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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-
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 (GEPARDUO) [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 cyclophosphamid (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 outrage 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      |         |
| Neoaltto*[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      |

Abbrevations: 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 chemotherapy 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      |

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].
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 an 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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References

[1] Carter CL, Allen C, Henson DE: Relation of tumour size, lymph node status, and survival in 24,740 breast cancer cases, Cancer 1989, 63:181-187
[2] Koscielny S, Tubiana M, Le MG, Valleron AJ, Mouriesse H, Contesso G, Sarrazin D: Breast cancer: relationship between the size of the primary tumour and the probability of metastatic dissemination, Br J Cancer 1984, 49:709-715
[3] Fisher B, Saffer E, Rudock C, Coyle J, Gunduz N: Effect of local or systemic treatment prior to primary tumour removal on the production and response to a serum growth-stimulating factor in mice, Cancer Res 1989, 49:2002-2004
[4] O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, Lane WS, Cao Y, Sage EH, Folkman J: Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma, Cell 1994, 79:315-328
[5] Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, Theriault RL, Singh G, Binkley SM, Sneige N, Buchholz TA, Ross MI, McNeese MD, Buzdar AU, Hortobagyi GN, Singletary SE: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy, J Clin Oncol 1999, 17:460-469
[6] Bear HD, Anderson S, Smith RE, Geyer CE, Jr., Mamounas EP, Fisher B, Brown AM, Robidoux A, Margolese R, Kahlenberg MS, Paik S, Soran A, Wickerham DL, Wolmark N: 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 2006, 24:2019-2027
[7] Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagussa P: Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial, Lancet Oncol 2012, 13:25-32
Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ, Panel m: Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011, Ann Oncol 22:1736-1747

von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Koncny GE, Denkert C, Nekljudova V, Mehta K, Loibl S: Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes, J Clin Oncol 2012, 30:1796-1804

Caudle AS, Hunt KK: The neoadjuvant approach in breast cancer treatment: it is not just about chemotherapy anymore, Current opinion in obstetrics & gynecology 2011, 23:31-36

Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margoese RG, Cruz AB, Jr., Hoehn JL, Lees AW, Dimitrov NV, Bear HD: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer, J Clin Oncol 1998, 16:2672-2685

Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B: Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18, J Natl Cancer Inst Monogr 2001, 96-102

van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L: Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902, J Clin Oncol 2001, 19:4224-4237

Gianni L, Baselga J, Eiermann W, Guillem Porta V, Semiglazov V, Lluch A, Zambetti M, Sabadell D, Rab G, Llobe Cussac A, Bozhok A, Martinez-Aguillo A, Greco M, Byakhov M, Lopez Lopez JJ, Mansutti M, Valagussa P, Bonadonna G: Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy, Clin Cancer Res 2005, 11:8715-8721

Scholl SM, Fourquet A, Asselain B, Pierga JY, Vilcoq JR, Durand JC, Dorval T, Palange T, Jouve M, Beuzeboc P, et al.: Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery: preliminary results of a randomised trial: S6, Eur J Cancer 1994, 30A:645-652

Mauri D, Pavlidis N, Ioannidis JP: Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis, J Natl Cancer Inst 2005, 97:188-194

Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, Margoese R, Theoret H, Soran A, Wickerham DL, Wolmark N: The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27, J Clin Oncol 2003, 21:4165-4174
[18] Heys SD, Hutcheon AW, Sarkar TK, Ogston KN, Miller ID, Payne S, Smith I, Walker LG, Eremin O: Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial, Clin Breast Cancer 2002, 3 Suppl 2:S69-74

[19] von Minckwitz G, Raab G, Caputo A, Schulte M, Hilfrich J, Blohmer JU, Gerber B, Costa SD, Merkle E, Eidtmann H, Lampe D, Jackisch C, du Bois A, Kaufmann M: Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group, J Clin Oncol 2005, 23:2676-2685

[20] Untch M, Mobus V, Kuhn W, Muck BR, Thomssen C, Bauerfeind I, Harbeck N, Werner C, Lebeau A, Schneeweiss A, Kahlert S, von Koch F, Petry KU, Wallwiener D, Kreienberg R, Albert US, Luck HJ, Hinke A, Janicke F, Konecný GE: Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer, J Clin Oncol 2009, 27:2938-2945

[21] Green MC, Buzdar AU, Smith T, Ibrahim NK, Valero V, Rosales MF, Cristofanilli M, Booser DJ, Pusztai L, Rivera E, Theriault RL, Carter C, Fyfe D, Hunt KK, Symmans WF, Strom EA, Sahin AA, Sikov W, Hortobagyi GN: Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks, J Clin Oncol 2005, 23:5983-5992

[22] von Minckwitz G, Kummel S, Vogel P, Hanusch C, Eidtmann H, Hilfrich J, Gerber B, Huober J, Costa SD, Jackisch C, Loibl S, Mehta K, Kaufmann M: Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial, J Natl Cancer Inst 2008, 100:542-551

[23] Thomas E, Holmes FA, Smith TL, Buzdar AU, Fyke DK, Fraschini G, Singletary SE, Theriault RL, McNeese MD, Ames F, Walters R, Hortobagyi GN: The use of alternate, non-cross-resistant adjuvant chemotherapy on the basis of pathologic response to a neoadjuvant doxorubicin-based regimen in women with operable breast cancer: long-term results from a prospective randomized trial, J Clin Oncol 2004, 22:2294-2302

[24] Wesolowski R, Budd GT: Neoadjuvant therapy for breast cancer: assessing treatment progress and managing poor responders, Curr Oncol Rep 2009, 11:37-44

[25] Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, Ah-See AK, Eremin O, Walker LG, Sarkar TK, Eggleton SP, Ogston KN: Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel, J Clin Oncol 2002, 20:1456-1466

[26] Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, von Minckwitz G, Buzdar AU, Smith IE, Symmans WF, Singh B, Winer EP: Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease, J Clin Oncol 2008, 26:814-819
[27] Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2, N Engl J Med 2001, 344:783-792

[28] Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Lang I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Ruschoff J, Suto T, Greaves V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer, N Engl J Med 2005, 353:1659-1672

[29] Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kuthe LA, Vogel VG, Visscher DW, Yotthers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle PM, Ingle JN, Wolmark N: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer, N Engl J Med 2005, 353:1673-1684

[30] Burstein HJ, Harris LN, Gelman R, Lester SC, Nunes RA, Kaelin CM, Parker LM, Ellisen LW, Kuter I, Gadd MA, Christian RL, Kennedy PR, Borges VF, Bunnell CA, Younger J, Smith BL, Winer EP: Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study, J Clin Oncol 2003, 21:46-53

[31] Wenzel C, Hussain D, Bartsch R, Pluschnig U, Locker GJ, Rudas M, Gnant MF, Jakesh R, Zielinski CC, Steger GG: Preoperative therapy with epirubicin and docetaxel plus trastuzumab in patients with primary breast cancer: a pilot study, J Cancer Res Clin Oncol 2004, 130:400-404

[32] Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer, J Clin Oncol 2005, 23:3673-3685

[33] Untch M, Loibl S, Bischoff J, Eidtmann H, Kaufmann M, Blohmer JU, Hilfrich J, Strumbel D, Fasching PA, Kreienberg R, Tesch H, Hanusch C, Gerber B, Rezai M, Jackisch C, Huober J, Kuhn T, Nekljudova V, von Minckwitz G: Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial, Lancet Oncol 2012, 13:135-144

[34] Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, Zambetti M, Vazquez F, Byakhow M, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansut-
ti M, Bozhok A, Baronio R, Feyereislova A, Barton C, Valagussa P, Baselga J: Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort, Lancet 2010, 375:377-384

[35] Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, Gomez H, Dinh P, Fauria K, Van Dooren V, Aktan G, Goldhirsch A, Chang TW, Horvath Z, Coccia-Portugal M, Domont J, Tseng LM, Kunz G, Sohn JH, Semiglazov V, Lerzo G, Palacova M, Probachai V, Pusztai L, Untch M, Gelber RD, Piccart-Gebhart M: Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial, Lancet 2012, 379:633-640

[36] Miles DW, Chan A, Dirix LY, Cortes J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencencher L, Puglisi F, Harbeck N, Steger GG, Schneeweiss A, Wardley AM, Chistalla A, Romieu G: Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer, J Clin Oncol 2010, 28:3239-3247

[37] Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer, N Engl J Med 2007, 357:2666-2676

[38] Bear HD, Tang G, Rastogi P, Geyer CE, Jr., Robidoux A, Atkins JN, Baez-Diaz L, Brufsky AM, Mehta RS, Fehrenbacher L, Young JA, Senecal FM, Gaur R, Margolese RG, Adams PT, Gross HM, Costantino JP, Swain SM, Mamounas EP, Wolmark N: Bevacizumab added to neoadjuvant chemotherapy for breast cancer, N Engl J Med 2012, 366:310-320

[39] von Minckwitz G, Eidtmann H, Rezai M, Fasching PA, Tesch H, Eggemann H, Schrader I, Kittel K, Hanusch C, Kreienberg R, Solbach C, Gerber B, Jackisch C, Kunz G, Blohmmer JU, Huober J, Hauschild M, Fehm T, Muller BM, Denkert C, Loibl S, Nekljudova V, Untch M: Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer, N Engl J Med 2012, 366:299-309

[40] Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Janicke F, Miller WR, Evans DB, Dugan M, Brady C, Quebe-Fehling E, Borgs M: Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial, J Clin Oncol 2001, 19:3808-3816

[41] Mauriac L, Debled M, Durand M, Floquet A, Boulanger V, Dagada C, Trufflardier N, MacGrogan G: Neoadjuvant tamoxifen for hormone-sensitive non-metastatic breast carcinomas in early postmenopausal women, Ann Oncol 2002, 13:293-298

[42] Barnadas A, Gil M, Gonzalez S, Tusquets I, Munoz M, Arcusa A, Prieto L, Margeli-Vila M, Moreno A: Exemestane as primary treatment of oestrogen receptor-positive
breast cancer in postmenopausal women: a phase II trial, Br J Cancer 2009, 100:442-449

[43] Eiermann W, Paepke S, Appfelstaedt J, Llombart-Cussac A, Eremin J, Vinholes J, Mauriac L, Ellis M, Lassus M, Chaudri-Ross HA, Dugan M, Borgs M: Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study, Ann Oncol 2001, 12:1527-1532

[44] Smith IE, Dowsett M, Ebbs SR, Dixon JM, Skene A, Blohmer JU, Ashley SE, Francis S, Boeddinghaus I, Walsh G: Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial, J Clin Oncol 2005, 23:5108-5116

[45] Semiglazov VF, Semiglazov VV, Dashyan GA, Ziltsova EK, Ivanov VG, Bozhok AA, Melnikova OA, Paltuev RM, Kletzel A, Berstein LM: Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer, Cancer 2007, 110:244-254

[46] Jones RL, Smith IE: Neoadjuvant treatment for early-stage breast cancer: opportunities to assess tumour response, Lancet Oncol 2006, 7:869-874

[47] Chollet P, Amat S, Cure H, de Latour M, Le Bouedec G, Mouret-Reynier MA, Ferriere JP, Achard JL, Dauplat J, Penault-Llorca F: Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer, Br J Cancer 2002, 86:1041-1046

[48] Chuthapisith S, Eremin JM, Eremin O: Predicting response to neoadjuvant chemotherapy in breast cancer: molecular imaging, systemic biomarkers and the cancer metabolome (Review), Oncol Rep 2008, 20:699-703

[49] Marinovich ML, Sardanelli F, Ciatto S, Mamounas E, Brennan M, Macaskill P, Irwig L, von Minckwitz G, Houssami N: Early prediction of pathologic response to neoadjuvant therapy in breast cancer: Systematic review of the accuracy of MRI, Breast 2012,

[50] Choi JH, Lim HL, Lee SK, Kim WW, Kim SM, Cho E, Ko EY, Han BK, Park YH, Ahn JS, Im YH, Lee JE, Yang JH, Nam SJ: The role of PET CT to evaluate the response to neoadjuvant chemotherapy in advanced breast cancer: comparison with ultrasonography and magnetic resonance imaging, Journal of surgical oncology 2010, 102:392-397
