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Review

Breast cancer: Role of neoadjuvant therapy

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ABSTRACT

Breast cancer is now considered to be a systemic disease from the outset, with no correlation seen between the intensity of local treatment and survival or recurrence. Adjuvant therapy has clearly demonstrated a reduction in local and distant relapse; neoadjuvant therapy is similarly being assessed. It aims to treat occult metastases and decrease tumour bulk. Its use has demonstrated down-staging of the tumour with increased rates of breast-conserving surgery. Though neoadjuvant therapy seems to be associated with an increase in loco-regional recurrence compared to adjuvant therapy, no overall difference in survival has been demonstrated. This paper reviews several trials that compare neoadjuvant to adjuvant therapy, and the controversies around managing the axilla in the neoadjuvant setting.

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1. Introduction

The management of breast cancer has gone through a significant change in the last few decades, with the super radical mastectomy no longer a common entity. Breast cancer is now considered to be a systemic disease from the outset, with most patients with early breast cancer developing metastases whatever the treatment undertaken.[1] Moreover, the intensity of local treatment does not correlate with survival and the risk of metastatic recurrence. A possible explanation to this may be the blood-borne micro-metastases that are present at initial diagnosis. These observations have lead to a more conservative approach to surgical intervention in breast cancer and the concurrent use of medical therapy. A clear survival benefit has already been shown with adjuvant therapy, presumably by eradicating occult metastases.[2] Neoadjuvant therapy is now being evaluated in this setting and has shown encouraging results.

The main aims of neoadjuvant therapy are to treat occult metastases, decrease the bulk of the tumour and allow breast-conserving surgery. It seems to have the potential of improving the results in more advanced cancers, for instance, in cancers with local fixity. Neoadjuvant therapy trials also offer a means for evaluating the effectiveness of the systemic agents compared to the adjuvant setting. The biological rationale for neoadjuvant therapy in breast cancer has been provided by Fisher and his colleagues. In a mice cancer model, they demonstrated that tumour excision was associated with an increase in metastases, and that preoperative chemotherapy prevented these changes.[3]

Several treatment modalities have been assessed as neo-adjuvant therapy. Most trials have been on neoadjuvant chemo-therapy, although more recently, neoadjuvant endocrine therapy and neoadjuvant trastuzumab have also been assessed.

2. Randomized trials of neoadjuvant chemotherapy

More than nine trials have compared neoadjuvant chemo-therapy against adjuvant treatment using the same combination of chemotherapy. Several outcomes have been measured, which are listed in Table 1.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial is the largest of these trials which has included 1523 patients with T1-3N0-1M0 breast cancers.[4–6] Patients were randomized to receive four cycles of cyclophosphamide and doxorubicin either pre- or post-surgery. In the neoadjuvant group, the clinical response rate (CRR) was 80%, with 30% showing a complete clinical response (cCR). The complete pathological response (cPR) was 13%. Though the breast conservation therapy (BCT) rate was higher among the neoadjuvant group (67% compared to 60% in the adjuvant group), the local recurrence rate was also higher (15% vs. 7%). In terms of survival, there was no significant difference in disease-free or overall survival between the two groups at a nine-year follow-up. The survival was, however, significantly higher in those that showed a complete pathological response (overall and disease-free survival rates of 85% and 75%, respectively). The European Organization for Research and

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Table 1
Outcome measures in clinical trials.

cRR	Clinical response rate
cCR	Complete clinical response
pCR	Complete pathological response, the absence of residual or *in situ* disease following therapy
OS	Overall survival
BCT	Breast-conserving therapy

treatment of Cancer (EORTC) 10902 trial is another large trial that recruited 698 patients with T1c-4b breast cancers.[7] These were randomized to a neoadjuvant and an adjuvant arm receiving four cycles of 5-fluorouracil, epirubicin and cyclophosphamide either pre- or post-operatively. The cRR, cCR rate, and pCR rate were 49%, 7%, and 4%, respectively. An improved survival was seen in patients receiving neoadjuvant chemotherapy with complete pathological response.

In the European Cooperative Trial in Operable breast cancer (ECTO), Gianni et al. randomized 1355 patients into a neoadjuvant and two adjuvant arms with a combination of chemotherapeutic agents.[8] Twenty-three percent of the patients in the neoadjuvant arm had a complete pathological response; the BCT rate was also better in the neoadjuvant arm (65% vs. 34%; $p < 0.001$). The disease-free and overall survival in all the arms was similar at 5 years of follow-up. Several other randomized trials comparing neoadjuvant and adjuvant chemotherapy have shown an advantage in terms of an increase in BCT, though no survival benefit has been shown (Table 2). In fact, it appears that neoadjuvant chemotherapy may increase the rate of loco-regional recurrence.

3. Hormonal influence on neoadjuvant chemotherapy

The response of breast tumours to neoadjuvant therapy appears to vary with the hormone expression profile of the tumour, with estrogen receptor (ER) positive tumours having a worse response. In the M.D. Anderson Cancer Centre (MDACC) trial, Buzdar et al. showed that ER-negative tumours have significantly higher pCR rates (21%) compared to ER-positive tumours (5%).[9] In the ETCO trial,[8] ER-negative tumours had a pCR of 42% compared to ER-positive tumours which was 12%. Similarly, in the NSABP B-27 trial, the pCR rates were 23% and 6% for ER-negative and ER-positive tumours, respectively.[10]

4. Neoadjuvant endocrine therapy

Neoadjuvant chemotherapy is associated with significant toxicity, especially in elderly patients. In this setting, neoadjuvant endocrine therapy has been emerging as an alternate option in hormone receptor positive breast cancer in post-menopausal women.

Tamoxifen has been used as primary treatment in patients with inoperable and locally advanced breast cancer in elderly patients for several years with response rates in excess of 30%.[11] In studies where tamoxifen was given in one group with surgical intervention in the other, a significant increase was noted in the local progression of the disease in the tamoxifen group.[12,13] Comparing tamoxifen only with surgery and tamoxifen, Mustacchi et al. demonstrated an even greater proportional increase in local recurrence in the tamoxifen only group.[14] It must be borne in mind, however, that these studies were not designed to assess tamoxifen in the neoadjuvant setting and merely show its effects as a primary treatment.

Focus has recently been placed on the aromatase inhibitors, several of which are now being used in the adjuvant setting. Letrozole, a highly selective aromatase inhibitor, was initially shown to benefit postmenopausal ER-positive patients in a non-randomized study in Edinburgh.[15] Thereafter, the PO24 trial was published that compared 4 months of letrozole and 12 months of tamoxifen in 337 postmenopausal patients with ER and/or PR-positive tumours.[16] At the time of diagnosis, all patients were considered ineligible for breast conservation. The letrozole group demonstrated a 55% objective clinical tumour response (determined by breast palpation) compared with a 36% in the tamoxifen group ($p < 0.001$). Objective response with ultrasound demonstrated a similar superior efficacy of letrozole compared to tamoxifen. There were more patients in the letrozole group who were found eligible for breast-conserving surgery after treatment (45%) compared to those in the tamoxifen group (35%, $p = 0.022$).

Two randomized trials have been published comparing the efficacy of anastrozole and tamoxifen in postmenopausal women with hormone receptor positive tumours in the neoadjuvant setting. The IMPACT study (IMmediate Preoperative Arimidex, Tamoxifen or Combined with Tamoxifen) was a large multi-centre trial that recruited 330 patients from Germany and the UK.[17] Patients were randomized to either anastrozole, tamoxifen or both for 3 months pre-operatively. No significant difference in objective response (measured by callipers and ultrasound) was noted between the groups. However, the number of patients that were considered suitable for BCT at 3 months was significantly higher in the anastrozole group (46% vs. 22%; $p = 0.03$). Interestingly, patients with her-2 positive tumours demonstrated a higher clinical response rate in the anastrozole group ($p = 0.18$). The PROACT (PReOperative Arimidex Compared with Tamoxifen) trial was another large, multi-centre trial performed in several centres in Europe and USA.[18] This trial recruited 451 postmenopausal women with large operable ER- or PR-positive tumours. Patients were randomized to receive either anastrozole or tamoxifen alongside chemotherapy. Surgery was undertaken at 3 months and the same treatment regime continued for a further 5 years. No significant difference in objective response rate, assessed by ultrasound and calliper measurement, was seen between the groups. However, in

Table 2
Randomized clinical trials of neoadjuvant chemotherapy.

Trial	Median follow-up (months)	cRR%	pCR%	BCT% (compared to adjuvant)	Overall survival (%) (compared to adjuvant)	Local recurrence (%) (compared to adjuvant)
NSABP B-18, Fisher et al., Woolmark et al.[4–6]	108	80	13	67 vs. 60	69 vs. 70	11 vs. 8
EORTC, Van der Hage et al.[7]	56	49	4	37 vs. 21	82 vs. 84	10 vs. 9
ECTO, Gianni et al.[8]	31	78	23	65 vs. 34	–	–
Mauriac[9]	124	81	–	NA	55 vs. 55	8 v 5
Scholl[10]	66	85	–	82 vs. 77	86 vs. 78	24 v 18
Makris[11]	48	83	10	89 vs. 78	80 vs. 80	3 vs. 4
Powles[12]	–		10		–	–
Semiglazov et al[13]	53	69	29	–	86 vs. 78	–
Gazet et al.[14,15]	60	–	–	65 vs. 87	79 vs. 87	–

those patients who had hormonal therapy alone, there was a slight trend in favour of anastrozole. In the same group ($n = 314$), 43% of patients initially considered ineligible for BCT were considered eligible in the anastrozole arm compared to 30.8% in the tamoxifen arm ($p = 0.04$).

Exemestane has similarly been shown to have a promising role in the neoadjuvant treatment of breast cancer. Most studies of exemestane are small, non-randomized studies with low number of patients. In one of these studies by Miller et al., exemestane was administered to 12 women with large operable or locally advanced primary breast cancer.[19] Of the 12 patients treated, 10 had a greater than 50% reduction in tumour size. Conversion rate to breast conservation surgery was high with only 2 of the 10 patients initially considered to require mastectomy actually requiring one (80% breast conservation rate). In another study, Tubiana et al. examined 42 postmenopausal women with ER-positive operable breast cancer by giving them exemestane for 16 weeks pre-operatively.[20] Seventy-three percent of the patients showed a clinical objective response, as measured by ultrasound, whereas 57% of the patients were able to have BCT. In the GENARI trial, 27 postmenopausal women with hormone receptor positive tumours were similarly treated with 16 weeks of exemestane pre-operatively.[21] Ten patients had a partial clinical response, whereas breast-conserving surgery could be offered to 14 patients. A comparatively larger study on exemestane in the neoadjuvant setting has been reported in which 151 women with hormone receptor positive breast cancer were randomized to either exemestane or tamoxifen for 3 months prior to surgery.[22] Clinical objective response as measured by palpation was higher in the exemestane group (76.3%) compared with tamoxifen (40.0%; $p = 0.05$), though there were no significant difference in the response rate when measured by ultrasound and mammogram. However, a higher rate of BCT was seen in the exemestane group compared to tamoxifen (36.8% vs. 20.0%; $p = 0.05$).

5. Trastuzumab as neoadjuvant therapy

HER-2, the human epidermal factor receptor, is over-expressed in 15%–25% of breast cancers.[23] Several studies have shown a survival benefit of trastuzumab, a HER-2 receptor antibody, in metastatic breast cancer in combination with chemotherapy. There are several small trials that have shown a benefit of using trastuzumab in the neoadjuvant setting. One of the trials with trastuzumab had to be closed early due to its significant superiority in the group in which this was used. In this randomized study by Buzdar et al.,[24] patients were being randomized to a preoperative chemotherapy only group (four cycles) and to a group with the same chemotherapy regime along with weekly trastuzumab for 24 weeks. With only 42 of the planned 164 patients recruited, the study showed a marked superiority in the trastuzumab plus chemotherapy arm with a pCR of 65% compared to a pCR of 26% in the other arm ($p = 0.016$). Several other smaller studies of trastuzumab-containing neoadjuvant chemotherapy have described pCR rates ranging from 7 to 78% (reviewed in[25]). Cardiac toxicity remains one of the main drawbacks of its use. Its optimal duration of administration and its impact on long term outcome await further details, with several trials in progress.

6. Neoadjuvant therapy and breast-conserving surgery

Most trials using neoadjuvant chemotherapy have shown an increase in BCT. In the NSABP B-18 trial, 67% of the patients in the neoadjuvant group underwent BCT compared to 60% in the adjuvant group.[4–6] Table 2 illustrates the rates of BCT in various trials. It thus appears that neoadjuvant therapies may offer the opportunity to down-stage the tumours and enable more women to undergo breast-conserving surgery.

7. Does neoadjuvant therapy alter loco-regional recurrence and survival?

Mauri et al. have published a meta-analysis of nine randomized trials of neoadjuvant vs. adjuvant therapy in patients with breast cancer.[26] The analysis included 4000 patients with 966 instances of death, 1310 disease progression, 520 loco-regional recurrences and 745 distant recurrences. The authors found no difference in death and distant recurrences between the different arms. There was a 22% increase in relative risk for loco-regional recurrence associated with neoadjuvant treatment ($p = 0.015$). However, this difference was less than 5% in seven trials and 16.1% in one trial. An interesting point highlighted in the meta-analysis was that the increased risk of loco-regional recurrence was mainly driven by three trials in which no surgical intervention had been adopted. In these trials, patients received radiotherapy only after the neoadjuvant chemotherapy. Though the other six trials did not show as significant a difference in loco-regional recurrence compared to the three trials mentioned, it still showed an increase, and interpretation of the review must be done with caution.

8. Management of the axilla in neoadjuvant therapy

Axillary lymph node status is regarded as a prognostic indicator in invasive breast cancer. Sentinel lymph node biopsy (SLNB) is being used increasingly in patients with early breast cancer in predicting node status. The remainder of the axilla can be considered to be tumour free when the sentinel lymph node is negative.[27] SLNB has an identification rate of 86–93% and a false negative rate of 7–13% (reviewed in.[23] SLNB assessment becomes difficult in the neoadjuvant setting due to the histological changes which may alter the accuracy of SLNB and lead to an increase in false negative results. Several small studies have examined the efficacy of SLNB in this setting. One of the largest of these, the NSABP B-27, involved 428 patients from several centres that underwent SLNB and axillary lymph node dissection following neoadjuvant therapy.[28] The sentinel lymph nodes were successfully identified and removed in 85% of the patients. The false negative rate was 11%, not far from the false negative rate of SLNB in the normal clinical setting. Charfare et al. have combined the results of 14 studies and describe an overall detection rate of SLNB in 89% of the patients with a false negative rate of 11%.[29] These figures are almost comparable to those obtained prior to neoadjuvant therapy and suggest that sentinel lymph node biopsy may be applicable in the neoadjuvant setting.

The timing of SLNB in the neoadjuvant setting is also controversial, with advocates for both pre- and post-neoadjuvant SLNB.[30] Performing the SLNB in the pre-neoadjuvant scenario may provide a more definite node status at presentation and provide the therapists with an opportunity to tailor the treatment based on the node status. However, it exposes the patients to a further surgical procedure. The number of positive lymph nodes may be altered by the neoadjuvant therapy and may alter further treatment plans in the axilla. In the NSABP B-18 trial,[4–6] axillary down-staging has been described following neoadjuvant chemotherapy (41% node positive in the neoadjuvant group compared to 57% in the adjuvant group). In patients where there has been a significant reduction in lymph node disease, a pre-neoadjuvant SLNB may subject them to an unnecessary axillary lymph node dissection later on. The other alternative may be to perform the SLNB after neoadjuvant therapy. This has also been met with several controversies. Though this may mean a reduction in the surgical procedure for the patient as this can be combined with the surgical procedure on the breast, the

identification rates may not be as good compared to when done before neoadjuvant therapy.[30] Moreover, performing the SLNB after adjuvant therapy may be technically more demanding and involve a significant learning curve.

9. Role of radiotherapy after neoadjuvant therapy

In patients treated with neoadjuvant chemotherapy and mastectomy, post-mastectomy radiation has been shown to lower the rate of loco-regional recurrence. Huang et al. performed a retrospective analysis of 542 patients who were treated in six prospective trials within the same institution and compared the data with 134 patients with similar treatment but without radiation.[31] They demonstrated a reduced loco-regional recurrence rate in irradiated patients (10-year recurrence rate 11% vs. 22%. $p = 0.0001$). The benefit was more in patients with clinical T3 & T4 stage, a tumour size of >5.1 cm and in those with more than four positive nodes. This led to their recommendation that patients with locally advanced disease at presentation or with four or more positive lymph nodes should be considered for radiation after neoadjuvant chemotherapy and mastectomy. Based on their review, it remains unclear whether patients with stage II breast cancer with less than three positive lymph nodes would benefit from radiation therapy in a similar setting.

10. Summary

Neoadjuvant therapy offers several benefits. It gives an opportunity to assess the tumour response to the agent *in vivo* by tumour size assessment at regular intervals. It also provides a unique opportunity to study the biology of the tumour. Several modalities of neoadjuvant therapy have been examined and have all shown variable success. Neoadjuvant chemotherapy has demonstrated a down-staging of the tumours which provides an opportunity for more breast-conserving surgery. Though no difference in survival has been demonstrated in trials comparing neoadjuvant with adjuvant chemotherapy, neoadjuvant chemotherapy seems to be associated with an increase in loco-regional recurrence. Neoadjuvant hormone therapy and trastuzumab have also shown promising results. The role of sentinel lymph node biopsy and radiotherapy in this setting is evolving. There are several ongoing trials and the publication of these may yield more conclusive therapeutic choices.

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