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Review

Time to stop operating on breast cancer patients with pathological complete response?

D. Rea [a,*], A. Tomlins [b], A. Francis [c]

[a] CR-UK Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Edgbaston B15 2TT, UK
[b] Department of Breast Surgery, City Hospital, Dudley Road, Birmingham B18 7QH, UK
[c] Department of Breast Surgery, University Hospital Birmingham NHS Foundation Trust, Edgbaston, Birmingham B15 2TH, UK

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Abstract

Surgery is an obligatory component of treatment for early breast cancer. The last 20 years developments in systemic neoadjuvant therapy have progressively increased pathological complete response (pCR). Pathological complete response is associated with excellent prognosis especially for hormone receptor negative cancers.

Therapeutic advances and recognition of the importance of pathological subtype in predicting pCR facilitate identification of subgroups with very high pCR rates. Treatment of HER2 positive hormone receptor negative cancers with combination chemotherapy and multiple targeted anti-HER2 agents results in consistently high pCR rates of 60–83%. Routine surgery in this setting where most patients have no potential to benefit is of questionable value and the option of omitting surgery in these patients should now be explored in a randomized trial. For HER2 positive disease not achieving pCR after neoadjuvant treatment the outcomes are poor. Trials are underway to determine if outcomes for these patients can be improved with alternative targeted therapy.

Keywords: Surgery; Breast cancer; Neoadjuvant; HER2 positive; Chemotherapy

Introduction

Modern targeted neoadjuvant systemic therapy regimens are producing increasingly impressive pathological complete response rates in subgroups of breast cancer patients. Is surgical management keeping up with the times?

Neoadjuvant chemotherapy

Initially introduced for patients with inoperable, locally advanced or inflammatory breast cancer, the use of neoadjuvant chemotherapy for patients with operable early breast cancer is now well established. It is as effective in terms of overall survival (OS) as adjuvant chemotherapy[1] with additional benefits of down staging disease and acting as an in vivo assay of chemo sensitivity. More patients can have breast-conserving surgery and multiple cycles of ineffective treatment with associated toxicity could potentially be avoided.[2–4] In defined breast cancer subpopulations the use of chemotherapy and multiple targeted treatments has progressed to the stage that it is appropriate to question whether surgery is now a redundant procedure in their management. This article describes the key improvements in neoadjuvant therapy that have resulted in the need for routine surgical treatment for some early invasive breast cancers to be re-examined.

A recent consensus statement[5] recommends that neoadjuvant chemotherapy should be considered a standard approach in the management of operable breast cancer. Neoadjuvant chemotherapy provides the same disease free survival and overall survival as adjuvant chemotherapy.[6,7]

Pathological complete response (pCR)

The tumour response, in particular the pathological complete response, to neoadjuvant chemotherapy has been shown to provide prognostic information regarding disease

* Corresponding author. Tel.: +44 1216978315.
E-mail address: d.w.rea@bham.ac.uk (D. Rea).

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free and overall survival.[8–12] Those patients with a pCR following neoadjuvant chemotherapy have a superior disease free and overall survival and pCR is used as an endpoint in many neoadjuvant treatment trials. The most recent and largest neoadjuvant meta-analysis has shown that prognosis is not affected by the presence if in situ disease and the combining of two classifications namely, absence of invasive and in situ disease in primary and lymph nodes (ypT0 ypN0) and absence of invasive disease in primary and nodes but with residual in carcinoma in situ present (ypT0/is ypN0) provides a clear prognostic advantage compared to all other post neoadjuvant pathological outcomes.[8] A refinement is to provide a semi-quantitative estimate of the degree of response to neoadjuvant chemotherapy with a graded scoring system of Residual Cancer Burden (RCB) to predict survival after neoadjuvant chemotherapy.[13] Using a grading system identifies a group of patients with minimal residual invasive disease that still have a favourable prognosis. Quality of pathological examination and reporting is also of considerable importance.[14]

Increasing pCR with cytotoxic chemotherapy scheduling

The first generation neoadjuvant studies used short anthracycline based regimens such as doxorubicin and cyclophosphamide (AC) with pCR rates of 10–15%. The addition of taxanes in a sequential fashion approximately doubles the overall pCR rates.[15,16] Longer duration of chemotherapy is also associated with an increase in pCR rates with more than 4 cycles of chemotherapy consistently more effective than four or less cycles. Patients with oestrogen receptor (ER) positive disease can have a further improvement in pCR by increasing treatment out to 8 cycles.[17] Adapting chemotherapy in response to clinical outcomes has the potential to allow tailoring of chemotherapy. The Aberdeen study reported better long term and pCR outcome in responding patients switched from anthracycline to taxane chemotherapy[2,3] and the Gepar–Trio study demonstrated better outcome with a response adapted approach.[4]

The effect of tumour subtype on attainment of pCR and its prognostic value

The rate of pCR has been shown to vary dramatically depending on tumour subtype.

A large meta-analysis of 11,695 patients in 30 studies[18] revealed pCR to be only 8.3% for patients with HER2 negative/hormone receptor positive tumours, rising to 18.7% for hormone receptor/HER2 positive, 31.1% for triple negative and 38.9% for HER positive/hormone receptor positive patients.

Interesting data has also begun to emerge revealing that the prognostic value of a pCR also changes with molecular subtype. Pathological complete response has been shown to be predictive of a better clinical outcome (disease free and overall survival) for patients with ER negative tumours (HER2 positive and triple negative) but not correlated with outcome for patients with grade I or II hormone receptor positive tumours treated with adjuvant hormone therapy.[19,20]

Neoadjuvant HER2 targeted treatment and its impact on pCR rates

Approximately 20% of primary breast cancers over express Human epidermal growth factor receptor 2 (HER2), The HER2 receptor is a transmembrane tyrosine kinase involved in cell signal transduction. Over expression is associated with multiple cellular effects that are thought to account for the poor prognosis of patients with HER2 positive disease in the absence of targeted treatment. Homodimerisation of HER2 or heterodimerisation with HER1/3/or 4 is required to activate the receptor, which in turn activates downstream signalling cascades. Trastuzumab a monoclonal antibody binds to the extracellular domain of HER2 and exerts its effect by blocking ligand independent dimerization of HER2, hence preventing downstream cell signalling.

The addition of neoadjuvant trastuzumab to contemporary chemotherapy has been shown to improve pCR rates from 21 to 26% to between 31.7% and 65% in patients with HER2 positive operable breast cancer, without any significant increase in toxicity.[12,21–23] Patients with HER2 positive disease, clinically negative nodes, high tumour grade and negative oestrogen receptor status were most likely to achieve pCR.[20] The TECHNO trial provided evidence that pCR in HER2 positive breast cancers treated with neoadjuvant anthracyclines, taxane and trastuzumab was prognostic for improved disease free (DFS) and (OS).[12]

The pivotal NOAH trial[24] recruited 334 patients with HER2 positive locally advanced and inflammatory breast cancer randomized to receive neoadjuvant chemotherapy either with or without trastuzumab. Within NOAH there was also a comparator group of HER2 negative patients receiving neoadjuvant chemotherapy. The trial reported a pCR rate of 16% in HER2 negative patients, 19% in HER2 positive patients without trastuzumab and 38% in the trastusumab treated HER2 positive group. The trial reported 3 year event free survival of 56% vs 71% corresponding to a 41% reduction in risk of recurrence or progression with the addition of trastuzumab.

Increasing pCR rates with dual HER2 receptor blockade

The introduction into routine clinical practice of trastuzumab, one of the first ‘targeted’ treatments routinely used in treating breast cancer, has been followed by development of other drugs targeting the HER2 receptor. The recently introduced monoclonal antibody pertuzumab acts by binding to