Neoadjuvant chemotherapy in breast cancer

Summary

Breast cancer is currently the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide.[1] Over the past decade we have seen a significant decrease of mortality of early breast cancer due to early detection, multidisciplinary approach and improved treatment options, i.e., chemotherapy, HER2 targeted therapy and endocrine therapy.[2] With the addition of taxanes to anthracyclines and cyclophosphamide in recent years, overall survival has clearly further improved.
Chemotherapy can be applied in the neoadjuvant or adjuvant setting. Neoadjuvant chemotherapy is an effective alternative to adjuvant chemotherapy in both early and locally advanced breast cancer.[3] Neoadjuvant therapy can help to optimize chemotherapy schemes and drug combinations to achieve higher pathologic complete response (pCR) rates and to better understand tumour biology by in vivo responsiveness testing. It may also allow assessment of efficacy of treatment in a shorter time period of months rather than years of follow-up.

This thesis addresses several aspects of neoadjuvant chemotherapy in breast cancer patients in relation to efficacy, response assessment and axillary strategy. In **chapter 1** a general introduction and outline of the thesis is presented. The first part of this thesis focuses on efficacy of taxane based chemotherapy schedules and the possible protective effect of prior G-CSF use or of a prior chemotherapy cycle on myelotoxicity in the subsequent chemotherapy cycle. The second part of this thesis addresses different methods of response assessment, accuracy of the sentinel node biopsy after neoadjuvant chemotherapy and the impact of timing of axillary staging.
The results are mainly based on the data of the Dutch phase III INTENS study, comparing sequential use of docetaxel after anthracyclines and cyclophosphamide (AC-T) and the upfront use of the triple combination of docetaxel with anthracyclines and cyclophosphamide (TAC). Moreover, the data presented in this thesis are based on the national, phase III Two-to-Six study[4] and the NEO-ZOTAC study.[5] In the Two-to-six study breast cancer patients were randomized to primary G-CSF prophylaxis during all six TAC-containing chemotherapy cycles or primary prophylaxis limited to the first two chemotherapy cycles only. The NEO-ZOTAC trial studied the impact of neoadjuvant chemotherapy (TAC) and use of zoledronic acid on pCR rate.

Research questions in the thesis

1. Are the chosen comparator and/or study design in taxane-containing chemotherapy schemes in metastatic and early breast cancer trials of influence on efficacy endpoints? **Chapter 2**
2. Is there a difference in the pCR rate in the breast in patients with newly diagnosed non-metastatic breast cancer comparing two different taxane-containing neoadjuvant chemotherapy schemes? **Chapter 3**

3. Is there a difference in 5-year disease-free and overall survival in patients with newly diagnosed non-metastatic breast cancer comparing two different taxane-containing neoadjuvant chemotherapy schemes? **Chapter 4**
4. Is there is a protective effect of a prior docetaxel-containing chemotherapy cycle or prior granulocyte-colony stimulating factor (G-CSF) prophylaxis on the next cycle blood cell counts? **Chapter 5**
5. Is there a difference in accuracy of clinical breast tumour size measurement post-neoadjuvant chemotherapy by magnetic resonance imaging or ultrasound? **Chapter 6**
6. What is the accuracy of sentinel node biopsy post-neoadjuvant chemotherapy? **Chapter 7**
7. What is the impact of timing of axillary staging before versus after neoadjuvant chemotherapy on final pathologic node-negative rate in patients with clinically node-negative breast cancer? **Chapter 8**

In recent years, new drugs have shown activity in metastatic breast cancer, but not always resulting in an overall survival benefit. The anthracyclines and taxanes, docetaxel and paclitaxel, represent the most potent drugs for use in breast cancer. Taxanes did not improve survival in metastatic breast cancer trials, whereas they did so in early breast cancer trials.[6,7] In chapter 2 we present a systematic review of phase III taxane-based chemotherapy studies in early and metastatic breast cancer to assess which factors may have contributed to the observed differential outcome. In total, 10 trials in the metastatic breast cancer setting and 21 trials in the adjuvant breast cancer setting were included. In the metastasized setting no improvement in progression-free and overall survival was seen for the taxane containing treatment. In contrast to the pooled analysis of early breast cancer trials, which showed a significant difference in favour of adding a taxane for both disease-free survival (hazard ratio 0·85; 95% CI 0·80-0·91) and overall survival (hazard ratio 0·85; 95% CI 0·79-0·91). In the majority of the metastatic breast cancer studies taxanes were substituting other active cytotoxic drugs, mainly cyclophosphamide, whereas in early breast cancer, many studies focused on the impact of taxanes when delivered at full dose in addition to anthracyclines, instead of substitution. We conclude that the negative results of taxanes in metastatic breast cancer studies seem to be caused by the design of the randomized trial.

It is accepted worldwide that taxanes should somehow be incorporated in the (neo-) adjuvant treatment of breast cancer patients at increased risk of relapse. The most optimal strategy for incorporating docetaxel is, however, still under investigation. In **chapter 3** we report the main results of the INTENS study, which was designed to determine whether delivering neo-adjuvant taxane-based chemotherapy at a higher dose in a shorter period of time would improve the outcome of early breast cancer patients. In total, 201 patients were included. 21% of patients treated with sequential

AC-T chemotherapy achieved a pCR in the breast as compared to 16% of patients treated with concurrent TAC-chemotherapy (odds ratio 1.44; 95% CI 0.67-3.10), when considering central pathology review results. AC-T without primary G-CSF prophylaxis was associated with more febrile neutropenia episodes as compared to TAC with primary G-CSF prophylaxis (23% versus 9%), and with more grade 3/4 sensory neuropathy (5% versus 0%). We concluded, that no statistically significant differences in pCR rates were observed between the two treatment arms consisting of the same drugs but at a different schedule and different cumulative dose. And, that to a great extent the differential toxicity profile could be explained by different use of primary G-CSF prophylaxis.

After a median follow up of 6 years we reported the disease-free survival and overall survival in chapter 4. For patients in the AC-T arm the 5-year disease free survival was 81% and for patients who received TAC chemotherapy 71% (log-rank P=0.015). Five-year overall survival was also significantly superior for the AC-T arm: 84% versus 76%, respectively (log-rank P=0.041). Hence, we concluded that sequentially delivered AC-T chemotherapy seemed to outperform concomitantly delivered TAC chemotherapy in terms of improved 5-year disease free and overall survival.

An anthracycline-taxane chemotherapy regime is effective in breast cancer, but it is also very myelotoxic with a substantial risk of febrile neutropenia (FN). In **chapter 5** we analysed if a prior chemotherapy cycle or use of primary G-CSF prophylaxis during a prior chemotherapy cycle had a myeloprotective effect in subsequent chemotherapy cycles. For this study we used data from the Dutch Two-to-Six study, a randomized study in patients with early stage breast cancer and increased risk of febrile neutropenia during neoadjuvant or adjuvant chemotherapy. We investigated the nadir blood cell counts of all cycles in the patients treated with primary G-CSF prophylaxis throughout all chemotherapy cycles (G-CSF 1-6 arm) and the nadir blood cell counts of cycles 3-6 in the patients treated with primary G-CSF prophylaxis during the first two cycles only (G-CSF 1-2 arm). In the G-CSF 1-6 arm the median nadir of the absolute neutrophil count decreased from 7.1 x 10^9/l in cycle 1 to 5.5 x 10^9/l in cycle 6. During treatment in the G-CSF 1-2 arm, when primary G-SCF prophylaxis was discontinued, the nadir absolute neutrophil count showed a persistent grade 4 neutropenia of 0.1 x 10^9/l in cycles 3 to 6. Hence, we conclude that there is no protective effect of prior G-CSF or of the prior chemotherapy cycle on myelotoxicity in the subsequent chemotherapy cycles.

In **chapter 6** we evaluated the accuracy of clinical imaging by magnetic resonance imaging and ultrasound of the primary breast tumour after neoadjuvant chemotherapy related to the post-operative histological tumour size (gold standard), and whether this varied with breast cancer subtype. Patients enrolled in the INTENS study of whom clinical imaging was available after the neoadjuvant chemotherapy

and known histopathological tumour size were included in this analysis. Magnetic resonance imaging estimated residual tumour size with ≤10 mm discordance in 54% of patients, overestimated tumour size with >10 mm in 28% and underestimated tumour size with >10 mm in 18% of patients. With ultrasound these figures were 63%, 20% and 17%, respectively. The negative predictive value in hormone receptor-positive tumours for both magnetic resonance imaging and ultrasound was low, 26% and 33%, respectively. In this study**,** ultrasound was at least as good as breast magnetic resonance imaging in providing information on residual tumour size after neoadjuvant chemotherapy. However, both modalities suffered from a substantial percentage of over-and underestimation of tumour size and in addition both showed a low negative predictive value of pCR.

Chapter 7 provides an overview of the current literature to determine the accuracy of a sentinel node biopsy after neoadjuvant chemotherapy. Twenty-seven studies were included in this review with a total study population of 2148 patients. We found a pooled sentinel node identification rate of 90.9% (95% CI 88.0-93.1) and a false-negative rate of 10.5% (95% CI 8.1-13.6). A majority of studies included both clinically node-negative and node-positive patient before start of neoadjuvant chemotherapy. Factors such as primary tumour size and clinical nodal involvement before and/or after neoadjuvant chemotherapy have been reported to affect the accuracy of the sentinel node biopsy. In 2009, we concluded that there might be a potential role for performing a sentinel node procedure following neoadjuvant chemotherapy, which could be considered on an individual basis, but that there was yet insufficient evidence to recommend this as a standard procedure. We recommended further research with subgroup analysis using variables reported to be associated with decreased sentinel node accuracy in order to clearly define its value in the subgroups of breast cancer patients.

In **chapter 8** we assessed the impact of timing of axillary staging before versus after neoadjuvant chemotherapy on final pathologic node-negative rate in two sequentially conducted Dutch phase III trials, the INTENS and NEOZOTAC trial. In the INTENS and NEOZOTAC studies, the impact of different neoadjuvant chemotherapy schedules and of zoledronic acid as an adjunct to neoadjuvant chemotherapy on pCR rate was primarily assessed. The research question regarding the most optimal timing of the sentinel node procedure was a secondary study endpoint. The results of this secondary endpoint are presented in this chapter, by a combined analysis of both studies. For this substudy, patients were included if they had a surgical axillary staging by sentinel node procedure and/or axillary lymph node dissection. Of the included patients, 230 (52%) had pre-treatment clinically node-negative disease. In this group a pathologically node-negative status was seen in 58% of patients with a sentinel node procedure post-neoadjuvant chemotherapy compared to 51% of patients with a sentinel node procedure pre-neoadjuvant chemotherapy including the results of the

axillary lymph node dissection. In multivariable analysis, timing of sentinel node procedure (pre- versus post- neoadjuvant chemotherapy) was, however, not significantly associated with final pN0/pN0(i+) status, with an odds ratio of 1.18 (95% CI 0.64-2.18) after correcting for age, clinical tumour status, histology, grade, hormone- and HER2 receptor. Of patients with clinically node-positive disease only 15% had a final pathologic node-negative status, with a false-negative rate of the sentinel node of 30%. We concluded that in early-stage breast cancer patients with clinically node-negative disease, a sentinel node procedure performed after neoadjuvant chemotherapy led to nodal down staging, although not statistically significant after multivariate correction for patient and tumour characteristics. In patients with clinical node-positive disease, nodal down staging to node-negative disease was seldomly achieved with a clinical relevant high false-negative rate.

Of note, in chapter 8 we further observed a very low axillary recurrence rate in patients with sentinel node negative disease who did not undergo completion axillary lymph node dissection, after a 5 year follow up period. Of the 77 patients with sentinel node negative disease who did not undergo completion axillary lymph node dissection, 28 were included in the INTENS study. With a median follow up of 6 years three patients had distance recurrence and none had a regional recurrence. In the NEOZOTAC trial, follow-up duration is still too short to assess 5-year recurrence or survival rates.

References

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