RESEARCH COMMUNICATION

Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer in a Malaysian Tertiary Hospital

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Abstract

Introduction: Neoadjuvant chemotherapy for locally advanced breast cancer is given with the aim of shrinking the disease sufficiently for surgery. However, many clinical trials investigating neoadjuvant chemotherapy regimens were conducted for operable breast cancer. Methods and Materials: Patients with T3-4, N2 M0 breast cancer diagnosed between January 2005 and December 2008 and who received at least one cycle of neoadjuvant chemotherapy were eligible for this study. Thirty-four patients were identified from the Chemotherapy Daycare Records and their medical records were reviewed retrospectively. The neoadjuvant chemotherapy regimen administered was at the discretion of the treating oncologist. Breast tumour size and nodal status was assessed at diagnosis, at each cycle and before surgery. Results: All 34 patients had invasive ductal cancer. The median age was 52 years (range 27-69). 65% had T4 disease and 76% were clinically lymph node positive at diagnosis. The median size of the breast tumour at presentation was 80 mm (range 42-200 mm). Estrogen and progesterone receptor positivity was seen in less than 40% and HER2 positivity, by immunohistochemistry, in 27%. The majority (85%) of patients had anthracycline based chemotherapy, without taxanes. The overall response rate (clinical CR+PR) was 67.6% and pathological complete responses were apparent in two (5.9%). 17.6% of patients defaulted part of their planned treatment. Recurrent disease was seen in 44.1% and the median time to relapse was 11.3 months. The three year disease free and overall survival rates were 52.5% and 58% respectively. Conclusion: Neoadjuvant chemotherapy for locally advanced breast cancer in a Malaysian setting confers response and pCR rates comparable to published clinical trials. Patients undergoing neoadjuvant chemotherapy are at risk of defaulting part of their treatment and therefore their concerns need to be identified proactively and addressed in order to improve outcomes.

Keywords: Neoadjuvant chemotherapy - locally advanced breast cancer - non-compliance

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Introduction

Breast cancer is the commonest cancer among Malaysian women, accounting for 31.3% of the total number of new cancer cases diagnosed in women between 2003 and 2005 (Lim et al., 2008). Studies in Malaysian institutions indicate that 30-40% of women present with stage 3-4 disease with a mean tumour size at diagnosis of 4.2 cm (Yip et al., 2006).

NSABP B-18 showed that neoadjuvant chemotherapy had similar survival outcomes to adjuvant chemotherapy in women with T1-3 N0-1 breast cancer (Fisher et al., 1998)]. However, the NSABP B-18 trial only enrolled women with a mean tumour size of 3.5 cm and only 13% had tumours larger than 5cm.

In Malaysia, neoadjuvant chemotherapy is often given to women with much larger or more advanced tumours that those seen in clinical trials. Due to concern that neoadjuvant chemotherapy may be less effective in such bulky tumours and the possible non-compliance with treatment, many surgeons prefer to operate first with the aim of debulking the tumour before chemotherapy or radiotherapy. We conducted a retrospective cohort study of patients with locally advanced breast cancer who received neoadjuvant chemotherapy in our institution to assess response and survival outcomes.

Materials and Methods

Patients with locally advanced breast cancer (T3, T4 or TxN2) who received at least one cycle of neaodjuvant chemotherapy between 1st January 2005 and 31st December 2008 were identified from the Chemotherapy Daycare Unit database. Patients' details were recorded inconsistently prior to 2005 which limited the identification of suitable patients. Patients with metastatic disease at presentation were excluded from the study. Histopathological confirmation of malignancy before the initiation of

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neoadjuvant chemotherapy was required for inclusion into this study.

Patients' clinical data, treatment and follow-up information were gathered from hospital, pathology and oncology records. Most patients had a chest radiograph and ultrasound examination of the abdomen done prior to chemotherapy. The few that did not, had a computed tomography of the chest and abdomen. An isotope bone scan was done in symptomatic patients to exclude bone metastases. Patients were staged at the time of diagnosis using the UICC TNM Classification of Malignant Tumours cancer staging manual, 6th Edition 2002. The survival status of patients lost to follow-up was obtained from the Malaysian National Registration Department.

The chemotherapy regimen prescribed was at the discretion of the treating oncologist. Taxanes were not prescribed routinely and only used if the patient was able to afford the cost of the drug. At least four cycles of neoadjuvant chemotherapy was planned unless there was lack of response or poor tolerance to chemotherapy.

Breast tumour size and nodal status were assessed at diagnosis, each cycle of chemotherapy and before surgery. Clinical complete response was defined as no evidence of palpable breast mass and nodal disease. Partial response was defined as a reduction of at least 50% in the product of the bi-perpendicular diameters of the breast mass. A reduction of less than 50% or an increase of less than 25% would be classified as stable disease. Progressive disease is an increase of this parameter by more than 25% or clinical or radiological evidence of new disease elsewhere. Pathological complete response (pCR) is classified as the absence of malignant cells in the resected breast and lymph nodes on histopathological assessment.

Table 1. Patients' Clinical and Tumour Histological Characteristics

Patients	n
	34
Age	years
Median	52
Range	27-69
Ethinicity	n (%)
Malay	24 (71%)
Chinese	6 (18%)
Indian	1 (3%)
Others	3 (8%)
Stage, clinical	n (%)
T3	12 (35%)
T4	22 (65%)
N0	8 (24%)
N1	16 (47%)
N2	6 (18%)
N3	4 (12%)
Tumour size	mm
Median	80
Range	42-200
ER status	n (%)
Positive	12 (35%)
Negative	17 (50%)
Unknown	5 (15%)
PR status	n (%)
Positive	13 (38%)
Negative	16 (47%)
Unknown	5 (15%)
HER2 status	n (%)
Positive	9 (27%)
Negative	20 (59%)
Unknown	5 (15%)
Grade	n (%)
1	5 (15%)
2	16 (47%)
3	8 (24%)
Unknown	5 (15%)

Surgery was done approximately 4-6 weeks after the last cycle of chemotherapy. Adjuvant chemotherapy was administered if less than four cycles of neoadjuvant chemotherapy was given. Hormonal therapy, either tamoxifen or an aromatase inhibitor, were prescribed for women with estrogen receptor (ER) positive disease. Adjuvant radiotherapy to the chest wall and/or nodal regions was done routinely. As trastuzumab was not funded by the government at that time, it was only prescribed for women who were financially able to purchase the drug.

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) programme version 12.0 (SPSS Inc, Chicago, IL, USA). Clinical and histological variables were assessed using descriptive statistics. Disease-free and overall survival was calculated using Kaplan Meier survival curves (Kaplan and Meier, 1958).

Disease free survival was defined as the time from diagnosis to recurrence, death from any cause or diagnosis of new primary cancer. Overall survival was defined as time from diagnosis to death due to any cause. A study close-out date of 31st May 2010 was chosen for the time to event analyses with survival times of living patients censored at this date.

Results

Patient demographics

A total of 34 patients were suitable for the review. The median follow-up was 25.3 months. Follow-up data was missing in two patients; both of whom were foreigners and they returned to their own countries after treatment.

Clinical and tumour histological characteristics are summarized in Table 1. All patients had invasive ductal carcinoma. The median age was 52 years (range 27-69) and the majority of patients were of Malay ethnicity. Sixty five percent of patients had T4 disease and 76% were clinically lymph node positive at diagnosis. The median size of the tumour at presentation was 80mm (range 42-200 mm). Estrogen and progesterone receptor positivity was seen in less that 40% of patients and HER2 positivity, by immunohistochemistry, in 27%. Assessment of HER2 positivity by FISH was not available at our institution at that time.

Six patients (17.6%) defaulted part of their planned treatment. Of the four patients who did not go for surgery after neoadjuvant chemotherapy, three had a partial response after six cycles of chemotherapy and one patient had stable disease after three cycles. Two patients did not attend for post-mastectomy radiotherapy after chemotherapy and surgery.

Table 2. Chemotherapy Regimens Used

Chemotherapy Regimen	No. of patients
FEC	12
AC	10
FAC	7
FEC-D	2
AC-D	1
Paclitaxel-Carboplatin	1
FAC-P	1

F- 5 fluorouracil, E - epirubicin, C - cyclophosphamide, D -docetaxel, A - doxorubicin, P - paclitaxel

Chemotherapy and response

There were a variety of chemotherapy regimens used and these are summarized in Table 2. The regimens were usually anthracycline based, mainly FEC or AC. Docetaxel or paclitaxel were added if there was a poor response to therapy and the patient could afford the additional cost. The median number of chemotherapy cycles was 6 (range 2-11).

Clinical complete or partial response was seen in 67.6% of patients. Stable disease was present in 23.5% and progressive disease in 2.9%. Response was not assessable in 6% of patients. Patients who were ER or PR negative disease had a response rate of 88% and those who were ER or PR positive had a response rate of 56%. However, this was not statistically significant due to the small sample sizes.

Pathological complete response was seen in 5.9% of patients. Both patients had T4b disease and were ER negative. Both remain alive with no evidence of recurrence.

Five patients had either docetaxel or paclitaxel, as part of their chemotherapy regimen. Two patients had 3 cycles of docetaxel after 3 cycles of FEC as initially planned at the first consultation. Two other patients had docetaxel or paclitaxel when there was no observable response to the initial anthracycline based chemotherapy. However, this only resulted in a response in one patient. One patient had paclitaxel instead of an anthracycline due to concern over her cardiac status pre-chemotherapy.

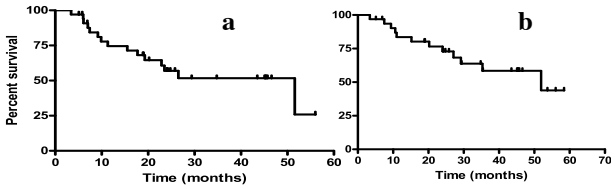

Figure 1. Disease Free (a) and Overall (b) Survival

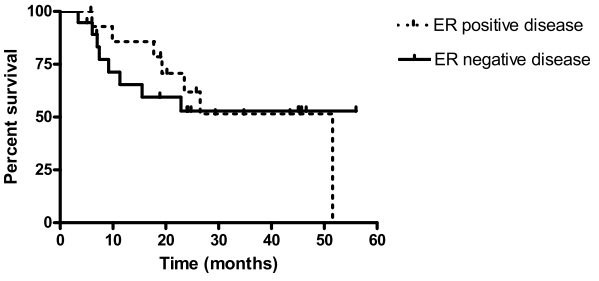

Figure 2. Disease Free Survival According to ER Status

Disease-free and Overall Survival

Fifteen patients (44.1%) developed recurrent disease. The median time to relapse was 11.3 months. The majority of recurrences were distant metastases (57.1%). Local and regional recurrences comprised 19% and 23.8%, respectively, of all recurrences. None of the loco-regional recurrences were salvageable surgically.

Twelve patients have died by the end of May 2010. Kaplan-Meier curves illustrating disease-free and overall survival are shown in Figure 1. The disease free and overall survival rates at 3 years are 52.5% and 58% respectively. Disease-free survival was also analyzed according to ER status and shown in Figure 2. Although patients with ER positive disease tended to relapse at a later date compared with patients with ER negative disease, this difference was not statistically significant (p=0.83; HR 0.89 (95% CI 0.33-2.48)).

Discussion

The NSABP B-18 and B-27 trials have been instrumental in shaping the thinking that underpins primary systemic therapy for operable and locally advanced breast cancer. NSABP B-18 confirmed the non-inferiority of neoadjuvant compared to adjuvant chemotherapy in operable breast cancer. NSABP B-27 investigated the addition of docetaxel to an anthracycline-based regimen. Although it did not improve disease-free or overall survival, there was a significant improvement in disease free survival in those patients who had a partial response to initial anthracycline chemotherapy and then had preoperative docetaxel (Bear et al., 2006). In addition, docetaxel improved the pCR rate, though this may also have been due to a longer duration of chemotherapy.

These two NSABP studies excluded those with T4 or N2 disease. Consequently, it is controversial as to whether such women benefit from neo-adjuvant chemotherapy. Deo et al., (2003) compared neoadjuvant with adjuvant chemotherapy in 101 women with T4b N0-2 disease. They were randomized to either 3 cycles of CEF before and after surgery or 6 cycles of adjuvant CEF. Although there was an overall response rate of 66% with 3 cycles of neoadjuvant CEF, there was no difference in overall or disease-free survival between the two arms. In locally advanced breast cancer, overall response rates may be just as important especially if the disease is initially inoperable. Table 3 summarises the results of several randomized controlled trials that compared various neoadjuvant chemotherapy regimens. It appears that T4, N2-3 breast cancers have lower overall response rates (60-70%) when only anthracycline based regimens are used compared to T1-3, N0-1 breast cancers (80-90%). The addition of taxanes may increase the overall response rates further as seen in the Aberdeen trial. A secondary analysis of the GeparTrio trial data compared pCR rates between patients with inflammatory, locally advanced or operable breast cancer who received neoadjuvant chemotherapy. Although the pCR and overall response rates were significantly lower for inflammatory and locally advanced breast cancer compared to operable breast cancer (pCR: 8-11% vs 17.7%, ORR: 70% vs 83.4%), there was no evidence

Table 3. Results of Randomised Controlled Trials Investigating Various Neoadjuvant Chemotherapy Regimens

Clinical Trial	Stage	ER positivity	Mean tumour size	Chemotherapy regimen	Overall response rate	Pathological complete response rate
NSABP B-18 (Fisher, 1998)	T1-3, N0-1	57%	3.5 cm	4*AC	79%	13%
MDACC (Buzdar et al., 1999)	T1-3, N0-1	55%/61%	N/A	4*FAC/T	79%/80.2%	16.4%/ 8.1%
Aberdeen (Smith et al., 2002)	T3-4, N2	61%	4.9 cm	8*CVAP/ 4*CVAP-4*D	66%/94%	16%/34%
EORTC-NCIC-SAKK (Therasse et al 2003)	T4, N2/3	38%/42%	N/A	6* CEF/DD-EC	58.9%/60.8%	14%/ 10%
SICOG (Frasci et al., 2006)	T4, N2	53%/57%	N/A	4*DD-XET/ET	88%/78%	16%/ 6%
ACCOG (Jeffry Evans et al., 2005)	≥3cm, T4	UK	6cm	6*AC/AD	61%/70%	24%/21%

A-adriamycin, C-cyclophosphamide, D-docetaxel, DD-dose dense, E-epirubicin, F-5fluorouracil, P-prednisolone, T-paclitaxel, V-vincristine, X-cisplatin

of a difference in response to neoadjuvant chemotherapy according to stage when the analysis was adjusted for baseline characteristics (Costa et al., 2010).

As mentioned earlier, the duration of therapy may also be important in improving pCR, at least in operable breast cancer. The randomized controlled trials by Han et al., (2009) and Steger et al., (2007) both separately showed that the pCR rate can be increased by increasing the number of cycles of epirubicin and docetaxel chemotherapy from 3 or 4 to 6. On the other hand, the GeparTrio trial compared an additional 4 or 6 cycles of the neoadjuvant TAC regimen in those patients with mainly T2-3 breast cancer who were assigned as responders after 2 cycles of the same regimen. Although more clinical and sonographic complete responses were observed with 8 cycles, pCR was not significantly different between the two arms (von Minckwitz et al., 2008). The GeparQuattro study showed that intensifying the chemotherapy regimen further by adding capecitabine to 4 cycles of docetaxel after 4 cycles of epirubicin and cyclophosphamide was not of any benefit in improving pCR. In addition, increasing the duration of neoadjuvant chemotherapy from 8 to 12 cycles did not offer an advantage in this study (von Minckwitz et al., 2010).

Two studies investigated the value of changing the chemotherapy drugs used in the event of a lack of response to the initial neoadjuvant regimen. The Aberdeen study noted that in those patients whose tumours failed to respond after 4 cycles of CVAP, a change to 4 cycles of docetaxel resulted in an overall response rate of 55% and a pCR of 2% (Smith et al., 2002). The GeparTrio study also compared the outcomes of non-responding patients who continued the same regimen, i.e. docetaxel, doxorubicin, cyclophosphamide (TAC), with that of patients who switched to a non-cross resistant regimen, vinorelbine and capecitabine (von Minckwitz et al., 2008). The outcome was sonographic response and this was not significantly different between the two arms (50.5% vs 51.2%). Thus it seems that patient who do not respond to an anthracycline regimen have a favourable chance of responding to a taxane but little value is gained by changing a combined anthracycline-taxane regimen if there is a lack of response. Kaufman et al found a partial response rate of 39% with lapatinib monotherapy in patients who had HER2-overexpressing relapsed or refractory inflammatory breast cancer (Kaufman et al., 2009). Of the 126 patients in this study, 60% had chemo-refractory disease and a significant proportion had had previous anthracycline, taxane and trastuzumab. Interestingly, they noted an overall response rate of 40% for clinically evaluable skin-disease and an objective response rate of only 15% by RECIST criteria of measurable sites of locally advanced or metastatic disease. The authors postulated that this difference may be due to a high incidence (67%) of PTEN deficiency in inflammatory breast cancer skin biopsies (Johnston et al., 2008). PTEN deficiency, which abrogates PI3K-Akt signaling, leads to trastuzumab but not lapatinib resistance (Nagata et al., 2004, Xia et al., 2007).

In NSABP B-27, the pathological complete response rate was found to be a highly significant predictor of improved disease-free and overall survival. Furthermore, this was true regardless of the chemotherapy received. An improvement in 5 year overall survival was also found in the NSABP B-18 study for women with a pCR compared with non-pCR to neoadjuvant AC chemotherapy. In addition, other older studies have indicated that pCR is a predictor of improved survival in operable breast cancer (Bonadonna et al., 1998; Kuerer et al., 1999). As a result, significant research has been undertaken to improve pCR as a surrogate endpoint to an improvement in survival as well as a means to investigate the early efficacy of new chemotherapy agents.

An important advance in neoadjuvant chemotherapy has been the results of the NOAH trial where patients with HER-2 positive T3N1, T4, N2 or 3 breast cancers received neoadjuvant chemotherapy with or without trastuzumab (Gianni et al., 2010). Trastuzumab was given with neoadjuvant chemotherapy and continued adjuvantly for a total of one year. Although the protocol stipulated that patients in the control arm were not to receive adjuvant trastuzumab, 16% crossed over to receive it after the results of the adjuvant trastuzumab trials were known. The addition of trastuzumab to the neoadjuvant chemotherapy increased the event-free survival from 56% to 71% and pCR in breast and lymph nodes from 19% to 38%. The GeparQuattro study showed a pCR of 31.7% in HER2 positive disease when trastuzumab was given with neoadjuvant chemotherapy, compared to 15.7% in the HER2 negative reference group. In this study, approximately 30% of the patients with HER2 positive disease in fact had T3-4 disease clinically (Untch et al., 2010).

Predictive biomarkers offer the tantalizing prospect of tailoring treatment to improve survival and minimize toxicity. Many biomarkers of chemosensitivity have been investigated in small studies but these need further validation before they can be used in routine clinical practice (Gianni et al., 2005; Prisack et al., 2005; Fiegl et al., 2008). On the other hand, assessment of hormone receptor status has been readily available for many years. As a result, ER negative tumours have been shown to have higher pCR rates with neoadjuvant chemotherapy compared to ER positive tumours (Colleoni et al., 2004; Ring et al., 2004). However, pathological complete response was shown to be associated with an improved outcome regardless of hormone receptor status in 1731 patients with stage 1-3 breast cancer who received neoadjuvant chemotherapy in a retrospective study by Guarneri et al., (2006).

Of significant concern is the 17.6 % rate of patients who default from subsequent treatment after undergoing neoadjuvant chemotherapy in this retrospective study. They may have decided to seek treatment at other medical centres and this would be difficult to ascertain from our hospital records. Although it is understandable for women who have a very good response to neoadjuvant chemotherapy to seek to avoid a mastectomy, other causes of non-compliance among cancer patients need to be identified and addressed.

Patients with infectious diseases, especially tuberculosis, have been used as a model to study predisposing factors and prevention strategies to reduce the likelihood of defaulting treatment. Poor doctor-patient rapport and communication, patient's economic constraints, poor understanding of the disease and treatment and additional inconveniences to the patient in the form of referrals and consultations in a large busy public hospital have been cited as predisposing factors for defaulting (Buu et al., 2003; Hill et al., 2005). The widespread use of traditional or alternative medicine and the patient's fear of losing her breast may be additional contributing factors. The value of a breast care nurse in alleviating anxiety, improving the continuity of care, relaying information and providing psychosocial support has been shown in numerous studies (Cruickshank et al., 2008; Chiarelli et al., 2010). The breast care nurse can play a vital role in allaying concerns and improving compliance rates. As a result, the inclusion of breast care nurses into the multidisciplinary team has been recommended by the UK NICE (2009) and New Zealand (2009) breast cancer guidelines.

In conclusion, this study of neoadjuvant chemotherapy in patients with T3-4, N2 locally advanced breast cancer treated at a Malaysian tertiary hospital showed that the overall response and pCR rates are comparable to those seen in clinical trials with a 3 year overall survival rate of approximately 55%. The rate of default was not as high as originally thought and measures to address obstacles in the patient's continuity of care in addition to the introduction of the breast care nurse as a vital part of the multidisciplinary team may help to reduce the default rate further. This is one area deserving stress in future interventions.

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