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Review

Current and future role of neoadjuvant therapy for breast cancer

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ABSTRACT

Neoadjuvant systemic chemotherapy is a possible therapeutic approach for the treatment of locally advanced operable, primarily non-operable or inflammatory breast cancer. Neoadjuvant systemic chemotherapy is an option for breast cancer patients who would require adjuvant chemotherapy otherwise based on clinical and histological examination and imaging. The use of neoadjuvant systemic therapy in operable breast cancer is currently increasing because of its advantages that include higher rates of breast conserving surgery and the possibility of measuring early in-vivo response to systemic treatment. The timing of axillary sentinel lymph node diagnosis (i.e. before or after neoadjuvant chemotherapy) is critical in that it may influence the likelihood of axillary preservation. It is not yet clear if neoadjuvant therapy might improve outcomes in certain subgroups of breast cancer patients. Neoadjuvant treatment modalities require a close collaboration between oncology professionals, including surgeons, gynecologists, medical oncologists, radiation oncologists, radiologists and pathologists. The most important parameter for treatment success and improved overall survival is the achievement of a pathologic complete response (pCR), although the role of pCR in patients with luminal A like tumours might be less informative. Identification of patient subgroups with high pCR rates may allow less invasive surgical or radiological interventions. Patients not achieving a pCR may be candidates for postoperative clinical trials exploring novel systemic treatments.

Introduction

Therapy of patients with early breast cancer involves three principal treatment modalities: surgery, systemic therapy and radiation therapy. Traditionally, systemic therapy has been administered to breast cancer patients after surgery. Recently, however, neoadjuvant systemic therapy has been regarded as an equally effective option when compared to adjuvant therapy. While neoadjuvant antihormonal therapy is mainly recommended for hormone receptor positive postmenopausal patients, neoadjuvant chemotherapy (NACT) is increasingly utilized for all breast cancer subtypes. Neoadjuvant chemotherapy increases the rate of breast conserving surgery [1] and allows monitoring of treatment response, and provides unique opportunities for development of both individualized treatment strategies and drug development. Modern treatment strategies are tailored to molecular subtypes [2], allowing for a more individualized approach to therapy. There is increasing evidence that a shift in the traditional sequence of treatment modalities may preferentially improve outcomes in certain subgroups of patients with early breast cancer [3,4].

Currently, the terms *neoadjuvant* and *primary systemic* or *presurgical* therapy are used. We recommend that in clinical trials, the term *neoadjuvant* be used when referring to a treatment given before surgery with therapeutic intent: The term *presurgical* should be used when referring to an intervention undertaken before surgery, with diagnostic intent to investigate the biologic or pharmacodynamic effect of a compound on breast cancer tissue. Presurgical trials are mostly referred to as biological window trials, such as those in which a short course of a compound is administered before surgery to test its short-term effect on a biologic or pharmacodynamic endpoint rather than a conventional efficacy endpoint. In the following manuscript we will use the term *neoadjuvant* as most of the clinical trials summarized in this review were conducted with therapeutic intent.

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Originally, it was recommended that neoadjuvant chemotherapy be only considered for women with large tumours or inflammatory disease. In the meantime, however, neoadjuvant chemotherapy is commonly used for the treatment of patients with high-risk operable primary breast cancer. Several international groups have developed guidelines for the use of neoadjuvant chemotherapy in operable breast cancer, with recommendations for patient selection and treatment regimens [5]. The guidelines provide the level of scientific evidence for each recommendation, and are the result of research collaborations (Table 1).

Defining patient groups for neoadjuvant chemotherapy

The results of the NSABP B-18 trial showed that breast conservation rates are higher after preoperative chemotherapy, especially in patients with tumours larger than 5 cm at study entry [6]. Although there were no significant differences in OS or DFS in protocol B-18, women younger than 50 years of age had more benefit from preoperative versus postoperative chemotherapy. In contrast, women aged 50 years and older had better outcomes with postoperative chemotherapy. These results were initially seen at 9 years median follow up and still persist after a median of 16 years [4]. These findings are in line with the overview analyses from the Early Breast Cancer Trialists' Collaborative Group which indicate that the effects of adjuvant chemotherapy are most apparent in younger women. It is possible that the benefit of neoadjuvant chemotherapy relative to postoperative chemotherapy could be age-dependent as well. Younger women are more likely to have oestrogen receptor (ER)–negative tumours and International Breast Cancer Study Group data suggest there may be a preferential benefit to early initiation of adjuvant chemotherapy in premenopausal women with ER-negative tumours [7]. These findings could help to explain why younger women seem to have a greater benefit from preoperative chemotherapy.

NSABP B-27 was a three arm, randomized, phase III trial of patients with invasive breast cancer treated with preoperative chemotherapy with AC (doxorubicin/cyclophosphamide) for 4 cycles followed by surgery alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by surgery, or AC followed by surgery followed by 4 cycles of postoperative docetaxel. Results from this study, which involved 2411 women, documented a higher pCR rate in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Disease free survival (DFS) and overall survival (OS) were not superior following the addition of docetaxel treatment in NSABP B-27. However in a subset analysis, a DFS advantage was observed (HR, 0.71; 95% CI, 0.55–0.91; $p = 0.007$) favouring preoperative versus postoperative docetaxel in patients experiencing a partial response to AC [8].

Role of surgery in neoadjuvant therapy

Systemic therapy administered prior to surgery can reduce the size and cellularity of the tumour, presenting unique challenges for surgeons, including increased difficulty in identifying the tumour bed and ensuring complete macroscopic and microscopic surgical excision. In order to enable optimal surgery, surgeons, oncologists, pathologists, radiologists and radiation-oncologists need to cooperate closely. The use of tissue marker clips before neoadjuvant therapy to mark the tumour facilitates later identification of the primary tumour area.

Available data suggest that locoregional therapy decisions should be based on both the pre-treatment clinical extent of disease and the response to neoadjuvant systemic therapy. An important advantage of pre-operative chemotherapy is that more patients with larger tumours can be treated with breast conserving surgery. Most neoadjuvant chemotherapy or endocrine trials, such as NSABP-B18 and B 27 [9], EORTC 10902 [1], Fem-024 [10] and the AGO B and GBG-trials [11], report an increase in the percentage of patients that could be treated with breast conservation. Approx. 10–30% of the patients who were initially candidates for mastectomy were treated with breast conservation after neoadjuvant therapy [12].

A meta analysis of nine breast cancer trials comparing adjuvant and neoadjuvant therapy reported an increase in the relative risk of locoregional recurrence of 1.22 (CI 1.04–1.43) after neoadjuvant treatment [13]. However, the results were largely influenced by the trials in which surgery was either omitted or breast conservation therapy was achieved with radiation alone [13].

Four factors are independently associated with an increased risk of local recurrence: Clinical stage N2–N3 disease before neoadjuvant treatment, lymphovascular invasion, multifocal residual disease and pathologic residual tumour larger than 2 cm after neoadjuvant chemotherapy [14]. Simple techniques such as the use of tissue marker clips to indicate tumour location at the time of diagnosis ensure appropriate imaging after neoadjuvant therapy and can make later identification of the tumour area easier. In a retrospective analysis of patient records, it has been demonstrated that clip placement is associated with better local control, independent of stage and other clinicopathologic factors [15]. The risk ratio of local recurrence in this study was 3.7 if clip insertion was omitted, compared with patients who did have clip placement. 5-year local control was 98.6% in patients who had radiopaque clips placed versus 91.7% in patients who did not have tumour marker clips placed [15].

To ensure best outcomes, a multidisciplinary team should take the following aspects into account: Molecular analyses (ER, PR, HER2 status) from the diagnostic core needle biopsies to guide subsequent treatment, insertion of tissue marker clips before neoadjuvant therapy to improve the chance for breast conserving surgery and clinical and sonographic assessment of the axillary nodes prior to neoadjuvant therapy to determine the need for a sentinel node biopsy or axillary surgery after neoadjuvant chemotherapy.

In breast cancer patients with T1–T2 tumours, no palpable adenopathy and 1–2 positive sentinel lymph nodes (SLNs), the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial compared observation only to complete axillary lymph node dissection (ALND) following sentinel node biopsy [16]. No significant differences in disease-free survival (DFS) and overall survival (OS) were noted between the two groups at a median follow-up of 6.3 years. Patients with 1 or 2 SLNs containing macro- or micrometastases who have had breast conserving surgery followed by tangential field radiation therapy and systemic therapy do not need further axillary lymph node dissection according to this landmark study. Importantly however, the Z0011-trial is not sufficient to provide recommendations concerning the management of axillary nodes after neoadjuvant therapy. To better understand the role of sentinel lymph node biopsies and ALND following neoadjuvant chemotherapy additional trials have been conducted.

In patients planning to receive neoadjuvant chemotherapy who have clinically negative axillary lymph nodes (ALNs) SLN biopsy can be considered. For those with clinically suspicious ALNs, the North American National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend consideration of either a core biopsy or FNA of these nodes, along with a sentinel node biopsy if FNA or core biopsy results are negative [17]. When administering neoadjuvant chemotherapy in women with clinically negative ipsilateral axillary nodes the current NCCN guidelines list SLN resection as the preferred option for surgical axillary staging. If the

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