Impact of age, tumor characteristics, and treatment on local control and disease outcome in early stage breat cancer : an EORTC translational research project

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CHAPTER 10

General Discussion

This thesis consists of three parts.

In part I, we demonstrate that neoadjuvant and perioperative chemotherapy are very feasible treatment options in early stage breast cancer patients. Both treatment strategies result in equal or better results in terms of disease outcome as compared to conventional postoperative adjuvant chemotherapy. In addition, the higher breast conserving therapy rate after neoadjuvant chemotherapy described in Chapter 3 and the potential to assess tumor response as a prognostic factor as stipulated in Chapter 4 are attractive characteristics of this type of treatment.

In part II, we demonstrate that locoregional treatment strategy may be based on tumor cell characteristics and patient age. Next, we describe the significant impact of adequate locoregional treatment on locoregional control as well as overall survival. For example in *Chapter 6*, we show in a selected subgroup of patients bearing 1 to 3 metastatic axillary lymph nodes, that adjuvant radiotherapy after mastectomy was associated with superior locoregional control and survival rates. In addition, in *Chapter 7* we attempt to identify baseline risk factors, i.e. factors assessed at time of diagnosis of the primary tumor, for locoregional recurrence.

In part III, we demonstrate that very young breast cancer patients can be divided in good- and bad prognosis groups based upon tumor characteristics. The current guideline that all very young breast cancer patients should receive chemotherapy irrespective of tumor characteristics can therefore be questioned. Next, we demonstrate that tumor grade is a strong and independent prognostic factor for distant metastasis-free survival and overall survival in this specific subgroup of very young breast cancer patients. Finally in *Chapter 9*, a trend is described suggesting inferior chemosensitivity in estrogen receptor (ER) positive and/or progesterone receptor (PgR) positive very young breast cancer patients as compared to their ER and/or PgR negative counterparts.

Breast cancer treatment is making progress. New therapies are introduced and existing ones are further modified. One of these modifications is the result of studies that focused on timing of administration of adjuvant systemic therapy which has resulted into the introduction of neoadjuvant chemotherapy in the treatment of breast cancer. Level I evidence is currently available for this type of treatment for both locally advanced breast cancer patients and early stage breast cancer patients [1-3].

While survival and progression free survival have not yet been improved by neoadjuvant chemotherapy in early breast cancer patients, breast conserving rates have risen with acceptable locoregional control rates when surgery is not omitted from the locoregional regime after neoadjuvant chemotherapy [1,4,5].

In the Netherlands however, neoadjuvant chemotherapy in early stage breast cancer patients is still not being administrated on a routine basis although these patients might definitely benefit from this treatment strategy. One of the potential reasons for this conduct could be the reluctance of doctors to administrate systemic treatment before definitive staging has been performed. However, the decision whether or not

systemic chemotherapy will be indicated in a case of early breast cancer can to a large extent very well be established by preoperative core needle biopsy and/or fine needle aspiration of tumor and potential suspect axillary lymph nodes in combination with physical examination and diagnostic imaging. In addition, the indications for the administration of adjuvant chemotherapy have widened which has resulted in a higher a priori probability for receiving chemotherapy. Therefore, a shift in paradigm concerning treatment strategy of early breast cancer patients in the Netherlands is needed.
Although the Dutch situation may cause some concern, research concerning neoadjuvant treatment in breast cancer has gained a lot of interest and many trials studying different neoadjuvant chemotherapy regimens are being conducted. Research concerning neoadjuvant trials in early stage breast cancer should be focused on four major topics:

1) Translational research. It is important to note that the response to neoadjuvant chemotherapy in vivo could provide a useful prediction of prognosis and help define strategies for an individual patient's future treatment with alternative chemotherapy regimens or molecular-targeting agents. Furthermore, the discovery of predictive markers for tumor response to neoadjuvant chemotherapy through the analysis of complementary DNA microarrays and proteomics may also help facilitate individualized chemotherapy, particularly by improving survival in patients with breast cancer with a poor prognosis. Therefore, translational research has to be focussed on classical and molecular tumor characteristics and their response, i.e. up- or downregulation, to established and experimental chemotherapeutic regimens and the assessment of chemosensitivity in terms of tumor response [6,7].

2) Tumor monitoring modalities. Adequate assessment of tumor response and pretreatment staging are vital in the neoadjuvant chemotherapy setting. Imaging of tumor response has several implications;
First, tumor response is considered as an independent prognostic factor on treatment outcome and therefore should therefore be monitored meticulously [8].

Second, diagnostic modalities such as MRI and CT need to be prospectively evaluated to study whether or not they yield superior results over classical ways of imaging like ultrasonography and mammography. Breast MRI has been assuming an important role in the assessment of the extent of cancer and may be more accurate than conventional modalities such as mammography and ultrasonography. On the other hand, MRI is associated with an increase in invasive therapeutic and diagnostic procedures for benign abnormalities due to high false-positive rates. Therefore, MRI may be feasible in a population of high risk patients but not in all early stage breast cancer patients. In conclusion, the exact role of MRI in breast cancer and the assessment of neoadjuvant chemotherapy needs to be determined [9-15].

Finally, imaging of tumor response is of significance considering optimalization of subsequent breast conserving surgery. Tumor margins after neoadjuvant chemotherapy have been a matter of concern. Tumor response does not always lead to a decrease in tumor volume but can result in less tumor density. Although EORTC

trial 10902 did not demonstrate a higher locoregional recurrence rate in downstaged patients who underwent breast conserving surgery, meta-analyses which included trials in which surgery was omitted after neoadjuvant chemotherapy demonstrated inferior local control rates. Therefore the diagnostic preoperative assessment of residual tumor after neoadjuvant chemotherapy is important [16,17].

3) Studies addressing the relation between locoregional treatment and neoadjuvant chemotherapy, for instance the feasibility of sentinel node procedure after neoadjuvant chemotherapy and quality of life studies concerning the psychological effect of breast conserving therapy after tumor downstaging. Sentinel node biopsy after neoadjuvant chemotherapy has been a matter of debate. Retrospective series have demonstrated acceptable accuracy rates comparable to sentinel node biopsies in the primary surgery setting. Recently, the first meta-analysis concerning sentinel node biopsy after neoadjuvant chemotherapy has been published and the accuracy rates in this study are in accordance with previous reports suggesting satisfactory feasibility of this surgical treatment modality [18,19].

4) The efficacy of neoadjuvant hormonal therapy either by tamoxifen or by aromatase inhibitors. With recent advances in endocrine therapy, and rapid and routine assessment of predictive factors of response such as estrogen (ER), progesterone (PR) and Her2 neu receptor status, endocrine therapy has come to the forefront of research investigating a neoadjuvant alternative to chemotherapy. Early studies of neoadjuvant endocrine therapy mainly evaluated the role of tamoxifen in the treatment of elderly postmenopausal women with LABC who were unselected for ER/PR status and who were unsuitable for either surgery or chemotherapy. Response rates in these patients were found to be inferior to those traditionally obtained from trials with neoadjuvant chemotherapy. Parallel to the superiority that third-generation aromatase inhibitors have shown over tamoxifen in the metastatic and adjuvant settings however, AIs have also demonstrated superiority in the neoadjuvant setting. Recent studies have shown response rates for neoadjuvant treatment with aromatase inhibitors in carefully selected hormone receptor positive patients to be comparable to those seen with neoadjuvant chemotherapy. This is particularly important as hormone receptor positive tumors have repeatedly been shown to have lower response rates to neoadjuvant chemotherapy than hormone receptor negative tumors [20-22].

Next, when neoadjuvant chemotherapy is not feasible and adjuvant chemotherapy will be administrated postoperatively, the first course of chemotherapy can be given in a perioperative setting which means that the patient receives the first course of chemotherapy within 36 hours after surgery. Perioperative chemotherapy, as mentioned previously in Chapter 2, is based principally upon evidence from murine models demonstrating surgery-induced proliferation of tumor cells that responded well to early administration of chemotherapy [23,24].

EORTC trial 10854, of which the long term results are presented in this thesis demonstrated that this is a safe and feasible treatment modality which may have an impact on locoregional control as well as on survival in selected groups of patients [25].

Concerning locoregional therapy, different strategies should be employed in different risk groups, for instance based upon age. Young breast cancer patients who are at a high risk for locoregional recurrence, especially with histologically aggressive tumors should be offered mastectomy with immediate or delayed reconstruction. Locoregional control rates and patient satisfaction could be improved [26-29].

On the other hand, standard administration of chemotherapy in young patients with node negative breast cancer can be questioned. Since risk ratios between young and older breast cancer patients have moderate differences, subgroups within the young age group could be identified where chemotherapy should not have been applied irrespective of other patient and tumor characteristics. For instance, node negative breast cancer patients bearing small grade I tumors have an excellent prognosis and might not receive a clinically relevant benefit from adjuvant chemotherapy but they do receive the burdens.

Thus, translational research concerning risk groups of young breast cancer patients who might benefit from chemotherapy is needed. Recently, translational research has been accelerated due to the introduction of micro-array analysis [30-33].

This highly promising technique using high throughput gene chips is not yet fully validated but may enable treatment tailored strategies in the future. However, until thorough validation of microarray is established and demonstrated, classical tumor prognostic factors have to be used. Currently, neoadjuvant chemotherapy trials are already being conducted with the incorporation of tumor markers in their study design [34-36].

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