ORIGINAL ARTICLE

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Neoadjuvant systemic therapy for breast cancer: the Westmead experience

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Key words
breast cancer, neoadjuvant therapy.

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This paper is based on a previous communication of the Leura 8 International Breast Cancer Conference, October 2016.

Accepted for publication 20 June 2017.

doi: 10.1111/ans.14158

Abstract

Background: Neoadjuvant systemic therapy (NAST) can be used to treat breast cancer. Pathologic complete response (pCR) is a surrogate marker for improved survival. This study examined response in the breast and axilla to NAST and identified features associated with pCR.
Methods: Patients undergoing NAST and surgery between January 2012 and June 2016 by surgeons at Westmead Breast Cancer Institute were identified. Patients with inflammatory or metastatic disease were excluded. Data were analysed to identify factors predictive of pCR.
Results: Ninety-one patients were identified. Mean age was 49 years. Forty-one patients had axillary metastases identified prior to NAST. Eighty-three patients received chemotherapy alone, six endocrine therapy alone and two had both. Thirty-seven patients had mastectomy and 54 had breast-conserving surgery. The overall breast pCR rate was 29% higher in patients with triple-negative (50%) or HER2-positive (39%) disease and lower in luminal disease (11.6%, $P = 0.001$). Forty percent of node-positive patients became node negative. The only variable associated with pCR was tumour biology. Patients with HER2-positive breast cancer were more likely to have axillary pCR than those with luminal cancer (odds ratio: 28, $P = 0.00005$).
Conclusion: pCR in either the breast or axilla was most likely to be achieved in patients with HER2-positive or triple-negative breast cancers. In patients with luminal cancers, the goal of NAST is best considered to facilitate surgical options rather than obtaining a pCR.

Introduction

Neoadjuvant systemic therapy (NAST) is increasingly utilized in breast cancer. NAST was originally used to facilitate surgery in previously inoperable breast cancer and has evolved to allow breast-conserving surgery (BCS) in patients who would otherwise require mastectomy, improve post-operative cosmesis and assess response to systemic therapy.[1] Neoadjuvant chemotherapy has demonstrated equivalence to adjuvant chemotherapy in regard to long-term survival and locoregional recurrence.[2]

During treatment, clinical and radiological response to NAST is assessed, although the false negative rate of apparent complete response is considerable.[3] Previous studies have demonstrated that it is not safe to avoid surgery in the breast regardless of response.[4] After surgery, histopathological response is determined and considered definitive. A pathologic complete response (pCR) – the absence of any viable invasive carcinoma in the pathology specimen – is associated with better survival than if residual disease is present.[1] A systematic review published in 2012 reported an overall breast pCR rate of 18.5%.[5] Tumour subtype was independently associated with likelihood of pCR, with HER2-positive and triple-negative diseases having pCR rates of approximately 30% compared with 8% in luminal cancers.[5] The higher response rate of HER2-positive and triple-negative cancers was emphasized in a recently published review.[6]

A recent systematic review reported an overall axilla pCR rate of 39.2%.[7] Clinical N1 disease was associated with increased likelihood of pCR compared with N2 and N3 diseases.[7] Tumour biology was not a significant factor in the likelihood of nodal pCR.[7]

This study examined response in the breast and axilla to NAST and identified features associated with pCR.

Methods

Following ethical approval from the Western Sydney Local Health District Research Governance officer, a retrospective database, chart and logbook review was undertaken to identify all patients treated by surgeons at Westmead Breast Cancer Institute undergoing NAST and surgery between January 2012 and June 2016. Exclusion criteria were inflammatory cancer, metastatic disease at the time of presentation and details of neoadjuvant treatment being unavailable.

Data including patient demographics, clinical examination, imaging and histopathology findings prior to NAST; details of NAST; post-NAST clinical examination and imaging findings; details of surgery; and final histopathology of the breast and axilla were extracted. Where available, the residual cancer burden (RCB) was documented.

All patients were discussed in a multidisciplinary team meeting; marker clips were placed in the breast before treatment; clinical and radiological response to NAST was assessed; and, if a sentinel lymph node biopsy (SLNB) was performed, dual tracers (radioisotope and blue dye) were generally used.

Data were analysed using SPSS version 23 (IBM, Armonk, NY, USA), and descriptive statistics was used to analyse tumour biology (luminal versus HER2 positive versus triple negative); and rates of pCR in the breast and axilla. Univariate analysis was performed to determine significant differences between groups (pCR versus no pCR). A multivariate regression analysis using stepwise logistic regression was performed to determine whether any variable was independently associated with likelihood of pCR.

Results

A total of 1090 patients underwent surgery for invasive breast cancer. Ninety-one (4.6%) underwent NAST. Patient characteristics are shown in Table 1. Ten patients were treated with NAST in 2012, eight in 2013, 16 in 2014, 38 in 2015 and 19 in the first half of 2016. Axillary nodal involvement was assessed before NAST using clinical examination and ultrasound, with needle biopsy of any abnormal nodes.

Table 1 Patient characteristics (n = 91)

Mean age (years)	49
Median tumour size on imaging (mm)	39 (range: 12–120)
Histological type of tumour	
Ductal	86
Lobular	5
Tumour biology	
Luminal	43
HER2 positive	28
Triple negative	20
Grade of tumour on core biopsy	
1	1
2	21
3	32
Unknown	37
Initial axillary status (clinical/imaging/biopsy)	
Positive	41
Negative	50

Neoadjuvant systemic therapy

Table 2 outlines the neoadjuvant regimens used. Eighty-three patients had chemotherapy alone, six had endocrine therapy alone and two both. Seventy-eight patients completed their NAST. Six patients who had chemotherapy alone did not complete the course due to side effects. Five patients terminated their course due to lack of response (three to endocrine treatment and two to chemotherapy). One patient changed from anthracycline-based to taxane and HER2 therapy due to lack of response. Of the two patients who had chemotherapy and endocrine therapy, one completed chemotherapy before commencing endocrine therapy after a venous thromboembolism delayed surgery and one still had a sizeable tumour post-chemotherapy and wished to pursue endocrine therapy to try and achieve BCS.

Clinical and imaging response

All patients were examined and 70 patients had imaging during or following NAST. The timing of both examination and imaging was variable. Seven patients had an apparent complete clinical and radiological response.

Response in the breast

BCS was performed in 54 patients and mastectomy in 37. Of the patients who had BCS, 15 had involved margins (28%). Seven of those patients had re-excision of margins; four had completion mastectomy; and four did not have further surgery after multidisciplinary team meeting discussion. Breast pCR was observed in 26% of patients. Patients with luminal disease (i.e. ER+ and HER2−) were less likely to have pCR (11.6%) than those with HER2-positive (39%) or triple-negative (50%) disease (P = 0.001; Fig. 1a).

Response in the axilla

The axillary operation/s and pathological results are outlined in Figure 2. Six of 50 patients who were node negative at presentation had axillary lymph node dissection (ALND) as their only axillary procedure: three with large tumours at presentation, one with a suspicious axillary node on ultrasound, one with clinically positive supraclavicular lymph nodes and one with nodal metastases detected on imaging during NAST. Of these six patients, three did not have any evidence of metastatic disease at ALND.

Table 2 Neoadjuvant chemotherapy/endocrine therapy/HER2-directed therapy administered to 91 patients

Regimen	Patients
Anthracycline† + taxane	36
Anthracycline only	19
Anthracycline + taxane + HER2-directed	15
Taxane + platinum + HER2-directed	9
Aromatase inhibitor only	6
Other‡	6

†Anthracycline = anthracycline-based regimens: AC (doxorubicin and cyclophosphamide) or FEC (5-fluorouracil, epirubicin and cyclophosphamide). ‡Other: anthracycline + tamoxifen (1); anthracycline + taxane + aromatase inhibitor (1): anthracycline + taxane + platinum (1); taxane + HER2-directed (1); taxane only (2).

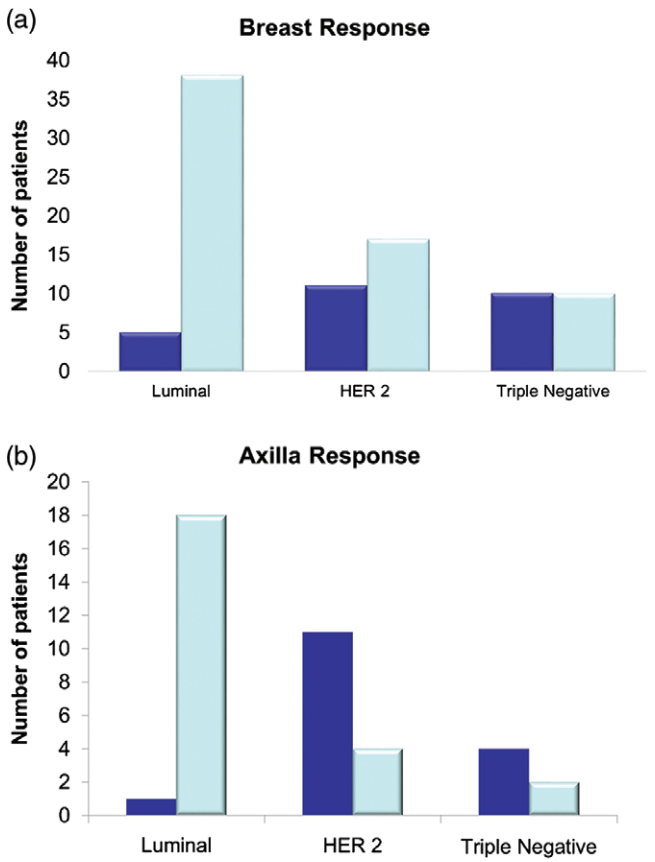

Fig. 1. Pathologic complete response (pCR) in the breast (■, pCR; ■, no pCR) (a) and axilla (b) (n = 40; ■, pCR; ■, no pCR).

The remaining 44 patients who were initially node negative had SLNB. Twenty-seven patients had negative SLNB; 17 were positive; of whom 11 proceeded to ALND. Six patients with positive SLNB after NAST did not proceed to ALND. Of these patients, one was treated with axillary radiotherapy after declining ALND. Two patients had micrometastases only; one was treated with axillary radiotherapy and the other did not have any further axillary treatment. Three patients had isolated tumour cells in the sentinel node and received axillary radiotherapy.

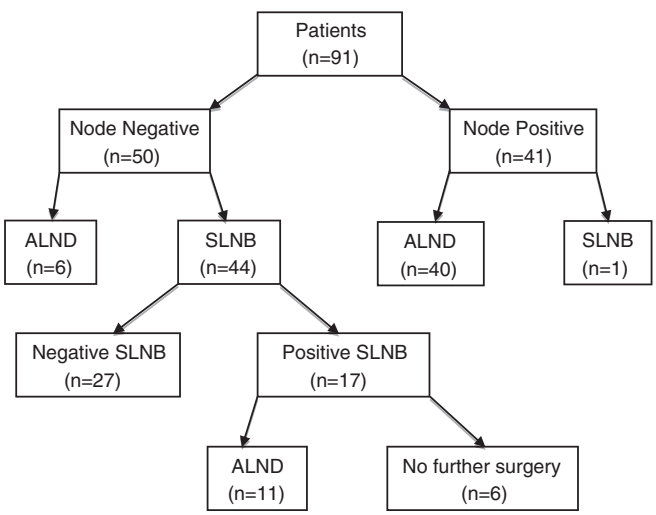

Fig. 2. Flow chart of axillary surgical management. ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Forty of the 41 patients were initially node positive; 40 had an ALND and one had SLNB. The patient who had SLNB alone (which was negative) was excluded in the axillary pCR analysis. Sixteen of the 40 pre-NAST node-positive patients did not have any residual invasive cancer. This equates to a pCR rate of 40%. Five percent of patients with luminal disease had pCR compared with 73% in HER2-positive patients and 67% in patients with triple-negative disease (Fig. 1b).

Residual cancer burden

RCB was calculated for 49 patients using the MD Anderson calculator (https://www.mdanderson.org/for-physicians/clinical-tools-resources/clinical-calculators.html). RCB was not used at the time of surgery for the remaining patients. Fifteen patients (25%) had a pCR (RCB Class 0); 13 RCB Class 1; 19 RCB Class 2; and 12 RCB Class 3. Nine patients (15%) had both breast and axillary pCRs.

Predictors of response

On univariate analysis using Fisher's exact test, tumour biology was the only statistically significant predictor of axillary pCR. Age and tumour size were not statistically significant. On multivariate analysis, after adjusting for age and tumour size, tumour biology remained a statistically significant predictor. Patients with HER2-positive tumours were 28 times more likely to have pCR than patients with luminal cancer (P = 0.00005). Age, tumour size and breast pCR were not predictive of axillary pCR.

Imaging studies were not consistently performed, precluding statistical analysis comparing apparent clinical or imaging response with pCR. Of the seven patients who had an apparent clinical and imaging complete response, four had breast pCR. One was initially node positive and had axillary pCR, and the remaining six underwent SLNB in which three had axillary metastasis.

Discussion

In this study, rates of breast and axilla pCR were similar to previously published data. An association between tumour biology and likelihood of breast pCR was identified and is consistent with previously published research.

Tumour biology

Distinguishing between luminal A versus luminal B disease can be difficult, especially in a neoadjuvant setting. Ki67 was performed on core biopsy specimens of only five of the 43 patients with luminal tumours, and grade was reported for 29 of those patients. Therefore, the distinction between luminal A and luminal B was not made.

Patients with luminal disease had a lower rate of breast and axilla pCR than those with HER2-positive or triple-negative disease. Neoadjuvant endocrine therapy was used in a small subset of our patients. While it is unlikely that a pCR will be achieved with this therapy, it still has an important role in terms of possibly shrinking the primary tumour and facilitating BCS. A combination of

neoadjuvant endocrine therapy and chemotherapy may have even better outcomes, and this is currently being investigated in the ELIMINATE study (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=366153).

Considerations for patient management: breast

A recent article highlighted concerns that the rate of BCS for patients following NAST is falling despite advances in systemic treatments and improved rates of pCR.[8] The breast pCR rate in our population was 26%, and nearly 60% of patients had BCS, so we do not feel that this is the case in our centre.

For patients with HER2-positive and triple-negative diseases, the rates of pCR were 39% and 50%, respectively, so there is a high likelihood of being able to facilitate BCS in these patient groups. In patients with large luminal cancers, NAST can allow BCS when mastectomy would have been required and allow BCS with less cosmetic impact. The fact that a pCR is not likely should not be considered a contraindication to NAST.

Considerations for patient management: axilla

Forty percent of patients who initially had axillary metastases did not have evidence of axillary involvement on ALND. Luminal cancers were unlikely to have pCR, whereas triple-negative and HER2-positive diseases had higher pCR rates.

It is now accepted that SLNB should be performed following NAST for initially node-negative patients.[9] SLNB has a high false negative rate in initially node-positive patients, with the lymph nodes containing metastases prior to NAST different to the sentinel node in up to 23% of cases.[10] The standard treatment for node-positive patients prior to NAST remains ALND. With axillary pCR rates around 40%, the question of whether it is possible to avoid an ALND in selected patients has been raised.[11]

Targeted axillary dissection aims to improve on the false negative rate of SLNB in this setting. This involves excision of the initially involved node (marked with a clip before NAST) and an SLNB using dual tracers with a minimum of three nodes excised. This approach has been shown to improve the accuracy of axillary staging significantly with false negative rates as low as 1–2%.[10,12,13] The impact on survival and locoregional recurrence of performing targeted axillary dissection rather than ALND in node-positive patients prior to NAST is unknown.[14]

Influence on institutional practice

This study has affected our practice in four ways. First, it has informed us that rates of pCR in the breast and the axilla, and the subgroups of patients who seem to get the greatest response to NAST, are in keeping with the experience of other centres across the world. Second, it encouraged us to especially target patients with HER2-positive and triple-negative diseases for neoadjuvant chemotherapy. Third, it raised the question of whether limited axillary surgery may be possible in patients with HER2-positive or triple-negative diseases and axillary metastases at diagnosis. The long-term safety and efficacy of such an approach needs further investigation, and the Alliance and NSABP-B51 trials should provide more information (http://www.kccop.org/cancer-trials/breast/index.cgi/summary?tID=110).[15] Fourth, it raised the question of the best timing of imaging to assess response to NAST, and led to us developing a protocol for this in our practice.

Limitations

NAST has many potential benefits other than achieving pCR: increased chance of BCS, higher rates of immediate breast reconstruction and increasing time available for patients to consider surgical options.[16] In our retrospective study, the aim of NAST was not widely documented, and therefore assessing outcomes other than pCR was not possible.

Conclusion

NAST is effective in downstaging breast cancer in both the breast and axilla. pCR in either the breast or axilla is most likely in patients with HER2-positive or triple-negative disease. Clear prospective documentation of the aim of NAST would enable assessment of whether it has achieved outcomes other than pCR.

Acknowledgements

We thank Assistant Professor Kerry Sherman, Ms Masrura Kabir and Dr Kirsty Stuart.

Conflicts of interest

None declared.

References

1. van der Hage J, van de Helde C, Mieo S. Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst. Rev.* 2007: CD005002.
2. Bear H, Anderson S, Smith R *et al.* Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2006; **24**: 2019–27.
3. Schaefgen B, Mati M, Sin H *et al.* Can routine imaging after neoadjuvant chemotherapy in breast cancer predict pathologic complete response? *Ann. Surg. Oncol.* 2016; **23**: 789–95.
4. Mauri D, Pavlidis N, Ioannidis J. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J. Natl. Cancer Inst.* 2005; **97**: 188–94.
5. Houssami N, Macaskill P, von Minckwitz G, Marinovich M, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur. J. Cancer* 2012; **48**: 3342–54.
6. Manguso N, Gangi A, Giuliano A. Neoadjuvant chemotherapy and surgical management of the axilla in breast cancer: a review of current data. *Oncology* 2015; **29**: 733–8.
7. Chehade H, Headon H, Tokhy OE, Heeney J, Kasem A, Mokbel K. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. *Am. J. Surg.* 2016; **212**: 969–81.

8. Criscitiello C, Curigliano G, Burstein H *et al.* Breast conservation following neoadjuvant therapy for breast cancer in the modern era: are we losing the opportunity? *Eur. J. Cancer Surg.* 2016; **42**: 1780–6.
9. Kaufmann M, von Minckwitz G, Mamounas E *et al.* Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann. Surg. Oncol.* 2012; **19**: 1508–16.
10. Caudle A, Yang W, Krishnamurthy S *et al.* Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J. Clin. Oncol.* 2016; **34**: 1072–8.
11. Tadros A, Yang W, Krishnamurthy S *et al.* Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. *JAMA Surg.* 2017; **152**: 665–70.
12. Boileau J, Poirier B, Basik M *et al.* Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC Study. *J. Clin. Oncol.* 2015; **33**: 258–64.
13. Boughey J, Suman V, Mittendorf E *et al.* Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013; **310**: 1455–61.
14. Krag D. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol.* 2010; **11**: 927–33.
15. Mamounas EP, White JR, Bandos H *et al*. NSABP B-51/RTOG 1304: randomized phase III clinical trial evaluating the role of postmastectomy chest wall and regional nodal XRT (CWRNRT) and post-lumpectomy RNRT in patients (pts) with documented positive axillary (Ax) nodes before neoadjuvant chemotherapy (NC) who convert to pathologically negative Ax nodes after NC. *J. Clin. Oncol.* 2014; **32** (Suppl.): TPS1141.
16. Read R, Flitcroft K, Snook K, Boyle F, Spillane A. Utility of neoadjuvant chemotherapy in the treatment of operable breast cancer. *ANZ J. Surg.* 2015; **85**: 315–20.