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Review

Neoadjuvant chemotherapy for locally advanced breast cancer: A review of the literature and future directions

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Abstract

Background: Most patients with locally advanced primary breast cancer have micrometastases at the time of presentation. Randomised trials on the use of neoadjuvant chemotherapy have not been carried out specifically in a population of breast cancer patients with locally advanced disease (LAPC). Despite this, its use for cytoreduction in these patients is an established option which may facilitate excision of the primary tumour and local lymph node metastasis for local control. Significant improvements in local disease control have been seen with recent advances in systemic chemotherapy regimens although thus far this has not shown in randomised trials to translate into overall survival benefits.

Methods: In this review, all studies where a large proportion (approximately 70%) of included patients with LAPC, were selected. A search of Medline and PubMed databases was performed. Specifically, the different chemotherapy regimens and their relation to oncological outcomes was assessed.

Results and conclusion: The studies assessed were heterogeneous with regard to patient selection and chemotherapy regimens used. A complete pathological response is the strongest predictor of disease-free and overall survival. Recent studies on the use of targeted biological therapies in addition to chemotherapy suggest that rates of complete pathological response may be significantly increased when compared to chemotherapy alone. Furthermore, improvements in localisation and imaging techniques, used in conjunction with the increasing use of oncoplastic breast-conserving techniques, highlight the possibility that a subgroup of these patients may safely be treated with breast conservation.

Keywords: Locally advanced primary breast cancer; Neoadjuvant chemotherapy; Clinical response; Pathological response; Oncoplastic conservation surgery

Introduction

Patients presenting with locally advanced primary breast cancer (LAPC) are a heterogeneous group with variable outcomes with regard to local recurrence rates and survival. There is no standard or international agreement on the definition of this type of breast cancer, but one commonly used clinical staging includes patients with large primary tumours greater than 5 cm (T3) or with fixed skin or chest involvement (T4), and/or fixed axillary (N2) or ipsilateral internal mammary lymph node involvement.[1,2] According to TNM staging system proposed by the American Joint Committee on Cancer (AJCC), all of stage III disease is therefore considered locally advanced, as is a subset of stage IIB (T3N0). In addition, inflammatory breast cancer (T4d), with its distinct clinical presentation and worse prognosis, is included within the scope of locally advanced disease. Although the TNM system is not as widely used in the UK, it is generally accepted that locally advanced breast cancers represent those cancers that are difficult to resect with primary surgery either because of their size or extension to chest wall or skin or involvement of regional axillary lymph nodes. Compared to patients with operable primary breast cancer, patients with LAPC are at significantly higher risk of local recurrence and distant metastases

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and have a worse overall survival; UK figures show that patients with stage II disease have a 10-year survival rate of just under 60%, whereas this is approximately 30% for patients with stage III disease.[3]

With the widespread use of breast cancer screening, breast cancers are increasingly being diagnosed at an earlier stage. Because of this, patients with locally advanced breast cancer are less commonly seen than before. Nevertheless, there remains a group of patients who either because they do not seek advice earlier or because the tumour is more aggressive, present with locally advanced disease. Data from the American National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program show that 7% of all breast cancer patients have stage III disease at diagnosis, although this percentage is less than 5% in the screening population.[4] Despite this, patients with LAPC still present a significant clinical problem and exemplify a subgroup of patients where a multidisciplinary approach is particularly important to outcome.

Initially, an aggressive single modality, local therapy approach, was commonly advocated for the treatment of patients with LAPC, either in the form of radical surgery or radiotherapy. This often provided temporary local control, although on follow-up of these patients, the morbidity and recurrence rates were high and survival poor.[5] Further modalities were introduced in subsequent studies and the sequence of these modalities did not seem to have an impact on the outcome.[6–9] Multimodal approach is now an established option in most patients with LAPC, especially oestrogen receptor (ER) negative tumours or aggressive ER positive tumours (e.g. some inflammatory cancers). This includes the combination of surgery and radiotherapy for local control and systemic therapy, usually chemotherapy +/− hormone therapy. For others, such as those with strongly hormone receptor positive tumours, local treatments (i.e. surgery +/− radiotherapy) plus endocrine therapy or even primary endocrine therapy may be appropriate options. This may for example be the case in many elderly patients, some of who are medically unfit for surgery.

Neo-adjuvant chemotherapy was first described in patients with LAPC and published by De Lena et al in the late 1970s.[10] Since then a large number of studies have assessed the use of neoadjuvant chemotherapy in operable primary breast cancer. Although the results in operable breast cancers suggest that the breast conserving rates can be increased, survival is no different when compared to post-operative adjuvant chemotherapy.[11] However, patients with LAPC often have inoperable disease at diagnosis and the main goal of neoadjuvant treatment is to achieve resectability, either in the form of standard mastectomy or breast-conserving surgery. Furthermore, the clinical and histological response to neoadjuvant chemotherapy has been shown to be important predictors of recurrence and survival in studies of operable breast cancer.

In this paper, we systemically review the literature on the use of neoadjuvant chemotherapy specifically in LAPC, analyse factors important in the prediction of outcome, and discuss the possible role of breast conservation in these patients.

Selection of studies

A search of Medline and PubMed databases of studies on neoadjuvant chemotherapy was performed. Key words used were neoadjuvant chemotherapy in locally advanced primary breast cancer, primary chemotherapy in locally advanced primary breast cancer, and preoperative chemotherapy in locally advanced primary breast cancer. Following this search, only trials and case series where approximately 70% of the patients with tumours larger than 5 cm or defined as locally advanced breast cancers according to the TNM classification were selected. Furthermore, only studies with surgery as the primary modality for local control of disease after chemotherapy were included. Even given these broad criteria, the number of randomised controlled trials is very small. The studies are listed in Table 1.

Response to chemotherapy

Type of chemotherapy

As shown in Table 1, the majority of chemotherapy regimens included an anthracycline regimen and clinical complete response (cCR) ranged from 4% to 62% and pathological complete response (pCR) rates ranged from 3% to 46%.[8,12–34] In the EORTC-NCIC-SAKK multicenter study,[14] the possible benefit of dose intensified anthracycline regimen versus a standard regimen was assessed. In this randomised controlled trial with 217 patients in one arm and 220 patients in the other, all of which were patients with tumours more than 5 cm, no significant difference in cCR rate or pCR rate was seen between the treatment arms.

In three phase 2 studies, which included a taxane in addition to anthracycline regimen, cCR ranged from 20% to 31% and a pCR ranged from 7% to 18%.[17–19] One randomised controlled trial in which around 60% of patients had tumours more than 5 cm compared an anthracycline regimen to an anthracycline plus taxane.[12] In this study the cCR increased from 34% to 62% and the pCR response increased from 16% to 34% in favour of the combination of anthracycline and taxane. Only patients who showed response to the initial anthracycline combination were included in this trial, which may explain the high pCR. A similar increase in response (cCR and pCR) has been noted in operable breast cancers in National surgical adjuvant breast and bowel project B27.[35,36] However in this study of 2411 patients, despite the pCR rate doubling from 13.7% to 26.1% the breast conservation rate did not increase (61.65% vs. 63.7%) nor did the overall survival.[36]

Recent studies to significantly improve the rates of pCR have shown promise. Minckwitz et al., in a phase 3 randomised trial (GEPARDUO) of 913 women with operable