



Neoadjuvant chemotherapy rates for breast cancer in Australia— “are we there yet?”

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Background: Neoadjuvant chemotherapy (NAC) is indicated in locally advanced breast cancer and being increasingly utilised in high risk, early stage breast cancer to improve surgical outcomes. This study examines the trend of NAC utilisation for early and locally advanced breast cancer in Australia.

Methods: A retrospective analysis of prospectively collected data from the BreastSurgANZ Quality Audit (BQA) database identified patients registered with early breast cancer who received NAC from 2011 to 2016. Trend analysis for NAC utilisation was performed using the Cox-Stuart and Chi-squared tests.

Results: A total of 55,757 cases of breast cancer were identified from 2011 to 2016, of which 2,469 (4.43%) cases underwent NAC. There were no significant trends for cancer diagnosis in this period ($P=0.5$). The proportion of patients receiving NAC increased from 3.08% in 2011 to 6.65% in 2016; this trend was statistically significant ($P\leq 0.001$).

Conclusions: Compared to other population-based studies on the administration of NAC for breast cancer, NAC is still underutilised in Australia.

Keywords: Neoadjuvant; chemotherapy; utilisation; rates; breast cancer

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Introduction

Neoadjuvant chemotherapy (NAC) in breast cancer treatment was initially indicated for locally advanced breast cancers (1), defined as invasive breast cancer that may be large, have metastasised to several lymph nodes in the axilla or invaded local structures (2). NAC enabled patients with locally advanced breast cancer who had adequate response to undergo breast conserving breast surgery with comparable long-term outcomes as patients with total mastectomy (3). Although the benefits of NAC are well documented in the literature there appears to be an ongoing reluctance for surgeons in Australia to offer NAC to appropriate patients. The Cancer Australia Statement on influencing best practice in breast cancer includes that it is appropriate to consider the pre-operative use of chemotherapy or hormonal therapy (systemic,

neoadjuvant therapy) informed by hormone and HER2 receptor status, for all patients where these therapies are clinically indicated (4).

Randomised prospective studies comparing neoadjuvant and adjuvant chemotherapy in early-stage operable breast cancer have demonstrated comparable overall survival (5). While also decreasing tumour size, downstaging axillary lymph node involvement, facilitating breast conserving surgery without significant increases in local recurrence and allowing time for genetic testing (6). The absence of residual invasive disease in the breast and axillary lymph nodes or pathologic complete response (pCR) after NAC and surgery is an important indicator of long-term outcomes (7). pCR is achieved in up to 20% of patients after NAC and the extent of this early response is useful as a guide for further treatment (8). The degree

of response following NAC allows clinicians to predict the benefits of adjuvant treatment (9), the probability of adjuvant treatment success and failure and allows for consideration of alternative treatment strategies if patients do not respond. In contrast to patients who only have adjuvant treatment after surgery, patients undergoing NAC potentially take advantage of the “window of opportunity” for early introduction of therapy for distant micrometastatic disease with less time delay in chemotherapy between diagnosis and surgery (10). For patients where genetic studies would alter their treatment algorithm, NAC allows for active treatment while these results, which often take weeks, are pending. In patients with breast cancer during pregnancy, it is at least as effective as if given after delivery and may provide the benefit of delaying surgery (11). Additionally, NAC appears to be associated with a lower rate of surgical site infections in comparison to adjuvant chemotherapy in breast cancer (12).

Given these potential benefits of NAC and meta-analyses that have demonstrated the equivalence of NAC to adjuvant chemotherapy in terms of overall survival and disease progression, an international expert consensus on primary systemic therapy in the management of early breast cancer have recommended that all early stage breast cancer patients identified as likely to require adjuvant chemotherapy should be considered for NAC (13). Despite the evidence and recommendations, NAC utilisation in clinical practice remains highly variable.

This article examines rates of NAC utilisation in Australia using data obtained from the BreastSurgANZ Quality Audit (BQA) between 2011 and 2016. It seeks to answer the following questions: what is the current trend in NAC utilisation in Australia; and how do our rates compare to the rest of the world?

Methods

This was a retrospective cohort study using a prospectively maintained database reviewed breast cancer diagnoses in Australia between 1 January 2011 and 31 December 2016 who were treated by breast surgeons participating in the BreastSurgANZ Quality Audit (BQA). The BQA is a national initiative which aims to improve the quality of care by surgeons for patients with early and locally advanced breast cancer in Australia and New Zealand. The BQA does not include patients with metastatic (stage IV) breast cancer at the time of initial diagnosis. It was originally initiated as a pilot study in 1998 and has been running continuously

since that time. The BQA data included in this study included: (I) age at diagnosis; (II) tumour characteristics including tumour size, tumour grade and oestrogen receptor, progesterone receptor and HER2 statuses; and (III) treatment characteristics including NAC and adjuvant chemotherapy utilisation. The pathologic characteristics are based on reported pathology after breast surgery and not on tissue biopsies prior. The correlation between preoperative and postoperative pathologic characteristics is therefore assumed to be similar.

Microsoft Excel was used to compile spreadsheet and calculate simple counts. R Studio was used to perform trend analysis using the Cox-Stuart test. Further statistical analysis of the data using Stata and Chi-squared test for trend. A P value of <0.05 was determined to be statistically significant for trend analysis.

BreastSurgANZ Breast Quality Audit team support the view that there are no ethical issues and negligible risk associated with this study which investigates NAC utilisation rates in Australia using retrospective de-identified patient data.

Results

There were 55,757 patients with early and locally advanced breast cancer entered into BQA between 2011 and 2016. There were no significant trends in the incidence of early and locally advanced breast cancers, HER2 positive breast cancers and triple negative breast cancers during the period of interest. A total of 2,469 (4.43%) patients underwent NAC. There was a gradual increase in the proportion of patients receiving NAC from 3.08% in 2011 to 6.65% in 2016 this increasing trend was statistically significant ($P \leq 0.001$). There were 1,644 (66.59%) patients who received NAC also received adjuvant chemotherapy after surgery (*Table 1*).

The use of NAC was associated with younger patient age, larger tumour size, higher tumour grade, HER2 positive breast cancers and triple negative breast cancers. Three hundred and eighty-one cases appeared to have a tumour size of zero and in 1,337 patients tumour size was either not recorded or missing. There did not appear to be a significant variance in the use of NAC in different states in Australia (*Table 2*).

Discussion

The results show that the proportion of patients receiving

Table 1 Incidence of early and locally advanced breast cancer, utilisation of NAC and utilisation of NAC in Australia from 2011 to 2016

Variable	2011	2012	2013	2014	2015	2016	Total
Early and locally advanced breast cancer in Australia	9,325	9,355	9,711	9,912	8,804	8,650	55,757
HER2 positive	1,122	1,160	1,201	1,231	1,061	980	6,755
TNBC	920	990	972	937	863	891	5,573
NAC, n (%)	287 (3.08)	332 (3.55)	370 (3.81)	407 (4.11)	498 (5.66)	575 (6.65)	2,469 (4.43)
Adjuvant chemotherapy, n (%)	4,253 (45.61)	4,400 (47.03)	4,505 (46.39)	4,241 (42.79)	3,764 (42.75)	3,687 (42.62)	24,850 (44.57)

TNBC, triple negative breast cancer; NAC, neoadjuvant chemotherapy.

Table 2 Use of NAC in each of the states and territories in Australia

State	Total cases	NAC	% NAC
ACT	885	35	3.95
NSW	17,661	716	4.05
NT	242	13	5.37
QLD	11,400	468	4.11
SA	6,536	270	4.13
TAS	854	41	4.80
VIC	12,821	680	5.30
WA	5,358	246	4.59

NAC, neoadjuvant chemotherapy.

NAC in early and locally advanced breast cancer is slowly but gradually increasing. In 2015, Read *et al.* reported that less than 3% of women with operable cancer in Australia received NAC (6). In the light of the evidence demonstrating the benefits of NAC, it is encouraging to see that this trend is increasing in Australia although it still falls short of the estimated 20% of patients with breast cancer that might benefit from NAC (14).

To better appreciate the relevance of the Australian data included in this study, it must be examined in an international context. In general, there has been a paucity of published literature on the national trends of NAC utilisation, although numerous trials on NAC in early and locally advanced breast cancer are available. The overall utilisation of NAC over the examined time period is lower than recent published international utilisation rates of NAC. In 2015, the United States National Cancer Data Base reported that between 2003 and 2011, 17.4% of 395,486 patients with stage I to stage III breast cancer who received adjuvant or NAC

received NAC. In this study, NAC utilisation increased with time from 12.2% to 24% (15). Similarly, the Dutch National Breast Cancer Organisation (NABON) Breast Cancer Audit which accumulated 49,073 patients between 2011 and 2015 reported an increasing trend of NAC utilisation from 8% in 2011 to 14% in 2015. In the Dutch audit, 9% of patients with cT2 breast cancer received NAC (16). A population-based review from Canada demonstrated that between January 2012 and June 2014, 8.53% of 4,186 patients underwent NAC, of which 31.1% were pre-treatment candidates for breast conserving surgery (17). Although there is consensus that NAC should be considered in all patients who are deemed to require adjuvant chemotherapy, its utilisation in clinical practice remains variable (18).

Rates of pCR were not able to be confidently reported from the available data. This limitation is thought to be due to missing data and the evolving minimum dataset requirements of the BreastSurgANZ BQA. Data is submitted to the BreastSurgANZ BQA by individual surgeons or institutional upload, making it susceptible to bias and may be retrospective and thus complete information may not be readily available at the time of entry.

The breast cancer incidence in Australia has been relatively stable from 2011 to 2016 (19). Similarly, the utilisation of adjuvant chemotherapy has not decreased significantly despite a modest increase in NAC utilisation. The purpose of adjuvant chemotherapy in patients with high risk early stage operable breast cancer is to eradicate micrometastatic disease, and although NAC has been demonstrated to achieve this same objective, only a minority of these patients receive NAC. Women younger than 40 years of age constitute only about 7% of breast cancer diagnoses but tend to have more aggressive, or metastatic, disease at the time of diagnosis and worse long-term outcomes (20). This is reflected in the literature, with the highest proportion of breast cancer patients receiving NAC

Table 3 Patient age, pathologic characteristics and the use of NAC in Australia

Characteristic	Cases	NAC	NAC (%)
Total	55,757	2,469	4.43
Age (years)			
<40	2,401	325	13.54
40–49	8,838	714	8.08
50–74	35,538	1,287	3.62
>74	8,980	143	1.59
Tumour size* (mm)			
0**	381	237	62.20
1–19	28,955	602	2.08
20–50	21,407	996	4.65
>50	3,677	525	14.28
Unstated	1,337		
Tumour grade			
I	10,367	123	1.19
II	25,215	947	3.76
III	18,146	1,134	6.25
Unstated	2,029		
Oestrogen receptor			
Positive	46,069	1,543	3.35
Negative	8,404	873	10.39
Unstated	1,284		
HER2			
Positive	6,755	699	10.35
Negative	46,698	1,697	3.63
Unstated	2,304		
Triple negative breast cancer	5,573	541	9.71

*, the maximum diameter in mm of the furthest point of extension of the invasive tumour cells; **, 0 = pathologic complete response (pCR)/unknown primary tumour. NAC, neoadjuvant chemotherapy.

coming from this age group. A recently conducted study demonstrated that in these younger patients where increased genetic risk had not been demonstrated, breast conserving surgery and whole breast radiotherapy have similar outcomes and survival rates as mastectomy (21). Early breast cancers are more likely to be diagnosed between 40 and 74 years

of age due to the implementation of the national breast screening program in Australia and New Zealand and there appears to be a concomitant decrease in the proportion of patients in this age group receiving NAC. Clinicians may argue that staging information provided from surgery may help in individualising adjuvant treatment. Increasing frailty and co-morbidities in elderly patients are the likely factors accounting for low NAC utilisation in these patients (*Table 3*).

Patients with HER2 positive breast cancer were more likely than HER2 negative breast cancer patients to receive NAC. The most compelling dataset for NAC in patients with HER2 positive breast cancer arguably comes from the NeoSphere study (22). Subjects assigned to receive trastuzumab/pertuzumab/docetaxel achieved a markedly higher pCR of nearly 46%. This was compared to the control arm of docetaxel/trastuzumab with a pCR rate of 29%. Without the chemotherapy and two antibodies alone (trastuzumab/pertuzumab), the pCR rate was 17% which is markedly lower than that achieved with the chemotherapy backbone. Docetaxel/pertuzumab, even without trastuzumab, compared favourably with the control arm which included trastuzumab (22). At present, pertuzumab is only available for metastatic (stage IV) HER2 positive breast cancer in Australia, although a minority of patients may choose to self-fund for pertuzumab to be used in the neoadjuvant setting. Information on chemotherapy and biologic therapy regimens used in HER2 positive patients who received NAC was not available from the BreastSurgANZ BQA database for the dates included in this study.

Triple-negative breast cancers lack steroid receptor expression and lack overexpression of HER2 (23). The GeparSixto trial demonstrated an increase in disease free survival rates in triple-negative breast cancer patients who received carboplatin (24). Patients affected by high grade, triple-negative and HER2-positive breast cancers appeared to receive the greatest benefit accounting for the higher proportion of these patients in this study receiving NAC (24).

There appears to be an ongoing reluctance for surgeons in Australia to consider utilising NAC, better education around NAC and sub-specialisation are central to changing attitudes and informing best practice. A 2016 survey looking at clinical practice in Australia and New Zealand found that patient and system related barriers need to be systematically addressed if neoadjuvant systemic therapy is to become a more common approach (25). One of the main concerns is that cancer may progress and become inoperable in poor or non-responders (25). A meta-analysis of 1,928 patients demonstrated that disease progression is infrequent with

a rate of 3% (26). Further research into identifying this subset of poor or non-responders will enable better patient selection for NAC and reduce the risk of NAC failure. We see this as one of the major limitations currently preventing greater utilisation of NAC in operable breast cancer.

Tumour size, location, unifocal or multicentric status are all factors which may affect the favourability of proceeding with breast conserving treatment in some patients, even after NAC. Arguably patients with unfavourable characteristics should proceed with upfront surgery to obtain pathological and staging information to guide adjuvant treatment. Judicious patient selection by the multidisciplinary team to assess the benefits and risks remains of paramount importance.

There is a need for ongoing evaluation of the utilisation of NAC in Australia for early and locally advanced breast cancer, as well as quantifying the benefits of NAC such as tumour down staging, its impact on breast conserving surgery, overall survival and locoregional and distant recurrence.

Conclusions

The trend of NAC utilisation in Australia is steadily increasing. However, taking into consideration the incidence of breast cancer in Australia and New Zealand, the current rates of high-risk disease and adjuvant chemotherapy utilisation and comparing our data with international rates in comparable populations, it can be concluded on the data that NAC is still being underutilised in Australia.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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