

Neoadjuvant chemotherapy in breast cancer

Citation for published version (APA):

Vriens, BEPJ. (2017). *Neoadjuvant chemotherapy in breast cancer: efficacy, response assessment and axillary strategy*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20171213bv>

Document status and date:

Published: 01/01/2017

DOI:

[10.26481/dis.20171213bv](https://doi.org/10.26481/dis.20171213bv)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Valorisation

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This thesis addresses several aspects of neoadjuvant chemotherapy in breast cancer patients in relation to efficacy, response assessment and axillary strategy. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide. The incidence of invasive breast cancer in the Netherlands increased the last decades to 14,551 patients in 2015. Due to its high incidence, breast cancer has an important societal and economic impact in the Netherlands, with annual incremental costs.

Over the past decades we have seen a significant decrease of mortality of early breast cancer due to early detection, multidisciplinary approach and improved options for systemic treatment, i.e., chemotherapy, HER2 targeted therapy and endocrine therapy. With the addition of taxanes to anthracyclines and cyclophosphamide in recent years, overall survival has clearly further improved. Quality of life of survivors is affected by the morbidity caused by this treatment. Recommendations for the use of systemic therapy are based on the individual patient's risk and the balance between absolute benefit and toxicity. Overall, chemotherapy regimens based on anthracyclines and taxanes reduce breast cancer mortality by about one-third.

This thesis is 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). Both regimens showed to be equally effective in achieving a pathologic complete response (pCR). After a median follow-up of six years, however, sequentially delivered AC-T showed a superior disease-free and overall survival for all patient subgroups compared to concurrent TAC chemotherapy. Not only improved outcome, moreover, the lower cumulative anthracycline dose with AC-T is attractive because of the lower risk of cardiotoxicity and risk of leukemia. Also, the reduced use of G-CSF during AC-T therapy, for only four cycles, in comparison with the use of G-CSF during all 6 cycles of TAC chemotherapy, can be considered as an advantage for sequentially delivered chemotherapy.

Clinical monitoring identifies the size of residual disease to plan the most appropriate surgical approach. It is important that the clinical response predicts the pathological response accurately. We compared the clinical tumour size as assessed by magnetic resonance imaging (MRI) and ultrasound (US) post neoadjuvant chemotherapy with the postoperative pathologic tumour size. MRI and US showed comparable (moderate) agreement with post chemotherapy pathological tumour size with a low predictive value especially in ER-positive tumours. These data are relevant because with comparable agreement, ultrasound is the most available and cost-effective approach compared to MRI.

Surgery for breast cancer has become less radical than it was several decades ago. For patients with earlier stages of breast cancer, down staging of the primary tumour may facilitate breast conserving therapy and bears the opportunity of down staging the axilla obviating the need of axillary treatment in some patients. For the axilla, the sentinel node biopsy has replaced the axillary lymph node dissection as a staging procedure. Axillary dissection provides excellent regional control in patients with nodal involvement, but is associated with more and often persistent side-effects, particularly lymph edema and restriction in shoulder mobility compared to sentinel lymph node biopsy. In patients with clinical node negative disease, a negative sentinel node can identify the patients without residual axillary disease to spare axillary lymph node dissection. The sentinel node can be performed pre-or post neoadjuvant chemotherapy. Because neoadjuvant chemotherapy has shown to eradicate nodal disease in 20% to 40% of patients, performing a sentinel node procedure post neoadjuvant chemotherapy might further de-escalate treatment. Based on our and other studies, we conclude that in breast cancer patients with clinically node-negative disease the sentinel node procedure is preferentially postponed till after the end of neoadjuvant chemotherapy to take maximum benefit of its effect on nodal down staging of subclinical disease.

In addition to the academic community, especially the clinicians who take part in multidisciplinary breast cancer treatment for breast cancer patients, the results of this thesis are relevant for newly diagnosed breast cancer patients with indication for systemic treatment because of the improved treatment option with least risk of long term toxicities. Also, the contents of this thesis are of interest to expert panels, which are responsible for the development of the national and international guidelines in breast cancer treatment.

Further research is needed to improve treatment options for patients with breast cancer with enhanced attention to avoid overtreatment in patients with pCR in breast and axilla (de-escalation) as well as on improved therapy options (escalation) for patients with non-pCR in breast and axilla after standard neoadjuvant therapy. More research is needed for optimal response monitoring, new imaging approaches or combinations of existing imaging modalities for response monitoring could be considered, possibly combined with biomarkers to predict the pathological response.

In conclusion, this thesis provides essential data of several aspects of neoadjuvant chemotherapy in breast cancer patients in relation to efficacy, response assessment and axillary strategy. These data will contribute to further improvement of breast cancer treatment and outcome.