Optimising preoperative systemic therapy for breast cancer

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Chapter 10

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General discussion

Preoperative systemic therapy

Breast cancer care has been the subject of vivid changes over decades. Our current beliefs and understandings of breast cancer are only a shadow of those in the so-called 'Halstedian' 1950s, when treatment for breast cancer encompassed radical mastectomy, with dramatic negative impact on post-surgical cosmetic outcome and quality of life.(1;2) Over the years, there have been drastic paradigm changes. Nowadays, systemic therapy, stratified on basis of hormone- or HER2-receptor status, targeting micrometastases, plays a central role in breast cancer care next to surgical treatment and radiotherapy. Furthermore, the last decade has been marked by the introduction of neoadjuvant systemic therapy in the management of early breast cancer. The main beneficial feature of this treatment modality is that it results in better surgical outcome, by rendering inoperable tumours operable and by making tumours eligible for breast-conserving surgery.(3;4) Furthermore, it provides a rapid model for evaluating drug efficacy, especially in triple-negative and hormone receptor negative/HER2 positive tumours.(5;6)

In this thesis, results are reported from investigations using the neoadjuvant setting to either evaluate drug efficacy, biological impact of systemic therapy, or possible predictive factors for sensitivity and toxicity of systemic therapy. In this final chapter of my thesis , I will further discuss our results in the context of the current state of the art of the treatment of breast cancer and in the near future.

Implications for surgical treatment

Preoperative systemic therapy increases the number of tumours feasible for breast-conserving surgery.(7) Breast-conserving surgery has been proven to be a safe treatment option with no difference in local recurrence compared to mastectomy.(7) Of note, a Cochrane systematic review on this matter delineated that this equivalent locoregional outcome was only observed in studies that included surgery as part of the treatment, even after complete clinical remission of the tumour after preoperative systemic therapy.(7) Current radiological modalities, for measuring residual disease, such as MRI, are not as accurate as the gold standard of histopathological evaluation.(8) In this thesis, we showed that especially in ER-positive/HER2-negative breast cancer cases the accuracy of MRI is limited, possibly resulting in inadequate surgical planning by overestimation of tumor size. Therefore, surgery should remain part of breast cancer treatment, at least for as long as there is no fully accurate response assessment modality available (11 (chapter 5).

Preoperative systemic therapy can downstage the axilla by rendering clinically node-positive tumours to pathologically node-negative tumours, by which axillary lymph node dissection can be spared in 20-44% of clinically node-positive patients.(3;9;10) In view of providing tailor-made treatment for breast cancer patients, it is recommended that sentinel lymph node biopsies are performed after neoadjuvant therapy, so that the downstaging advantage of neoadjuvant therapy is utilized to the maximum extent.

Developments in primary systemic therapy

Preoperative systemic therapy can be broadly divided into two groups: chemotherapy and targeted therapy (hormonal therapy and anti-HER2 agents. Neoadjuvant chemotherapy is highly effective for achieving pathological complete response of tumours, especially in patients with triple-negative breast cancer or patients with hormone receptor negative/HER2-positive breast cancer that are concurrently treated with trastuzumab.(11) Studies have shown that the occurrence of a pathological complete response after neoadjuvant therapy is associated with improved survival in all breast cancer subtypes.(6;11) This has led to the establishment of an accelerated approval program by the United States Food and Drug Administration for drugs used for high-risk, early stage breast cancer.(12) For example, in 2013, pertuzumab became the first drug that was approved in a fast track when added to trastuzumab in addition to neoadjuvant chemotherapy for HER2-positive breast cancer, despite lack of survival data compared to neoadjuvant trastuzumab alone with chemotherapy.(13;14)

Another drug that can potentially increase pathological response, and thus survival, after preoperative systemic therapy is the bisphosphonate zoledronic acid.(15) Currently bisphosphonates are indicated for prevention of chemotherapy-induced osteoporosis and for the symptomatic treatment of bone metastases. However, bisphosphonates may also confer a survival benefit. A well-conducted Oxford meta-analysis in 17.000 patients showed that the upfront addition of bisphosphonates to adjuvant systemic therapy resulted in reduced risk for bone metastases and breast-cancer mortality in postmenopausal women.(16) Bisphosphonates may also be of value in the neoadjuvant setting (chapter 2).(17) In this thesis results from the prospective phase III NEOZOTAC study are described (chapter 3).(18) In this study, no benefit of zoledronic addition was observed in the total population in terms of pathological complete response in breast and lymph nodes, although postmenopausal women tended to experience benefit from the intervention. A pooled analysis of all four randomized trials investigating addition of zoledronic acid to neoadjuvant therapy showed that postmenopausal women significantly more often achieve pathological complete response after addition of zoledronic acid than their premenopausal counterpart (chapter 4).(19) This finding raises two important questions. The first question is in which way zoledronic acid exerts its suggested anti-tumour mechanism. It is still unclear how a bone-targeting drug can result in disappearance of tumour cells in breast tissue, which is 'distal' from the bone. One of the proposed mechanisms is that zoledronic acid can modulate immunological cells in the tumour microenvironment. For example, a study by Chinault et al. showed that zoledronic acid rather affects macrophages than tumour cells after sequential short-term administration with doxorubicin.(20) The second question concerns the specific benefit in postmenopausal women. This may be explained by the fact that postmenopausal women have increased bone turnover.(21) Also, estrogen deficiency is associated with increased inflammatory response, possibly enhancing the immunomodulatory effect of zoledronic acid, in case such an effect will prove to be the main determinant of increased pathological tumour response.(22) Further basal and translational investigations will hopefully provide answers to these two questions.

Neoadjuvant chemotherapy administration can result in adverse events such as vomiting, diarrhoea and haematological toxicity, making it unsuitable for subsets of frailer patients.(18)

In these women, in order to achieve tumour shrinkage and breast-conserving surgery, endocrine treatment targeting hormone-responsive tumours may be a suitable alternative with a less dramatic toxicity profile than chemotherapy (chapter 7).(23) In addition, neoadjuvant endocrine treatment may be administered as a primary treatment in elderly patients that are unfit for surgery and have a relative short life-expectancy. In a study by Dixon et al., elderly patients were treated with letrozole with treatment durations up to 2 years.(24) Continuous tumour size shrinkage was observed after 3 months. Nonetheless, so far, most studies on neoadjuvant endocrine therapy have used treatment durations of 3-4 months.(23;25-27) The TEAMIIa trial aimed to investigate whether longer treatment duration results in safe and continuing tumour response. Indeed, after 6 months of exemestane treatment, patients had significantly smaller tumours than after 3 months (chapter 8).(28) This result is in line with the advise given at the 13th St. Gallen International Breast Cancer Conference in 2013., The majority of the attending breast cancer experts in the opinion based consensus panel voted for treatment with neoadjuvant endocrine therapy upon maximum response in patients with endocrine-sensitive breast cancer.(29) Nonetheless, it appears that there is still a kind of reluctance amongst breast cancer specialists to treat patients with (6 months of) neoadjuvant endocrine therapy, instead of perfornming immediate surgery. This is exemplified by the slow accrual of the TEAMIIa study, which resulted in a change from the original phase III design, comparing 3 and 6 months treatment duration, to a phase II study in which all patients were allocated to 6 months of exemestane treatment. Hopefully, results from our study in combination with the experts' opinion will lead to better acceptance of this treatment option.

As regards neoadjuvant exemestane therapy, we found that adverse events causes by estrogen depletion, such as hot flashes and musculoskeletal adverse events, are positively associated with tumor shrinkage (chapter 9). Sharing this information with patients experiencing these detrimental effects may positively influence treatment compliance. Further research is warranted in order to investigate whether monitoring changes in circulating estrogen levels may also be a measure for aromatase inhibitor efficacy.

To date, the only other registered targeted breast cancer therapy available in the neoadjuvant setting in Europe is the blockade of the HER2 receptor with the monoclonal antibody trastuzumab . Addition of trastuzumab to chemotherapy for HER2-positive breast cancer has shown a large increase of the chance to obtain a pathological complete response. For example, in the NOAH trial, pathological complete response reached an impressive 43% in the trastuzumab intervention arm.(30)

Next to endocrine therapy and HER2-targeted therapy no other targeted therapies are thus far clinically available. In the past few years several possible new players in targeted treatment for breast cancer agents have emerged, such as the selective inhibitor of the mammalian target of rapamycin (mTOR) everolimus, phosphoinositide 3-kinase inhibitor (PI3K inhibitor) inhibitors, CDK4/6 inhibitors and poly(ADP ribose) polymerase (PARP) inhibitors. These agents have shown promising results in patients with metastatic breast cancer and are currently tested in the neoadjuvant setting.

From stratified to individualized therapy

Currently, treatment decisions are partly stratified on basis of the receptor status of tumours. Hormone-receptor positive tumours can be treated with endocrine therapy and HER2-positive tumours can be treated with trastuzumab and in the metastatic setting also with pertuzumab, lapatinib and trastuzumab-emtansine. Initially, endocrine adjuvant therapy with tamoxifen was given to patients independently from their ER-status. This changed after the Oxford overview in 1998 showing that survival benefit after tamoxifen treatment is confined to ER-positive patients only, resulting in treatment stratification based on the ER-status tumour characteristic.(31) Another manner in which treatment is nowadays stratified on basis of tumour receptor status is the use of the HER2-blocker trastuzumab. In 2006, this drug was approved for use in early breast cancer after results from the HERA trial were reported, which showed that one year trastuzumab treatment after adjuvant chemotherapy resulted in significantly improved disease-free survival.(32) Today, efforts are being made to further define tumour characteristics that may provide information on the efficacy of systemic therapies, with the aim to achieve a shift from stratified therapy to individualised therapy for breast cancer. Unfortunately, for chemotherapy there are at the moment no other predictors of chemosensitivity than the hormone receptors, overexpression of the HER2-receptor and the degree of proliferation (mitotic rate /KI 67). A large EORTC study attempted to identify TP53 mutation status as a predictor of sensitivity to taxanes, however results were negative.(33) Biomarkers for specific chemotherapeutic agents are urgently needed as chemotherapy entails severe toxicity. Overtreatment of patients, often frail, must be prevented. The neoadjuvant NEOZOTAC study provided a platform for investigating determinants and markers for tumor response to chemotherapy. For example, we investigated whether serum vitamin D levels influence response to chemotherapy, as it was previously suggested that vitamin D levels were of prognostic value (chapter 6). We found that vitamin D levels decrease under influence of chemotherapy and that a decrease of vitamin D levels may be associated with a worse pathological response. Such findings from our research shed more light on what determines whether tumours will respond to chemotherapy or not. Furthermore, it shows how much information can be yielded by using the neoadjuvant setting for research on drug efficacy.

Conclusion and future perspectives

Preoperative systemic therapy, or neoadjuvant therapy, has great advantages, which are increasingly exploited for clinical and investigational purposes. The coming years, novel agents based on other targets than hormone- and HER2- receptor status may become relevant in clinical practice, partly based on proven efficacy benefit in the neoadjuvant setting.

For example, as described in this thesis, zoledronic acid may become a player in the field of neoadjuvant chemotherapy. Furthermore, the PI3K/Akt/mTOR may provide potential substrates for targeted therapy. Beelen et al. showed that after adjuvante endocrine therapy a significant difference in phosphorylated mTOR measured with immunohistochemistry was found between primary and metastatic lesions, with a significant increase in mTOR activity in metastatic lesions.(34) A hypothesis-generating translational study using samples from the TEAM study, seemed to identify a gene signature based on the PI3K/Akt/mTOR pathway that was more effective for survival prognostication than conventional markers.(35)

These preliminary data add to the hypothesis that patients with certain expression of genes in the PI3K/Akt/mTOR pathway may be candidates for targeted therapy in order to overcome endocrine therapy resistance. In order to adequately assess the clinical response induced by anti-tumor agents, it is important that adequate biological and radiological response assessment methods are developed. Novel imaging modalities may prove to be useful to this end in the future. Also, promising results have been observed in a substudy of the NEOZOTAC study with optical mammography using diffuse optical spectroscopy for treatment response monitoring.(36)(37) Furthermore, image-guided surgery using real-time intraoperative detection of residual breast cancer using near-infrared fluorescence imaging may improve localization of tumor tissue, positively influencing surgical management of breast cancer. Importantly, as current response assessment modalities such as MRI are not nearly as accurate as the gold standard of evaluation on the surgical specimen (chapter 5) surgical resection of breast tumours will continue to be the mainstay after neoadjuvant therapy. Finally, breast cancer treatment has two main goals: to prolong survival and to maintain an acceptable quality of life. With respect to the first goal, in the upcoming decades optimized systemic therapies with more specific tumor targets will be developed in order to obliterate tumor cells throughout the whole body of patients. In view of this goal, it is of upmost importance that breast cancer patients should be treated following the principle "treat the patient, not the tumor". For example by choosing neoadjuvant endocrine therapy instead of neoadjuvant chemotherapy in patients with endocrine sensitive tumors who are unfit for chemotherapy and by adequate management of toxicities associated with systemic therapy. These goals can only be achieved with optimal multidisciplinary cooperation including surgeons, medical oncologists, radiation oncologists, pathologists , radiologists, nurse practitionars and pschychologists with active input and feedback from breast cancer patients

Summary

This thesis was divided in two parts. Part I demonstrated benefit of zoledronic acid addition to chemotherapy in terms of pathological response in postmenopausal women. Part II is all about neoadjuvant endocrine therapy, and discusses the optimal duration of this treatment and the information on treatment efficacy that aromatase-inhibitor specific adverse events may provide.

Part I

Chapter 2 elaborates on the potential role of zoledronic acid in neoadjuvant treatment for breast cancer and reviews the current pre-clinical and clinical evidence supporting addition of zoledronic acid to systemic therapy. Possible anti-tumour mechanisms are discussed. The putative anti-tumour mechanism of zoledronic acid was tested in the NEOZOTAC trial, which is described in **chapter 3**. In this study, pre- and postmenopausal women with stage II/III HER2-negative breast cancer were included. Zoledronic acid did not confer better pathological response in the total studied population, although a numerical 'hint' for a benefit was observed in postmenopausal women. However, this finding was not statistically significant, presumably because of the small size of the subgroup. Therefore, in **chapter 4**, a pooled analysis was performed of all randomized trails investigating zoledronic acid in the

neoadjuvant setting. A significant benefit was found in postmenopausal women. These exciting findings are beginning to change clinical practice, making addition of zoledronic acid to neoadjuvant chemotherapy clinically relevant in the upcoming years.

For evaluation of treatment efficacy, adequate radiological response modalities are necessary. **Chapter 5** investigated the accuracy of MRI after neoadjuvant chemotherapy. This evaluation found that tumour size on MRI is weakly correlated with the actual tumour size on the surgical specimen in ER-positive/HER2-negative patients, influencing surgical treatment by increasing tumour-positive margins and subsequent re-excision rates. **Chapter 6** is an example of how a neoadjuvant study can be used to investigate the effect of chemotherapy on biological determinants and how this relates to treatment efficacy. Chemotherapy resulted in a significant decrease of vitamin D levels. Furthermore, changes in vitamin D levels during chemotherapy treatment tended to be associated with pathological response. Better response was observed in patients who had stable or increased vitamin D levels in comparison to patients with a decrease in vitamin D levels. Therefore, adequate monitoring of vitamin D levels may possibly be advised and further investigations are needed in order to define optimal vitamin D suppletion.

Part II

Chapter 7 is a review of studies investigating response to neoadjuvant endocrine therapy. This review concluded that aromatase inhibitors are more effective than tamoxifen for inducing tumour response and increasing breast-conserving surgery rates. In addition, in studies that utilised treatment periods of longer than 3 months, continuous tumour shrinkage was observed, suggesting that longer treatment periods are feasible. In **chapter 8** results from the TEAMIIa study are reported, which investigated 6 months of neoadjuvant endocrine therapy. As hypothesized, treatment response persisted after 3 months and significant differences were found between tumour sizes at 3 months and at the last measurement. Feasibility of breast-conserving surgery improved by 10%. Nonetheless 7 patients developed progressive disease during the study. Therefore it is advised that longer treatment durations are accompanied by frequent monitoring of the tumour size. Although neoadjuvant endocrine therapy has a favorable toxicity profile compared to chemotherapy, it does not come without adverse events. Aromatase-inhibitors are associated with several specific adverse events such as vasomotor symptoms (e.g. hot flushes/(night)sweating) and musculoskeletal adverse events (e.g. arthralgia). These adverse events are suggested to be the effect of estrogen depletion. We observed that occurrence of these specific adverse events was associated with clinical response (**chapter 9**).

Finally, the general discussion of this thesis elaborated on the current status of neoadjuvant therapy and future perspectives.

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