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Overview

Neoadjuvant Therapy in Early Breast Cancer: Treatment Considerations and Common Debates in Practice

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Abstract

Neoadjuvant treatment offers a number of benefits for patients with early breast cancer, and is an important option for consideration by multidisciplinary teams. Despite literature showing its efficacy, the use of neoadjuvant therapy varies widely. Here we discuss the clinical evidence supporting the use of neoadjuvant therapy in early stage breast cancer, including patient selection, monitoring response, surgery and radiotherapy considerations, with the aim of assisting multidisciplinary teams to determine patient suitability for neoadjuvant treatment.

Key words: Breast cancer; chemotherapy; endocrine therapy; multidisciplinary; neoadjuvant treatment; patient management

Introduction

Originally a means to downstage patients with inoperable locally advanced breast cancer, neoadjuvant therapy is now integral to the treatment of patients with early stage disease. Large clinical trials such as EORTC 10902 and NSABP B-18 have shown no differences between the same systemic therapy given pre- or post-surgery on disease-free (DFS) and overall survival [1–3]. Other benefits (i.e. the conversion of patients requiring mastectomy to breast-conserving surgery [BCS]) and some potential concerns have been investigated and are well recognised (Table 1). It is therefore important for the multidisciplinary team (MDT) to consider the benefits and risks when selecting patients who may benefit from neoadjuvant therapy.

Anthracycline plus taxane-based chemotherapy is the most widely used neoadjuvant chemotherapy (NAC) regimen for all early breast cancer subtypes and is associated with high rates of clinical response (up to 90% in NSABP B-27) [15]. Progression during NAC is infrequent, with a rate of 3% in one meta-analysis of 1928 patients [16]. In patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, trastuzumab with or without pertuzumab should be administered concomitantly with a taxane [17–19]. For patients with triple negative breast cancer (TNBC), the addition of carboplatin in the GeparSixto [9] and CALGB 40603 [20] studies have shown an increased pathological complete response (pCR) rate, although with increased toxicity and without a significant increase in BCS rate. Ongoing studies such as NRG-BR003 (NCT02488967) [21] and M14-011 BRIGHTNESS (NCT02032277) [22] will provide additional data on the effects of platinum agents as neoadjuvant or adjuvant treatment, respectively, on survival outcomes.

To date, neoadjuvant endocrine therapy has been used less frequently than chemotherapy. Aromatase inhibitors

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Table 1
Clinical benefits and potential concerns associated with neoadjuvant treatment for early breast cancer

	Benefits	Potential concerns
Impact on surgery	• Downstage tumours to permit breast-conserving surgery rather than mastectomy [4–6], improving cosmetic outcomes. • De-escalate surgical treatment of the axilla [7]. • Provide time for germline mutation test results (i.e. *BRCA1/2*) that may influence surgical plan.	• Cancer may progress and become inoperable (a rare event with appropriate monitoring of response). • Reduced window of opportunity for fertility preservation [8]. • Increasing tumour response may not achieve a reduction in mastectomy rates, regardless of downstaging and effectiveness of therapy regimen [9,10]. • Increased locoregional recurrence rates in patients who do not undergo surgery after neoadjuvant treatment [11].
Disease information and monitoring	• Provide individualised post-treatment prognostic information (e.g. pathological complete response, residual cancer burden) for management decisions. • Permits clinicians to monitor response to therapy at an early stage; potentially allowing time and flexibility to switch therapies if patients do not respond [12,13].	• Potential loss of staging information. • Potential for over-treatment, if decision is based on incomplete information (e.g. size of lesion is overestimated because of associated ductal carcinoma *in situ* seen radiologically). • Potential for under-treatment if therapy is stopped or changed mid-course [14]. • Limited evidence base to guide adjuvant radiotherapy decisions or management of patients with residual disease.

are used in selected patient subgroups (i.e. postmenopausal women with larger, hormone receptor-rich breast cancers), usually when systemic chemotherapy is not indicated either due to tumour biology or patient characteristics [17,18,23]. This may include node-positive or node-negative patients [23,24]. With appropriate patient selection, the risk of disease progression is low, although treatment duration is longer than for NAC [25]. A trial of 182 patients treated with neoadjuvant letrozole showed a 69.8% BCS rate at 3 months, rising to 83.5% after 2 years of treatment [26]. Llombart-Cussac *et al.* [27] reported a median time to maximum response with letrozole of 4.2 months. However, over a third of responding patients required more than 6 months of treatment. A recent meta-analysis of 20 studies indicated that neoadjuvant endocrine therapy may be as effective as NAC, but with lower toxicity [28]. Therefore, neoadjuvant endocrine treatment should be considered in selected patients.

Initiating Neoadjuvant Treatment

Factors to Consider when Selecting Patients for Neoadjuvant Therapy

Although there is consensus on the patient subgroups most likely to benefit from neoadjuvant treatment [17,18], its utilisation in clinical practice remains highly variable [29–31]. All early stage breast cancer patients identified as likely to require adjuvant chemotherapy should be considered for NAC, as they may potentially benefit from treatment before surgery. Factors favouring NAC in patients with operable breast cancer include:

- high tumour volume-to-breast ratio;
- lymph node-positive disease;
- biological features of primary cancer (high grade, hormone receptor-negative, HER2-positive, TNBC);
- younger age.

The efficacy of neoadjuvant treatment is assessed by evaluating the clinical and radiological response during and after therapy, and the pathological response after surgery. The likelihood of achieving a significant response is predicted by cancer phenotype; patients with HER2-positive and TNBC have the highest probability of achieving pCR after NAC (up to 50.3% for hormone receptor-negative/HER2-positive patients receiving HER2-targeted therapy, and 33.6% for TNBC) [32], making them good candidates for NAC consideration [32,33]. By contrast, pCR rates are lower for hormone receptor-positive/HER2-negative cancers; however, patients in this group may still achieve a meaningful clinical and radiological response from NAC, particularly younger patients with grade 3 cancers and low hormone receptor levels. Careful selection within these subgroups is required.

Histological subtype is also important. Invasive lobular cancers (ILCs) represent 10–15% of breast cancers and are typically hormone receptor-positive and histological grade 2. NAC is less beneficial in this group: fewer patients are downstaged to permit successful BCS, re-excision rates after BCS are higher and the likelihood of pCR is significantly lower than invasive cancers of no special type (NST) [34].

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