of diagnostic possibilities and treatment options are reflected by the multidisciplinary approach of these patients. Chemotherapy is one of the treatment modalities, as breast cancer is considered by many as a systemic illness.

At first sight it seems that there is a clear difference between adjuvant chemotherapy after a curative primary treatment and palliative chemotherapy for metastatic disease. However, patients with a high number of positive axillary lymph nodes have an unfavorable prognosis and a poor chance of survival, despite adjuvant chemotherapy. With high dose chemotherapy in combination with autologous bone marrow transplantation (ABMT) or peripheral blood stem cells transplantation (PSCT) it seems possible for a subset of these patients to reach long term survival and possibly even cure.

In this thesis a number of tumor and patient characteristics, treatment options with emphasis on chemotherapy and several aspects of quality of life and long term toxicities are discussed. The optimization of standard adjuvant CMF (cyclophosphamide, methotrexate and 5-fluorouracil) with the help of a growth factor is described, but the main part of the thesis concerns the experience with high dose chemotherapy in combination with ABMT and/or PSCT and growth factors.

In **chapter 1** a review is given with respect to the question how to fit the appropriate treatment to each breast cancer patient. Tumor and patient characteristics should be the basis, on which treatment decisions are taken.

Different treatment options are discussed: standard, new and high dose chemotherapy in primary, metastatic and special forms of

breast cancer and for special patient groups. The dose and dose-intensity of the chemotherapy appear to be important with respect to the efficacy of the treatment in the adjuvant as well as in the metastatic setting. The role of the anthracyclines as well as new drugs such as the taxanes are discussed. High dose chemotherapy with a tenfold higher dose compared to standard is feasible because of the support of growth factors, ABMT and/or PSCT. However, randomized studies with respect to high dose chemotherapy are not yet available and high dose chemotherapy should therefore still be considered an experimental treatment.

Aspects of quality of life and long term toxicities, such as cardiotoxicity are increasingly studied and recognized as highly important in the choice of treatment.

In **chapter 2** a cytological scoring system is evaluated with the intention to use it as a prognostic factor. The histological grade of the tumor is a well known and reproducible method, used to predict prognosis.

As cytology is an earlier and easier diagnostic procedure compared to histology, the cytological score is evaluated in this chapter on the potential to predict the histological grade.

In conclusion, the cytological scoring system we have tested reliably predicts the presence of well or moderately histologically graded tumors, as shown by 80% concordance (95% confidence interval 63-92%) between a low cytology score and low histology grade. However, the number of high grade tumors is overestimated, as shown by only 45% concordance (95% confidence interval 23-68%) between a high cytology score and high histology grade. Cytological grading did not have independent prognostic value at a median follow up of 8 years.

In **chapter 3** a method is studied, which can detect low numbers of epithelial tumor cells in peripheral blood and bone marrow. The significance of micrometastasis detection in blood and bone marrow

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is as yet unknown, but is of potential prognostic importance. Because it is likely that tumor cells are reinfused to the patient with the autograft when using the support of ABMT and/or PSCT for high dose chemotherapy, the quantitative detection of tumor cells in the graft is of clinical interest. With the possibility to detect low numbers of tumor cells it is also possible to evaluate the effect of techniques, who eliminate tumor cells from blood or bone marrow (the so called 'purging').

To detect low numbers of epithelial tumor cells, an epithelial glycoprotein (EGP-2) based, quantitative nested, reverse transcriptase-polymerase chain reaction (RT-PCR) assay is evaluated in this chapter. In this study, a considerable range in EGP-2 transcript levels was found in different carcinoma cell lines and normal bone marrow. An unexpected low expression of EGP-2 was found in peripheral blood mononuclear cells. The expression in normal blood prevents reliable estimations of low number of epithelial tumor cells in clinical samples, as the detection level of the highest EGP-2 expressing carcinoma cells added to peripheral blood was not better than one tumor cell in 2×10^4 normal cells.

Chapter 4 reviews the treatment in elderly patients, because age is a patient characteristic directly or indirectly influencing the breast cancer treatment in clinical practice.

The incidence of breast cancer is increasing with age; 30-50% of the patients are over 65 years. This large group of patients receives less screening and treatment compared to younger patients. How to treat elderly patients should not be based on age, but should be balanced with relative and absolute contraindications in patients who might also have other age related diseases.

The first choice for adjuvant treatment is often hormonal, as in other postmenopausal patients. In palliative treatment hormonal therapy will be first choice as well, but there may be some indications for the use of chemotherapy, such as irresponsiveness to hormonal therapy, estrogen receptor-negative tumors or in progressive or life-threatening

disease. Different chemotherapeutic possibilities are described, focusing on pharmacodynamics, pharmacokinetics and drug interactions in elderly patients.

In **chapter 5** a clinical study is presented in which the growth factor granulocyte-colony stimulating factor (G-CSF) is used with the goal to reduce the hematological toxicity, optimizing the dose and dose intensity of standard adjuvant CMF chemotherapy.

This study was started, because total dose and dose intensity are important means to improve disease free survival (DFS) and overall survival (OS) and hematological toxicity, mainly consisting of inadequate leukocyte recovery, is the most important cause of dose and dose intensity reduction. Bonadonna et al. have shown in a retrospective analysis that the efficacy of the routinely used adjuvant CMF is dependent on the total dose actually administered. A cumulative of 65-85% of the projected dose was associated with a worse DFS, compared to a delivered dose over 85%. For a dose under 65% the DFS was similar to controls, who received no adjuvant treatment. In our study the use of G-CSF resulted in adequate hematological recovery in 83% of the following chemotherapy cycles. In patients with inadequate leukocyte recovery at the start of a planned chemotherapy cycle, the dose intensity of the patients who received G-CSF was higher compared to those who received no G-CSF. It was however not possible to reach the maximum dose intensity comparable to the patients with spontaneous adequate hematological recovery. A negative impact of radiotherapy on hematological recovery of leukocytes and platelets was found in this study.

In **chapter 6** a review is given addressing some aspects relevant to the administration of high dose chemotherapy.

This article discusses the optimization of bone marrow recovery after high dose chemotherapy by the addition of PSCT and growth factors to ABMT and the issue of tumor cell contamination of peripheral

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The pros and cons and different options of PSCT are reviewed. A peripheral blood stem cell is harvested after mobilization with a growth factor alone, chemotherapy alone or after chemotherapy followed by a growth factor, mostly G-CSF or GM-CSF, but combinations of various growth factors including the interleukins 3 and 6 are of potential advantage with regard to the quality of the graft. It is concluded that high dose chemotherapy in solid tumors is nowadays a feasible treatment due to the reduction of hematological complications such as infections and bleeding due to PSCT, ABMT and the improved support by growth factors.

The relevance of tumor cells in reinfused blood stem cells or bone marrow is as yet unknown. As it is thought that only a low number of circulating tumor cells are 'successful' in establishing metastatic colonies, techniques such as immunocytochemistry and PCR are being developed. Several 'purging' techniques to eliminate tumor cells from peripheral blood stem cells and bone marrow, such as lectin separation, immunoseparation and immunomagnetic beads-separation in combination with toxins or chemotherapy are discussed.

In **chapter 7** the efficacy and toxicity of an intensive induction regimen as preparation for high dose chemotherapy was studied. Patients with locally advanced or metastatic breast cancer were treated 4 weekly with an regimen consisting of 6 cycles methotrexate, 5-fluorouracil alternating with 6 cycles doxorubin, vincristine and prednisone.

In conclusion, the induction regimen is effective, as it carries 77% overall responses with 43% complete responses and the toxicity profile is acceptable, except for the patients with liver metastases, as their incidence of leucopenic fever was 32% and cerebellar 5-fluorouracil neurotoxicity amounted to 25%.

Chapter 8 describes the use of adjuvant high dose chemotherapy in combination of ABMT for breast cancer patients, who have a poor

prognosis based on the presence of 5 or more positive axillary lymph nodes. After pretreatment with the induction regimen as described in chapter 7, the high dose chemotherapy consisted of a combination of either cyclophosphamide+etoposide or mitoxantrone +thiotepa.

The conclusion of this study is that the regimen appears to be effective, as the 5-year predicted DFS is 84%. However, the treatment is toxic, because 2 out of 24 patients died due to the treatment. It is still impossible to draw definite conclusions on the superiority of high dose chemotherapy, as it is necessary to await randomized studies comparing standard with high dose adjuvant chemotherapy.

In **chapter 9** the effect of PSCT in addition to ABMT and a growth factor in the adjuvant treatment with high dose chemotherapy for breast cancer patients with 5 or more positive axillary lymph nodes is described. The addition of PSCT to ABMT and a growth factor improves the rate of hematopoietic reconstitution with a decrease of 4.5 days in duration of neutropenia (leukocytes under $0.5 \times 10^9/l$ decreased from 14.5 days to 10 days) and of 9 days in thrombopenia (platelets under $20 \times 10^9/l$ decreased from 25 to 16 days).

The addition of PSCT also diminishes hematopoietic complications such as infections and reduces the number of platelet- and blood transfusions and days of hospitalization. With the addition of PSCT, the safety of high dose treatment has increased, although it is still considered an experimental treatment, the toxicity of it has decreased substantial.

In **chapter 10** attention is paid to the occurrence of long term cardiotoxicity as one of the late complications of high dose chemotherapy in combination with radiotherapy.

With the improvement of the efficacy of the treatment, especially in the adjuvant setting leading to more long term survivors, it is relevant to pay attention to aspects of quality of life and long term complications.

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In a group of 86 patients, treated with high dose chemotherapy and radiotherapy, the estimated 7-years percentage of clinical and subclinical cardiac dysfunction is 22% (95% confidence interval 5-39%).

The observed cardiac dysfunction in this study concerns 6 patients. One patient (1%) died three months after high dose chemotherapy of subacute cardiac failure. One patient, who was treated exceptionally with two transplantations, has serious congestive heart failure. Minor subclinical cardiac dysfunction, as measured on the radionuclide angiography measuring the left ventricular ejection fraction (LVEF), was found in 4 out of 26 evaluated patients.

In conclusion, long term cardiotoxicity should receive more attention, but thus far it does not hamper the use of high dose chemotherapy in patients who will otherwise have a poor chance of survival.

Further remarks

Breast cancer is a considerable medical, emotional and economical problem. It is at life-time observation diagnosed at 1 out of 10 women in the Netherlands.

Due to the heterogeneity of the tumor and the patients the clinical course is very variable. It is important to make a treatment tailored to the tumor, but also to patient characteristics. The improvement in breast cancer prognosis appears less impressive compared to other types of cancer, such as testicular carcinoma and the hematological malignancies, but in breast cancer progress is still ongoing in early detection, screening, recognition of hereditary factors and more effective chemotherapy.

The introduction of adjuvant chemotherapy by Nissen-Meyer et al. from Norway by cyclophosphamide monotherapy in 1965 and of CMF in 1973 by Bonadonna et al. from Milan, which is at present a standard treatment, has given an absolute improvement in 10-year OS of approximately 10%. The profit in survival, due to adjuvant

chemotherapy, depends on the number of positive axillary lymph nodes. Anthracycline-containing schedules, introduced in the eighties, carry an improved survival over CMF in the case of 4-10 positive axillary lymph nodes. In the adjuvant situation, the place of new drugs such as the taxanes still have to be defined. The survival gains achieved with chemotherapy in the treatment of metastatic disease is modest and cure is rarely obtained.

The use of high dose chemotherapy supported by ABMT and/or PSCT with growth factors is the subject of extensive research over the last years. High dose treatment is nowadays a feasible treatment with a reduced number of hematological complications such as infections and bleedings as a result of ABMT, PSCT and the improved support with growth factors. Still too little is known about the quality of life and the long term toxicity inherent to this treatment. The results of non-randomized studies with high dose chemotherapy in the adjuvant situation are promising, but the results of the in the early nineties started randomized studies have to be awaited. With the use of high dose chemotherapy it seems possible for a small subgroup of patients with metastatic disease to achieve long term survival and maybe even cure, but in this situation it is necessary to await further randomized studies.

The importance of high dose chemotherapy weighing efficacy against toxicity will not be clarified before the 21st century. To achieve further improvements in the future, a protocolized and multidisciplinary handling of breast carcinoma is necessary, treating as much as possible of these patients in randomized trials as a primary goal, in order to reach valid conclusions about the value of these intensive and expensive treatment modalities.