香港乳癌資料庫
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Neoadjuvant Chemotherapy Induces Tumour Size Reduction and Enables Breast-Conserving Surgery in Hong Kong Breast Cancer Patients

Introduction

Neoadjuvant chemotherapy (NAC) refers to the administration of chemotherapy before surgery in treating cancer. It was first adopted in the 1980s as a treatment for locally advanced, often inoperable, breast cancers with the objectives of reducing tumour size and enabling surgery. In the last decades, NAC has been extended to patients with early operable breast cancers with promising results in tumour size reduction [1-3]. This facilitates breast-conserving surgery (BCS) to be performed for patients in whom mastectomy would otherwise be indicated. BCS improves postoperative recovery, psychosocial and cosmetic outcomes over mastectomy [4].

Literature has shown that NAC is equivalent to adjuvant chemotherapy in preventing breast cancer recurrence [5]. The latest St. Gallen 2017 consensus report [6] suggested preference for NAC is given to patients with human epidermal growth factor receptor 2 (HER2) positive, triple negative, as well as stage II or stage III diseases.

The objectives of this study are:

1. To investigate the use of NAC over time in patients registered with the Hong Kong Breast Cancer Registry (HKBCR);
2. To assess the effectiveness of NAC among local breast cancer patients in terms of:
   i) Pathological complete response (pCR) [7] rates;
   ii) Breast-conserving surgery rates
   iii) Alterations in breast cancer biomarkers, including estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 proliferation index

Methodology

Records from the HKBCR on 12,763 female patients who were diagnosed with invasive breast cancer in 2006-2015 were retrieved. Among these 12,763 patients, 962 patients received NAC; of them, 9 patients who received NAC outside Hong Kong were excluded because the clinical practice at where they received NAC might be different from the local practice. Also excluded from the study were 25 patients who received both NAC and neoadjuvant endocrine therapy concurrently or subsequently before surgery as our objective was focused on the benefit from NAC. Thus, a total of 12,729 patients registered in the HKBCR were included to investigate the use of NAC and data of 928 patients who received NAC were studied on the outcome of NAC in terms of pCR by biological subtypes and BCS rates. The definition of different biological subtypes was given in Table 1 [8]. pCR was defined as no histological evidence of malignancies (ypT0) or only in situ residuals in breast tissue (ypTis) and complete disappearance of lymph node metastasis (ypN0) after surgery [7].

Table 1 **Biological subtypes of breast cancer based on immunohistochemistry**

Biological subtype	ER and/or PR	HER2	Ki-67 index
Luminal A	Positive	Negative	<14%
Luminal B (HER2 negative)	Positive	Negative	≥14%
Luminal B (HER2 positive)	Positive	Positive	Any
Luminal A/B (HER2 negative)	Positive	Negative	Data not known
HER2 positive (ER and PR negative)	Negative	Positive	Any
Triple negative	Negative	Negative	Any

ER: estrogen receptor; PR: progesterone receptor;
HER2: human epidermal growth factor receptor 2

Results of study

A. Increased use of NAC between the period of 2006-2010 and 2011-2015

Based on the year of diagnosis, 12,729 patients being studied were divided into two groups, 2006-2010 and 2011-2015, for the purpose of examining the changes in adopting NAC. The two groups of patients were found similar in terms of: a) cancer stage at diagnosis, b) biological subtypes and c) distribution of sector (private or public) at where they received chemotherapy. Despite this, we observed that the proportions of patients treated with NAC was almost doubled, significantly from 4.8% in the period of 2006-2010 to 9.4% in the period of 2011-2015 ($p<0.001$) (Table 2).

Further analysis indicated that the significantly increased use of NAC were observed for patients in all cancer stages, except stage I (Table 2). This was most noticeable for stage IIB (from 5.9% in the period of 2006-2010 to 13.3% in the period of 2011-2015, $p<0.001$) and stage III (from 18.1% to 32.4%, $p<0.001$) (calculated based on the total number of patients treated with or without NAC in the study period). Significantly increased use of NAC were also observed in all biological subtypes. In particular, notable increase was found in patients with triple negative (almost tripled from 4.8% to 12.3%), HER2 positive (ER and PR negative) (increased from 5.7% to 13.1%), and luminal B (HER2 positive) (increased from 7.9% to 16.1%) subtypes over the two study periods ($p<0.001$).

Table 2 **Number (%) of patients treated with NAC in the two periods of diagnosis of breast cancer**

	All patients			No. (%) of patients 2006-2010			2011-2015			P value (use of NAC in two periods)
	Total	With NAC		Total	With NAC		Total	With NAC		
Total	12,729	928	(7.3)	5,881	284	(4.8)	6,848	644	(9.4)	<0.001
Age group										
<40	1,304	160	(12.3)	678	41	(6.0)	626	119	(19.0)	<0.001
40-69	9,979	749	(7.5)	4,548	235	(5.2)	5,431	514	(9.5)	<0.001
70+	775	15	(1.9)	337	6	(1.8)	438	9	(2.1)	0.783
Not known	671	4	(0.6)	318	2	(0.6)	353	2	(0.6)	0.917
Cancer stage*										
I	4,528	3	(0.1)	2,089	1	(<0.1)	2,439	2	(0.1)	N/A
IIA	3,581	104	(2.9)	1,746	25	(1.4)	1,835	79	(4.3)	<0.001
IIB	1,831	181	(9.9)	846	50	(5.9)	985	131	(13.3)	<0.001
III	2,033	524	(25.8)	939	170	(18.1)	1,094	354	(32.4)	<0.001
IV	348	0	(0.0)	141	0	(0.0)	207	0	(0.0)	N/A
Unstaged	408	116	(28.4)	120	38	(31.7)	288	78	(27.1)	0.247
Biological subtype										
Luminal A	2,328	50	(2.1)	1,130	13	(1.2)	1,198	37	(3.1)	0.004
Luminal B (HER2 negative)	2,437	180	(7.4)	984	47	(4.8)	1,453	133	(9.2)	<0.001
Luminal B (HER2 positive)	1,484	179	(12.1)	725	57	(7.9)	759	122	(16.1)	<0.001
Luminal A/B (HER2 negative)	3,214	127	(4.0)	1,465	38	(2.6)	1,749	89	(5.1)	0.001
HER2 positive (ER and PR negative)	1,241	113	(9.1)	668	38	(5.7)	573	75	(13.1)	<0.001
Triple negative	1,439	129	(9.0)	643	31	(4.8)	796	98	(12.3)	<0.001
Not known	586	150	(25.6)	266	60	(22.6)	320	90	(28.1)	0.293

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2
* Cancer stage referred to clinical stage for patients treated with NAC and pathological stage for other non-NAC patients
N/A: chi-square test not available due to the small number of patients treated with NAC (stage I) or no patient was treated with NAC (stage IV).

B. Characteristics of patients treated with NAC

Among the 928 patients who were treated with NAC, the median age was 48 years old (interquartile range: 42 – 55 years, range: 21.0 - 80.0 years) and half (54.7%) of them were premenopausal. The median invasive clinical tumour size was 4.0 cm (range: 0.3 – 20.0 cm). The characteristics of the patients treated with NAC, including menopausal status, biological subtypes, clinical tumour, nodal and cancer stages, were shown in Table I in Annex.

12.3% of our patients aged less than 40 years old were treated with NAC, which was higher when compared to 7.5% and 1.9% of those aged 40-69 and 70 and above, respectively (Table 2). The administration of NAC was positively correlated with cancer stage at diagnosis, in that the proportions of patients treated with NAC increased from 2.9% for stage IIA disease to 25.8% for stage III disease (Table 2). Our data also shows that higher proportions of patients with luminal B (HER2 positive) or HER2 positive (ER and PR negative) or triple negative subtypes of breast cancer received NAC, which were 12.1%, 9.1% and 9.0%, respectively (Table 2).

C. NAC used

Table 3 shows the types of NAC regimens used in our patients. Anti-HER2 regimens were used by two-thirds of the HER2 positive patients, and the proportions increased from 47.9% in the period of 2006-2010 to 73.9% in the period of 2011-2015. Among patients with HER2 negative or unknown HER2 status, anthracycline and taxane-based regimens were the most common NAC used.

Table 3 **Types of NAC regimens used**

NAC regimens used	No. (%) of patients Total		2006-2010		2011-2015	
Among patients with HER2 positive (N=293)						
Anti-HER2 agents-containing	192	(65.5)	45	(47.9)	147	(73.9)
Anthracycline-based	42	(14.3)	36	(38.3)	6	(3.0)
Taxane-based	23	(7.8)	7	(7.4)	16	(8.0)
Anthracycline and taxane-based	28	(9.6)	6	(6.4)	22	(11.1)
Others	0	(0.0)	0	(0.0)	0	(0.0)
Not known	8	(2.7)	0	(0.0)	8	(4.0)
Among patients with HER2 negative or unknown HER2 status (N=635)						
Anti-HER2 agents-containing	31	(4.9)	7	(3.7)	24	(5.4)
Anthracycline-based	142	(22.4)	85	(44.7)	57	(12.8)
Taxane-based	80	(12.6)	31	(16.3)	49	(11.0)
Anthracycline and taxane-based	336	(52.9)	60	(31.6)	276	(62.0)
Others	22	(3.5)	3	(1.6)	19	(4.3)
Not known	24	(3.8)	4	(2.1)	20	(4.5)

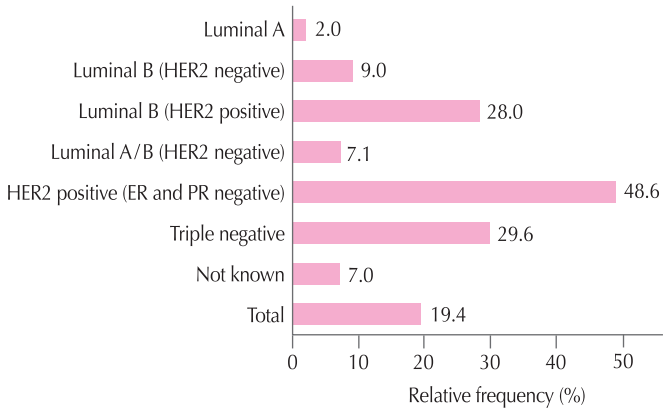
HER2: human epidermal growth factor receptor 2

D. Responses to NAC

i) *Pathological complete response (pCR) rates*

Among our breast cancer patients treated with NAC, one-fifth (19.4%) of them achieved pCR in the breast and axillary lymph node (Figure 1). Subsequent analysis of pCR by biological subtypes revealed that the best result was observed in patients with HER2 positive (ER and PR negative) subtype, in which almost half (48.6%) of them achieved pCR (p<0.001). The proportions of patients who achieved pCR in patients with Luminal B (HER2 positive) and triple negative subtypes were 28.0% and 29.6%, respectively, which were also significantly higher when compared to the other subtypes.

Univariate and multivariate analyses were conducted to study the factors that may be associated with pCR (data not shown). Multivariate analysis found that the significant factors that were favourable to pCR included PR negativity and HER2 positivity. Other factors, including age, menopausal status, clinical tumour and nodal stages, ER status, and Ki-67 proliferation index were not associated with pCR.



ER: estrogen receptor; PR: progesterone receptor;
HER2: human epidermal growth factor receptor 2

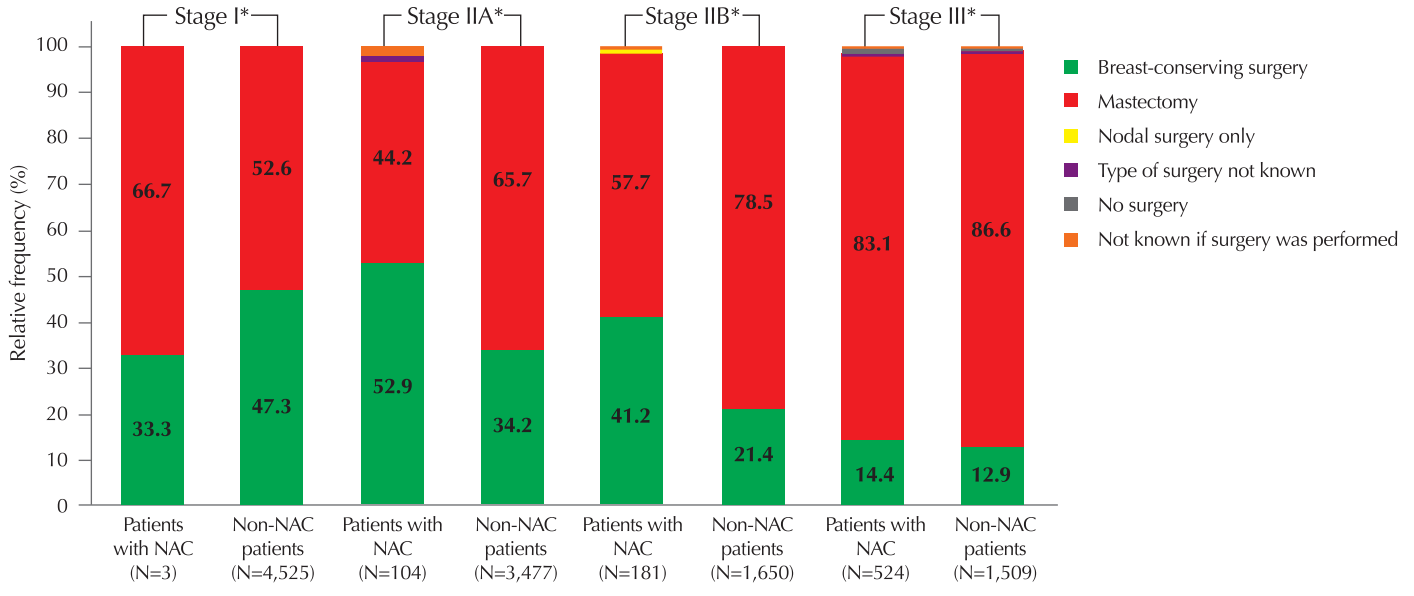
Figure 1 **The percentage of patients achieving pCR in different biological subtype (N=906) (p<0.001)**

ii) *Breast-conserving surgery rates among patients treated with NAC*

One of the benefits of NAC is to enable breast-conserving surgery (BCS) to be performed after NAC. Figure 2 shows the proportions of patients treated with NAC undergoing different types of surgery by their clinical cancer stages. Our data revealed that the best results were observed in patients with clinically stage IIA disease, of them 52.9% underwent BCS, compared to 34.2% for all non-NAC patients with pathological stage IIA disease; followed by patients with clinically stage IIB disease, of them 41.2% underwent BCS after NAC. Even for patients with clinically stage III disease, 14.4% of them underwent BCS after NAC.

iii) *Alteration in breast cancer biomarkers after NAC*

Table 4 shows the alterations in estrogen receptor, progesterone receptor, and HER2 status among patients treated with NAC. Patients without data on the biomarkers in either pre-NAC or post-NAC or both were excluded from the analysis. Majority of the patients had no change in the ER status, but 6.2% changed from positive to negative or vice versa (p<0.001). For PR status, over 80% of the patients had no change, but shifting occurred in 17.4% of the patients (p<0.001). Change in HER2 status was observed in 12.2% of the patients treated with NAC (p<0.001). Ki-67 proliferation index was also evaluated, with 102 (41.3%) patients showed altered proliferation indices after NAC (p<0.001) among the 247 patients assessed (Table 5).



Non-NAC patients referred to those who did not receive chemotherapy or those who underwent adjuvant chemotherapy after surgery
* Cancer stage referred to clinical stage for patients treated with NAC and pathological stage for other non-NAC patients

Figure 2 **Type of surgery among patients treated with NAC and non-NAC patients by cancer stage**

Table 4 **Biomarker status change after NAC**

Biological subtype	ER	PR	HER2
Data available for assessment	518	511	508
Positive to negative	11	25	30
Negative to positive	21	64	32
Total changes (%)	32 (6.2)	89 (17.4)	62 (12.2)
p-value	P<0.001	P<0.001	P<0.001

ER: estrogen receptor; PR: progesterone receptor;
HER2: human epidermal growth factor receptor 2

Table 5 **Ki-67 index levels before and after NAC (p<0.001)**

	Pre-NAC, No. (%) of patients		
Post-NAC	<14%	≥14%	Total
<14%	46 (18.6)	100 (40.5)	146 (59.1)
≥14%	2 (0.8)	99 (40.1)	101 (40.9)
Total	48 (19.4)	199 (80.6)	247 (100.0)

Discussion

Pathological complete response is one of the commonly used study endpoints in studies to assess NAC efficacy. Although it has been demonstrated that pCR may not predict survival[9] and its use as a surrogate endpoint marker for long- term outcomes is still under debate[10], a meta-analysis showed that patients achieving pCR after NAC have favourable outcomes[11]. Future study will be conducted to correlate the surrogacy relation of pCR with survival data in the local context.

NAC is equivalent to adjuvant chemotherapy in preventing breast cancer recurrence[5]. However, when segregated by pathologic response to treatment with NAC, patients who had residual tumour had poorer outcomes than those who achieved pCR[12]. There are ongoing studies looking at the need for further chemotherapy in suitable patients who have residual disease after treated with NAC. Reported recently, the CREATE-X trial[13] which studied the use of capecitabine for HER2 negative patients who had residual disease after NAC showed very encouraging results. However, there is absence of confirmatory data and there is historical lack of substantial benefit for adjuvant capecitabine[6]. Further study is warranted to investigate whether further chemotherapy is needed for this group of patients.

Conclusion

Changes in clinical practice for breast cancer management occurred in that increased use of NAC were observed over the two study periods in Hong Kong breast cancer patients registered in the HKBCR, especially for those with triple negative, HER2 positive (ER and PR negative) and luminal B (HER2 positive) subtypes, as well as patients with clinically stage IIB and stage III of breast cancers at diagnosis. NAC was found effective in downsizing tumour, in which one-fifth of the patients achieved pCR in the breast and axillary nodal status after NAC. In particular, higher pCR rates were observed in patients with HER2 positive and triple negative biological subtypes. We also found that higher proportions of clinically stage IIA or IIB patients treated with NAC underwent breast-conserving surgery. Alterations in breast biomarkers were found in some patients treated with NAC meaning that retesting these biomarkers on the residual tumour would be useful in tailoring further adjuvant therapies. Further studies are to be conducted to evaluate the effectiveness of treatment in terms of survival outcomes among this group of patients treated with NAC.

Editor's message

This issue intends to complement the "Hong Kong Breast Cancer Registry Report No. 9" on the use of NAC and its effectiveness in the management of Hong Kong breast cancer patients. Our findings suggested that NAC has played an increasing role in breast cancer management over the study period and has been proven to be effective in downsizing tumours and enabling breast-conserving surgery. Our study aims to provide insights into breast cancer management to encourage more research and discussion conducive to policy change in synch with our mission to mitigate the threat and sequelae of breast cancer.

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References

(Please refer to Chinese version)

Annex

Table I **Characteristics of patients treated with NAC (n=928)**

	No. (%) of patients	
Total	928	
Menopausal status		
Premenopausal	508	(54.7)
Postmenopausal	395	(42.6)
Not known	25	(2.7)
Biological subtype (Pre-NAC)		
Luminal A	50	(5.4)
Luminal B (HER2 negative)	180	(19.4)
Luminal B (HER2 positive)	179	(19.3)
Luminal A/B (HER2 negative)	127	(13.7)
HER2 positive (ER and PR negative)	113	(12.2)
Triple negative	129	(13.9)
Not known	150	(16.2)
Clinical tumour stage		
Tis	10	(1.1)
T1	48	(5.2)
T2	315	(33.9)
T3	202	(21.8)
T4	251	(27.0)
Not known	102	(11.0)
Clinical nodal stage		
N0	201	(21.7)
N1	316	(34.1)
N2	107	(11.5)
N3	172	(18.5)
Not known	132	(14.2)
Clinical cancer stage		
I	3	(0.3)
IIA	104	(11.2)
IIB	181	(19.5)
IIIA	156	(16.8)
IIIB	192	(20.7)
IIIC	176	(19.0)
Unstaged	116	(12.5)
Sector at where NAC was administered		
Public	757	(81.6)
Private	167	(18.0)
Not known	4	(0.4)

ER: estrogen receptor; PR: progesterone receptor;
HER2: human epidermal growth factor receptor 2