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Neoadjuvant Chemotherapy for Breast Cancer

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1. Introduction

1.1. Rationale of neoadjuvant chemotherapy in treatment of breast cancer

Neoadjuvant chemotherapy (NAC), also termed as preoperative, induction or primary chemotherapy, is defined as the administration of systemic chemotherapeutic agent prior to local control of surgery or radiation. Giving chemotherapy before performing a resection of tumour was initially introduced in locally advanced breast cancer where large inoperable tumour can be converted to operable cancer.

Moreover, at the time of breast cancer diagnosed with 2 to 3 cm in size, the risk of occult metastasis either in axillary lymph node or distant micrometastasis is greater than 50% [1] [2]. There were some evidences demonstrated in animal model that after surgical removal of primary cancer, metastases might be exacerbated [3] [4]. The administration of systemic chemotherapy in this setting might be a benefit to decrease the mortality risk from systemic spreading of the disease. Therefore, control of the disease prior to surgical treatment might produce a better treatment outcome. It was debated that NAC might delay the operation. However, the result from many studies showed that during the course of NAC breast cancer rarely progressed, or if it progressed that likely reflected the aggressive tumour which did not response to chemotherapy postoperatively.

Another main benefit of NAC is monitoring response to the treatment, so as a good model for *in vivo* test for the cytotoxic agents. The good response to NAC with complete pathological response (pCR) is a surrogate marker for overall survival. Recent advance in development of high potential but less toxicity chemotherapy as well as other targeted therapy has brought to higher rate of pCR. Significantly double increased rates of pCR was documented in breast cancer women who had docetaxel following 4 cycles of anthracycline-based NAC treatment, though overall survival (OS) was affected only if pCR in the breast and axillary nodes was achieved [5], [6]. The pCR rate was even higher in the addition of trastuzumab

and pertuzumab [7]. However, with recent breast cancer subtypes identifying by estrogen receptor (ER), progesterone receptor (PR) and HER-2 expression status documented in the recent St. Gallen guideline [8], pCR is likely associated with only in non-luminal subtype [9].

Furthermore, increased rate of breast conserving surgery (BCS) was documented in operable breast cancer with lower risk of local recurrence, in particular when pCR was achieved [10].

2. Neoadjuvant chemotherapy versus adjuvant chemotherapy

Preoperative or NAC has been compared with standard adjuvant chemotherapy as the treatment of breast cancer in several phase III studies. The primary end points mainly are disease-free survival (DFS) and OS. These studies showed that using the chemotherapy preoperatively did not improve DFS and OS, compared with using the same regimen as an adjuvant treatment. A pivotal study from the National Surgical Adjuvant Breast and Bowel Project (NSABP18) [11] compared the use of neoadjuvant adriamycin plus cyclophosphamide (AC) with the same regimen administering postoperatively. With 4-cycle of neoadjuvant AC, the complete clinical response rate (cCR) and pathological complete response rate (pCR) were 36% and 13%, respectively. In primarily operable breast cancer, NAC can downstage tumor and lead to small increase of breast conserving rate (60% vs 67%, $p = 0.002$). Although substantial response was found with neoadjuvant approach, there was no statistically significant difference in terms of DFS and OS at a 9-year follow up [12]. Another study from the European Organization for Research and Treatment of Cancer (EORTC) compared the efficacy of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) preoperatively or postoperatively [13]. Consistent with the NSABP-B18 trial, the OS, PFS and relapse rate were similar between both groups. Also, several smaller studies exploring the benefit of NAC did not find any survival benefit for the neoadjuvant approach [13][15].

Recent meta-analysis addressed directly the benefit of neoadjuvant versus adjuvant chemotherapy [16]. This meta-analysis included nine randomized trials with the total of 3946 patients. There was no difference of death and disease progression. Surprisingly, the patients who received neoadjuvant treatment experienced higher local relapse (risk ratio of 1.22, $p=0.015$). This greater risk of local recurrence mainly occurred in the trials that the patients received radiotherapy without surgery in patients who achieved clinical complete response.

To date, the evidence-based literatures support the benefit of NAC as an approach to convert inoperable breast cancer to an operable tumor, or downstaging to increase breast conserving rate. These seems to be no difference in survival in patients with operable breast cancer whether chemotherapy is given before or after surgery.

3. Types of neoadjuvant chemotherapy for breast cancer

There was no inherent reason to believe that a regimen that works postoperatively will not work preoperatively. Therefore, a standard neoadjuvant regimen is an acceptable postopera-

tive regimen. Previously, anthracycline-based chemotherapy was approved as standard of care for adjuvant treatment of operable breast cancer. It is justified to use at least three to four cycles of anthracycline-based regimen and additional cycles may be considered to maximize response. Later, combination of taxane and anthracycline using as an adjuvant treatment has been proven to be superior to anthracycline alone and become a standard of care in node-positive and high-risk node negative breast cancer. Therefore, several clinical trials have explored the different chemotherapy combinations using as the primary systemic treatment. The best type and schedule administration of preoperative taxanes were investigated in several phase III studies.

The study of NSABP-B27 is the largest study to demonstrate the benefit of adding docetaxel to anthracycline-based regimen [17]. Over 2000 patients were randomized to receive 1) 4 cycles of preoperative AC, 2) 4 cycles of neoadjuvant AC followed by 4 cycles of docetaxel and then surgery, and 3) 4 cycles of AC followed by surgery and then 4 cycles of adjuvant docetaxel. The results showed superiority of clinical response, pCR in patients who received the addition of docetaxel preoperatively (14% vs 26%, $p < 0.001$), but similar breast conserving rate (63% vs 62%). Furthermore, adding docetaxel either preoperatively or postoperatively modestly reduced local recurrence rate with comparable DFS and OS [6].

In the Aberdeen trial, the locally-advanced breast cancer patients were initially treated with 4 cycles of the combination of cyclophosphamide, vincristine, adriamycin and prednisolone (CVAP). The patients who had response to CVAP were randomized to receive another 4 cycles of CVAP or 4 cycles of docetaxel. Among total 162 patients, 66 percent experienced clinical response following the CVAP. Of these, changing to docetaxel provided much better response rate (85% vs 64%, $p = 0.03$), pCR rate (31% vs 15%, $p = 0.06$) and 5-year survival rate (97% vs 78%, $p = 0.04$) [18].

Numerous trials have addressed to answer how best to incorporate taxane to anthracycline-based regimen. The German Preoperative Adriamycin and Docetaxel study II (GEPAR-DUO) [19] and the Arbeitsgemeinschaft Gastroenterologische Onkologie (AGO) study [20] explored whether using taxane sequentially or concurrently with anthracycline is the best approach. Both studies demonstrate significantly higher pCR and breast conserving rate in sequential arm. However, it is impossible to demonstrate that the better outcome of sequential arm is a result of sequential use itself or the higher cumulative dose of chemotherapy and longer duration of treatment with sequential administration. Another randomized study compared the efficacy of paclitaxel administered either weekly or every 3 weeks schedules, followed by the combination of 5-FU, adriamycin and cyclophosphamide (FAC). Weekly schedule associated with better pCR and also breast conserving rates [21].

Taken together, these data support the sequential use of anthracycline and taxane as the neoadjuvant treatment in both locally advanced and operable breast cancer. However, the usage of taxane in low-risk patients or ER-positive patients may provide minimal benefit outweigh of the risk of adverse effect. Optimizing chemotherapy regimen should be considered individually based on reliable prognostic factor, patient's status and their preference after discussing of the risk and benefit of the treatment.

The patients who achieve poor response to initial neoadjuvant chemotherapy, i.e. non-responder, have a worse prognosis. Modification of chemotherapy after observing poor response has not resulted in better outcome [22], [24]. In the German Preoperative Adriamycin and Docetaxel Study III (GEPAR-TRIO) study [22], the breast cancer patients who had poor response to 2 cycles of neoadjuvant docetaxel, adriamycin and cyclophosphamide (TAC) were randomized to receive another 4 cycles of TAC or alter to 4 cycles of vinorelbine plus capecitabine (NX). The results showed no difference in terms of breast conserving rate, clinical and pathological response. On the other hand, in the Aberdeen trial, the patients who received docetaxel after achieving poor respond to 4 cycles of cyclophosphamide, vincristine, doxorubicin and prednisolone (CVAP) ultimately had substantial overall response rate (66%) [25]. On the basis of limited benefit to neoadjuvant chemotherapy in non-responders, adjuvant therapy such as hormonal treatment as well as targeted therapy is considered as the standard treatment to improve outcome [26].

4. Other neoadjuvant therapies in treatment of breast cancer: evidence-based information

4.1. Neoadjuvant therapy for HER2-positive breast cancer

Overexpression of human epidermal growth factor receptor (HER2) is found in approximate 20-30 percent of breast cancer. Trastuzumab, a humanized antibody against HER2, combined with chemotherapy improved survival in metastatic HER2-positive breast cancer [27]. Moreover, 1-year of adjuvant trastuzumab has been established as standard treatment in HER2-positive breast cancer based on improvement of overall survival in several studies [28], [29]. With the promising activity of trastuzumab, its combination with neoadjuvant chemotherapy to enhance response has been proposed. There were several small phase II trials explored different combination of preoperative trastuzumab and chemotherapy. The pCR rate ranged from 12-45% [30], [31]. To date, there was a randomized controlled trial evaluated the efficacy of preoperative trastuzumab combined with anthracycline-based chemotherapy [32]. The stage II and III HER2-positive breast cancer patients were treated with 4 cycles of paclitaxel followed by 4 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) with or without trastuzumab. The patients in trastuzumab arm had significantly higher pCR rate (65% vs 26%, $p=0.016$), but no difference in breast conserving rate. There was no incidence of clinical congestive heart failure. However, this study does not demonstrate whether preoperative trastuzumab impact survival compared to using trastuzumab postoperatively. Risk of cardiotoxicity and benefit of improving response are needed to be discussed individually.

Recently, there are several clinical trials comparing the efficacy of emerging anti-HER2, lapatinib and pertuzumab, as its efficacy using with chemotherapy or the addition to trastuzumab. The GeparQuinto trial compared the efficacy of lapatinib and trastuzumab, both concurrently with chemotherapy in operable HER2-positive breast cancer [33]. The pCR rate was significantly higher with the treatment of trastuzumab plus chemotherapy (30% vs 22%,

p=0.04). However, breast conserving rate was not different and long-term outcomes are awaited. With the hypothesis of using dual anti-HER2 might inhibit HER2 receptor more efficiently, the clinical trials exploring the efficacy of dual anti-HER2, as neoadjuvant therapy in HER2-positive breast cancer were developed. Dual anti-HER2, eg. Lapatinib or pertuzumab plus trastuzumab, did increase pCR rate, but did not increase breast conserving rate compared to the patients who received trastuzumab plus chemotherapy. The studies of HER2-targeted therapy combined with chemotherapy as neoadjuvant setting in HER2-positive breast cancer are summarized in Table 1.

Studies	N	Treatment	pCR (%)	BCS (%)
Buzdar A et al*[32]	42	3wPx4->FECx4	26	53
		Same CMT+H	65	57
NOAH*[34]	235	CMT	20	NA
		CMT+H 1 year	39	
Neosphere*[7]	417	D+T	29	NA
		D+T+P	46	
		T+P	17	
		D+P	24	
Neoalto*[35]	455	L->wP	25	31
		T->wP	30	28
		L+H->wP	51	26
GeparQuinto*[33]	620	ECx4->Dx4+H	30	63
		ECx4->Dx4+L	22	59

Abbreviations: N, number of patients; BCS, breast conserving rate; 3wP, Paclitaxel every 3 weeks; FEC, 5-FU+epirubicin+cyclophosphamide;H, Trastuzumab; CMT, chemotherapy; D, docetaxel; P, pertuzumab; L, lapatinib; wP, weekly paclitaxel; EC, epirubicin+cyclophosphamide; NA, not available; *The studies that reported significant different of pCR rate and breast conserving rate.

Table 1. Neoadjuvant therapy in HER2-positive breast cancer

4.2. Bevacizumab combined with chemotherapy as a neoadjuvant therapy in HER2-negative breast cancer

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, was shown to improve response rate and progression-free survival when added to chemotherapy in metastatic HER2-negative breast cancer patients [36], [37]. Two recent phase III trials [38], [39] determined whether the addition of bevacizumab to chemotherapy would increase pCR rate in HER2-negative operable breast cancer. Both studies confirmed that bevacizumab did increase pCR rate. However, there was a controversial result whether which specific subgroups would gain benefit from bevacizumab. It was claimed that bevacizumab added benefit in terms of pCR in only triple-negative patients from GeparQuinto trial [39], whereas only patients with positive estrogen receptor from the NSABP-B40 trial had higher pCR rate following bevacizumab treatment [38]. Because of contradictory results of these trials with premature long-term

data as well as economic argument, therefore, bevacizumab is not recommended for neoadjuvant treatment in non-metastatic HER2-negative breast cancer.

4.3. Neoadjuvant endocrine therapy

Endocrine therapy has been used as a standard treatment in metastatic ER-positive breast cancer with the objective response of 30-40 percent. Because of low profile of toxicity, it is commonly used as the first option in low-risk metastatic breast cancer, ie asymptomatic, long disease-free interval and limited metastatic disease. Conversely, neoadjuvant endocrine therapy is not recommended as a standard of care because of its lower response rate compared with response rate in the study of neoadjuvant chemotherapy. The small studies reported response rate of 0-2 percent following tamoxifen [40], [41] and 2-3 percent after aromatase inhibitor treatment [40], [42]. The studies of neoadjuvant endocrine therapy are summarized in Table 2.

Studies	N	treatment	ORR (%)	BCS (%)
Eiermann et al*[43]	337	Letrozole	55	45
		Tamoxifen	36	35
Smith et al [44]	330	Anastrozole	37	46
		Tamoxifen	36	22
		Combine	39	26
Ellis et al*[40]	324	Letrozole	60	48
		Tamoxifen	41	36

Abbreviations; N, number of patients; ORR, overall response rate; BCS, breast conserving surgery rate; *The randomized studies with the significant difference of overall response rate and breast conserving rate.

Table 2. Randomized trials comparing different neoadjuvant endocrine therapy

Although the objective response of primary endocrine treatment is not promising, endocrine therapy remains a reasonable option in selected ER-positive breast cancer patients, for instance, the elderly patients who are not suitable for chemotherapy, or has organ function impairment, or desires to avoid adverse effect from chemotherapy. According to a randomized study comparing the efficacy of neoadjuvant chemotherapy and aromatase inhibitor in postmenopausal ER-positive breast cancer patients, clinical response and pCR were not significantly different [45] . However, possibility of breast conserving surgery following primary endocrine treatment is still infrequent.

With the rationale of the superiority of aromatase inhibitor to tamoxifen in metastatic setting of postmenopausal woman with breast cancer, the study of aromatase inhibitor in neoadjuvant setting compared to tamoxifen has been performed. Several studies showed higher overall response rate and also breast conserving rate with aromatase inhibitor [40], [43], [44] .

At present, there are no data available about neoadjuvant endocrine therapy in premenopausal woman.

5. Predicting of response to NAC

Although, recent chemotherapeutic regimen for NAC treatment in breast cancer containing anthracycline followed sequentially by a taxane can produces the good clinical response rates [46]. A cPR is still less than 30% [46], [47]. However, these chemotherapeutic agents are associated with significant morbidity. Therefore, the main benefit would be maximum if it were possible to identify patients who are most likely to benefit from NAC before or shortly after commencing the treatment. Recently, various biotechnologies, including both imaging and biomolecular platforms, have been investigated in order to find novel biomarkers or tests to predict responses to NAC. These technologies include molecular imaging, PET-CT, scintigraphy, genomics and proteomic platforms [48]. However, there is not any promising result demonstrated so far.

Amongst the above technologies, the most recent and feasible is the use of magnetic resonance imaging (MRI) as a early predictor of response to NAC. In a recent systematic review study, where dynamic contrast enhanced (DCE) MRI performed pre and after 1-2 cycles of NAC were compared, good sensitivity and specificity in predicting response to NAC was demonstrated, depending on various MRI parameters used for interpretation. Substantial reductions in tumour volume could be accurate parameters in discriminating responders and non-responders after 1-2 cycles of NAC [49].

PET-CT using 18 F-FDG seemed to be a good technology in predicting response to NAC due to its combination of anatomical and functional characteristics of cancer cells. However, in a small study comparing ability of PET-CT, MRI and ultrasonography in predicting response to NAC, MRI was superior to PET-CT and ultrasonography [50].

6. Summary

With the rationale of NAC in term of controlling distant or micrometastasis, NAC should be a good approach in breast cancer for both early and locally advanced disease. However, in some early breast cancer, addition of chemotherapy might be an overtreatment with more harmful than useful. Evidence from various clinical studies confirmed the benefit of NAC by avoiding mastectomy in some responders. In the recent day, therefore, use of NAC is the treatment of choice for locally advanced or some early breast cancer. Combination of NAC and other targeted therapy such as trastuzumab have given even better outcome. Finally, further research is still required in order to predict response to NAC as early as possible so that patient who would not respond well to NAC could be identified early and would allow seeking for the other treatment.

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