Can trastuzumab emtansine be replaced by additional chemotherapy plus targeted therapy for HER2-overexpressing breast cancer patients with residual disease after neoadjuvant chemotherapy?

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Abstract

Human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer is an aggressive phenotype with a poor prognosis, and can easily metastasize and recur. Currently, chemotherapy plus HER2-targeted therapy is the standard systemic treatment for most of these patients. Given that neoadjuvant chemotherapy (NAC) has an efficacy equivalent to that of adjuvant chemotherapy and some additional benefits, many patients, especially those with more advanced tumors, prefer NAC and generally will not receive additional chemotherapy after surgery, irrespective of the pathological response. However, achieving pathological complete response to NAC is strongly correlated with prognosis, especially in triple-negative and HER2-overexpressing breast cancer. Therefore, postoperative treatment of these patients with residual diseases should be optimized to achieve favorable outcomes. The CREATE-X study has confirmed that additional chemotherapy can improve the outcomes of patients with HER2-negative residual disease after NAC. In addition, chemotherapy plays an indispensable role in the treatment of patients who receive surgery directly or who have recurrent lesions. Therefore, can additional chemotherapy improve prognosis of patients with HER2-overexpressing residual breast cancer? At present, no studies have compared the efficacy of additional chemotherapy plus trastuzumab with that of anti-HER2 therapy alone in residual cancer. The KATHERINE study revealed that trastuzumab emtansine (T-DM1) can reduce the risk of recurrence or death by 50% compared with trastuzumab in patients with HER2-positive residual invasive breast cancer after neoadjuvant therapy. T-DM1 is an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine, and thus, to an extent, T-DM1 is equivalent to simultaneous application of chemotherapy and targeted therapy. However, high cost and low accessibility limit its use especially in low- and middle-income countries and regions. Hence, we proposed this perspective that additional chemotherapy plus trastuzumab should be given to HER2-overexpressing breast cancer patients with residual disease after NAC to improve their prognosis by discussing that the efficacy of additional chemotherapy plus trastuzumab is superior to that of anti-HER2 therapy alone and not inferior to T-DM1. Additional chemotherapy plus trastuzumab-based HER2-targeted therapy can be used as an alternative regimen to T-DM1 when T-DM1 is unavailable. However, further clinical research on the selection of chemotherapeutic agents is warranted.

Keywords: Additional chemotherapy; HER2-overexpressing breast cancer; residual disease; T-DM1

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**Introduction**

Human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer, which is defined as hormone receptor (HR) negative and HER2 positive, accounts for approximately 15%–25% of all invasive breast cancers and is characterized by aggressive metastatic behavior and relapse (1,2). HER2 gene amplification is associated with high-grade tumors, increased cell proliferation, tumor invasiveness and distant metastasis (3). A previous study demonstrated that that poorly differentiated or undifferentiated tumors, which were over 20 times as likely as well-differentiated tumors, were presented in triple-negative and HER2-overexpressing breast cancer cases (4).

For this subtype of breast cancer, chemotherapy combined with targeted therapy is the most effective adjuvant treatment, which has been validated in several large clinical trials (5-8). Approximately a quarter of HER2-overexpressing breast cancer patients who receive surgery and chemotherapy plus anti-HER2 therapy are at risk of relapse after 8–10 years (5,7). As an indispensable systemic anti-tumor treatment, chemotherapy can be utilized preoperatively or postoperatively. Neoadjuvant chemotherapy (NAC) has an efficacy equivalent to that of adjuvant chemotherapy (9-11) and has the additional advantages of down-staging tumors to increase surgical opportunity and shrinking tumor volume to allow for breast-conserving surgery (12). In addition, it provides an opportunity to assess the chemosensitivity of tumors in vivo so that postoperative chemotherapy can be tailored according to the outcome of the NAC (13). Thus, NAC is widely used in systemic treatment of breast cancer. Nevertheless, prior studies have revealed that the majority of patients have residual disease after NAC, and only approximately 18% of patients achieve pathological complete response (pCR) after NAC (14,15). The prognosis of patients with residual disease has been shown to be significantly inferior to that of those experiencing pCR and the correlation between pathologic response and long-term outcomes is the strongest in triple-negative and HER2-overexpressing breast cancer. HER2-overexpressing breast cancer is one of the most aggressive subtypes, with a high probability of lymphatic metastasis. The poor prognosis of patients with residual disease, particularly those with a positive axillary lymph node, which is a risk factor for recurrence (16-18), raises the question of how to optimize the postoperative treatment for these patients.

Recently, the KATHERINE study (19) showed that administration of trastuzumab emtansine (T-DM1) to residual HER2-positive breast cancer patients after neoadjuvant therapy can reduce the risk of recurrence or death by 50% compared with trastuzumab alone. T-DM1 is an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), which is a maytansine derivative and microtubule inhibitor released within target cells though degradation of compounds in lysozyme (20). To an extent, T-DM1 is equivalent to simultaneous application of chemotherapy and targeted therapy. The CREATE-X study confirmed that additional chemotherapy improves the outcomes of patients with HER2-negative residual disease after NAC. In addition, chemotherapy plays an indispensable role in the treatment of patients that receive surgery directly or have recurrent lesions. At present, no studies have compared the efficacy of chemotherapy plus trastuzumab with that of T-DM1 and trastuzumab alone in residual cancer. Given that the low accessibility and high cost of T-DM1 limit its use, especially in low- and middle-income regions, could additional chemotherapy combined with trastuzumab-based targeted therapy be given to patients with residual HER2-overexpressing breast cancer after NAC to improve their prognosis?

**Relationship between residual disease and prognosis**

Several studies have revealed that pathological response to NAC is a strong and independent predicator of outcome, regardless of intrinsic breast cancer subtype, tumor size, and lymph node status (9,14). The correlation between pathologic response and long-term outcomes is the strongest in triple-negative and HER2-overexpressing breast cancer. For different definitions of pCR, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ (ypT0/is ypN0), is commonly used in clinical studies (16), and achieving pCR can significantly improve outcomes, especially in patients with aggressive breast cancer such as the HER2-overexpressing and triple-negative subtypes (15,21,22). A prior study demonstrated that pCR resulted in a 50% reduction in the risk of death. By contrast, those patients with a clinical complete response but invasive cancer on pathological examination, clinical partial response and clinical nonresponse showed an 8%, 28% and 45% increase in the risk of death, respectively (9). Although pCR to primary therapy is what we all want to see, meta-analysis has
demonstrated that only approximately 18% of patients achieve pCR, and the proportion is relatively higher in patients with HER2-overexpressing breast cancer, reaching more than 30% (14,15). The pCR rate of HER2-positive breast cancers after NAC varies with initial tumor stage and the treatment protocol, but half or more of patients do not experience pCR and have significantly poor prognosis (23-30). For these patients, the postoperative adjuvant therapy regimen should be strengthened to improve prognosis.

Axillary lymph node positivity, a detectable indicator of residual cancer, is a high risk factor for recurrence or death (31). Studies have shown that residual disease is more aggressive in lymph nodes than in primary breast tumors and the number of involved axillary lymph nodes is inversely related to survival. A retrospective analysis of 1,600 women diagnosed with breast cancer stages II–III with cytologically confirmed axillary metastases conducted by Mougalian et al. demonstrated that only 28.4% of patients achieved axillary pCR after primary systemic chemotherapy (32). Among the patients who did not experience pCR to primary chemotherapy, the 8-year disease-free survival (DFS) rate of patients with negative lymph nodes reached 70%, compared with only 40% in patients with 4–9 positive axillary lymph nodes (33). Arsenault et al. (34) found that more than 50% patients with HER2-overexpressing breast cancer had positive axillary lymph nodes after NAC. In addition, patients with 4 or more and 1–3 positive axillary lymph nodes had a 19.99-fold (P=0.008) and 10.8-fold (P=0.031) locoregional recurrence risk, respectively, relative to those without positive axillary lymph node. As the residual cancer burden (RCB) index increases, the risk of relapse increases, and the rate of distant relapse at 5 years was found to be 2.4% and 53.6% in patients with minimal residual disease (RCB-I) and extensive residual disease (RCB-III), respectively (35).

Another histological grading system to assess the response of breast cancers to primary chemotherapy, Miller-Payne grading (MPG), can also be used as an indicator to guide treatment in the adjuvant setting. According to MPG, approximately 86% of patients did not achieve pCR (grade 5: no malignant cells identifiable in sections from the site of the tumor and ductal carcinoma in situ may be present) after NAC, among which more than 30% of cases were grade 1 or 2 (the number of tumor cells did not change or decreased by less than 30%), indicating that these patients were not sensitive to the primary chemotherapy regimens and that the adjuvant chemotherapy agents need to be changed (36,37).

Residual disease, especially positive lymph nodes, has a profound effect on prognosis, which should be noted and actively treated. Moreover, the adjuvant therapy can be tailored by the response to NAC and MPG.

**Current systemic treatment for HER2-overexpressing breast cancer**

Chemotherapy plus targeted therapy for HER2-positive breast cancer is generally recognized as the most basic systemic treatment, both before and after surgery. With the advent of anti-HER2 agents, the natural history of HER2-positive breast cancer has been dramatically changed. Almost all relevant clinical studies have confirmed that chemotherapy combined with trastuzumab can markedly improve the prognosis of HER2-positive breast cancer patients (5,6,38,39). Moreover, with the publication of the results of the NeoSphere (25), TRYPHAENA (28), and APHINITY studies (8), pertuzumab plus trastuzumab in combination with chemotherapy has been gradually accepted for treatment of early HER2-positive breast cancer in the neoadjuvant or adjuvant setting. Nevertheless, to date, the efficacy and feasibility of anti-HER2 agent monotherapy for HER2-positive breast cancer patients are controversial, although a majority of the Panel at the 2007 St Gallen Expert Consensus meeting (40) was prepared to offer trastuzumab without chemotherapy for selected women despite the absence of supporting clinical trial evidence. A previous study (41) demonstrated that anti-HER2 agent monotherapy brought benefits to selected patients for whom chemotherapy was contraindicated, but the long-term survival benefits in the targeted monotherapy group was significantly inferior to those in patients who received chemotherapy. Therefore, chemotherapy is essential and irreplaceable for HER2-overexpressing breast cancer.

In the neoadjuvant setting, a phase II clinical trial (NeoSphere) (25,42) randomly assigned 417 eligible women with HER2-positive breast cancer to four groups; two of the groups were treated with either trastuzumab plus docetaxel or with anti-HER2 monotherapy (pertuzumab and trastuzumab). At surgery, the pCR rate was 29.0% and 16.8%, respectively, and subgroup analysis suggested that the HER2-positive patients with negative HR (HER2-overexpressing subtype) who were treated with anti-HER2 monotherapy had a notably lower pCR rate (27.3%) compared with the trastuzumab plus docetaxel group (36.8%). Among the four experimental groups, the
dual HER2-targeted group without chemotherapy had the lowest response rate in the clinical and pathological assessment despite the hormone receptor and node status, and their 5-year progression-free survival (PFS) and DFS were also inferior to those in the chemotherapy groups (42). Thus, chemotherapy is irreplaceable in the treatment of HER2-positive breast cancer. Furthermore, in all groups, less than 50% of patients achieved pCR, and the risk of relapse in patients who did not achieve pCR was nearly twice as high as in patients with pCR. This indicates that a majority of patients have residual diseases after neoadjuvant therapy, leading to poor survival outcomes, and the chemotherapy-free approach is not desirable for most patients.

In the adjuvant setting, for patients with HER2-overexpressing breast cancer who undergo surgery directly, the National Comprehensive Cancer Network (NCCN) (43) panel recommended doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab with or without pertuzumab, even if the axillary lymph nodes are negative. By contrast, patients with HER2-overexpressing residual breast cancer who completed entire chemocycles preoperatively were recommended to receive either T-DM1 alone or trastuzumab ± pertuzumab to complete one year of therapy after surgery, with no more additional chemotherapy, regardless of the lymph nodes status. However, currently, most patients only receive trastuzumab due to the high price and low accessibility of T-DM1 and pertuzumab. In general, tumors are more aggressive in patients receiving neoadjuvant therapy than in those undergoing direct surgery, as the candidates for preoperative systemic therapy are usually patients with inoperable tumors or those with operable cancer but who desire breast-conserving surgery. Although previous randomized trials (9-11) showed similar long-term outcomes when patients were given the same treatment preoperatively or postoperatively, the trials also revealed that the prognosis of patients with residual disease, especially those with positive lymph nodes, after NAC is significantly worse than that of those with pCR. Given that the effect of residual axillary disease on prognosis is greater than that of primary breast lesions (32,34,44), eradicating the positive axillary lymph node is extremely important, especially for HER2-overexpressing breast cancer patients with a high probability of lymphatic metastasis. A previous study revealed that patients with residual disease after NAC had significantly worse survival than patients receiving adjuvant chemotherapy [hazard ratio (HR)=0.51, P=0.007] (45). In this case, compared with postoperative treatment of patients undergoing surgery directly, HER2-overexpressing breast cancer patients with residual disease, particularly those with positive lymph nodes after NAC, should be given additional chemotherapy plus trastuzumab, rather than anti-HER2 therapy alone (Figure 1).

For recurrent or metastatic breast cancer patients, the NCCN panel recommends pertuzumab plus trastuzumab in combination with a taxane as the first-line treatment to prolong survival and enhance quality of life. The results of a phase II clinical trial (PERNETTA) (46), which intended to investigate the feasibility of de-escalation for HER2-positives patients, were recently presented at the inaugural European Society for Medical Oncology (ESMO) Breast Cancer Congress (46). This study randomly divided 210 HER2-positive breast cancer patients with distant metastasis into trastuzumab plus pertuzumab with or without chemotherapy groups until progression. The results showed that PFS was only 8.4 months in the solely HER2-directed therapy group but was 23.3 months in those with additional chemotherapy, and the results were similar regardless of HR status. The scores for quality of life were also similar between the groups. Multiple studies exploring treatment regimens for recurrent or metastatic breast cancer have also been designed on the basis of chemotherapy drugs, and thus, chemotherapy is also indispensable for advanced breast cancer unless the adverse reactions are intolerable. Since chemotherapy is essential in the whole treatment course for breast cancer, why can it not be applied in cases of residual breast cancer to decrease recurrence or death risk and improve prognosis? Similar to treatment of patients undergoing surgery first or with recurrence or metastatic cancer, it is rational to speculate that additional chemotherapy will bring benefits to patients with residual disease after NAC.

Management of breast tumor heterogeneity

It is generally accepted that breast cancer is a highly heterogeneous disease (47). The intra-tumor heterogeneity denotes the coexistence of subpopulations of cancer cells, resulting from the interaction of genomic instability and selective pressure (48). Cancer cells within a tumor can exhibit remarkable morphologic, genetic and behavioral variability (49). So, there are different cell phenotypes in a single tumor. Intra-tumor heterogeneity is related to disease progression and drug resistance, which become one of the greatest barriers in cancer therapeutics (48,50,51).
According to the differential expression of receptors within a tumor, breast cancer can be divided into four different intrinsic subtypes, luminal A, luminal B (HER2−/HER2+), HER2-overexpressing (HER2+, HR−) and triple-negative breast cancer (TNBC) (52). Moreover, the therapeutic approaches vary by subtype, for example, a selective estrogen receptor (ER) modulator and aromatase inhibitor for HR-positive cells and monoclonal anti-HER2 agents for HER2-positive cells. However, the most commonly used chemotherapeutic agents have a killing effect on all actively multiplying cells. Therefore, the detection of HR and HER2 is very important and can directly affect the treatment strategy for breast cancer.

With regard to HER2 testing in breast cancer, American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) jointly issued a clinical protocol for HER2 testing (53), which recommended that when 10% or more of tumor cells exhibit complete and intense circumferential membrane staining, the breast lesion can be considered as immunohistochemistry (IHC) 3+ (i.e., HER2-positive). The cutoff point of the evaluation criteria is just 10% of all tumor cells, and the staining judgment of tumor cells is relatively subjective. Hence, some tumor cells may be HER2-negative within HER2-overexpressing breast cancer and residual lesions. Moreover, on account of the negative HR expression (tumors exhibiting less than 1% of tumor cells with staining for ER or progesterone receptor (PgR) of any intensity (54), there are triple-negative tumor cells in this breast cancer subtype. Therefore, given the intra-tumor heterogeneity, sole anti-HER2 targeted therapy for HER2-overexpressing residual breast cancer is not sufficient.

A previous study (CREATE-X) conducted by Masuda et al. demonstrated the benefits of administering additional chemotherapy to patients with residual invasive breast cancer after NAC (55). In this study, 910 HER2-negative breast cancer patients who had residual invasive disease after NAC (containing anthracycline, taxane, or both) were randomized to receive standard postsurgical treatment with capecitabine or not (control group). The results revealed that the capecitabine group had longer DFS and overall survival (OS) than the control group. Capecitabine also reduced the risk of death by approximately 40%, and the efficacy in TNBC was more obvious (5-year DFS of 69.8% for the capecitabine group vs. 56.1% for the control group, and 5-year OS of 78.8% and 70.3%, respectively). This
study indicated that more attention should be paid to residual cancer and the additional chemotherapy is effective in improving the prognosis of patients with residual disease after NAC. Meanwhile, the application of capecitabine in residual TNBC has been written into the NCCN Breast Cancer clinical practice guideline (43). Likewise, HER2-overexpressing breast cancer patients can also benefit from additional chemotherapy, since some HER2-negative and triple-negative tumor cells present in HER2-overexpressing breast cancer and residual disease. HER2-targeted therapies, the only systemic therapeutic approach for HER2-overexpressing breast cancer patients after NAC and surgery, only target the HER2-positive tumor cells and neglect the HER2-negative and triple-negative cells which likely account for a large proportion of the tumor cells. However, chemotherapeutic agents can act on all tumor cells that proliferate actively and are effective against both HER2-positive and triple-negative tumor cells (Figure 2). Because the notable efficacy of chemotherapy against triple-negative cells in residual cancer has been verified, and considering tumor heterogeneity, it is reasonable to administer additional chemotherapy along with targeted therapy and radiotherapy (if indicated) to HER2-overexpressing breast cancer patients with residual disease, especially those with positive axillary lymph nodes, after NAC to decrease the death and recurrence risk and improve patient prognosis and quality of life.

**Figure 2** Efficacy of targeted therapy plus additional chemotherapy or targeted therapy alone against HER2-overexpressing breast cancer with residual disease after neoadjuvant chemotherapy, especially when positive axillary lymph nodes are present. HER2, human epidermal growth factor receptor 2.

**Analysis of T-DM1 application and cost-effectiveness**

T-DM1 was approved by the Food and Drug Administration (FDA) as a second-line treatment for HER2-positive advanced breast cancer, based on a phase III clinical trial called EMILIA (56). This research demonstrated that T-DM1 significantly prolonged PFS and OS with less toxicity than lapatinib plus capcitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane. Subsequently, additional clinical trials (57-59) (Table 1) also confirmed the efficacy of T-DM1 for HER2-positive advanced or metastatic breast cancer. Compared with T-DM1, chemotherapy plus anti-HER2 therapy has relatively less efficacy and more adverse events (AEs) in the treatment of HER2-positive advanced breast cancer, especially for patients who had previously been treated with taxane and HER2-directed regimens in the advanced setting. However, one study showed that chemotherapy plus trastuzumab was not inferior to T-DM1 when utilized as the first-line treatment for metastatic or recurrent breast cancer patients. In the MARIANNE study (59), 1,095 patients with locally advanced or metastatic breast cancer were randomized to receive first-line treatment with T-DM1 with or without pertuzumab or trastuzumab plus a taxane. The results showed no significant differences among the three experimental groups, indicating that trastuzumab plus a taxane is not inferior to T-DM1 in terms of efficacy and tolerability for advanced breast cancer.

Several studies on early breast cancer (Table 1) (19,60), have attempted to investigate the therapeutic effect of T-DM1. Hurvitz et al. performed the KRISTINE trial (60) to explore the effectiveness of T-DM1 in the neoadjuvant setting. T-DM1 plus pertuzumab led to a lower pCR rate than chemotherapy plus dual HER2-targeted blockade (pertuzumab + trastuzumab) (44.4% vs. 55.7%, P=0.016) but fewer AEs. Given that pertuzumab was used in both groups, the effect of pertuzumab could be considered equivalent in the two groups, and thus, chemotherapy plus single anti-HER2 agents seems to be superior to T-DM1 with regard to efficacy. In the adjuvant therapy setting, the KATHERINE study (19), was the first research to optimize the treatment of HER2-positive breast cancer with residual lesions after neoadjuvant systemic treatment, and results revealed the conspicuous advantages of T-DM1 compared with trastuzumab. In total, 1,486 patients were
randomized to receive adjuvant T-DM1 or trastuzumab after receiving neoadjuvant therapy and the primary endpoint was invasive disease-free survival (iDFS). The results manifested that the T-DM1 group showed a

| Clinical trial | Phase | Study population                                                                 | Study design                                                                 | Results                                                                                     | AEs                                                                 |
|----------------|-------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| **Advanced or metastatic breast cancer** |       |                                                                                  |                                                                                              |                                                                                              |                                                                      |
| EMILIA (2012) (56) | III   | Patients (n=991) with HER2-positive advanced breast cancer, who had previously been treated with trastuzumab and taxane | G1: lapatinib plus capecitabine G2: T-DM1 | Median PFS: G1 vs. G2: 6.4 months vs. 9.6 months (HR=0.65, P<0.001) Median OS: G1 vs. G2: 25.1 months vs. 30.9 months (HR=0.68, P<0.001) ORR: G1 vs. G2: 30.8% vs. 43.6% (P<0.001) | Grade ≥3: G1 vs. G2: 57% vs. 41% G1: diarrhea, nausea, vomiting G2: thrombocytopenia and increased serum aminotransferase levels |
| TDM4450 g (2013) (57) | II    | Patients (n=137) with HER2-positive MBC or recurrent locally advanced breast cancer | G1: trastuzumab plus docetaxel G2: T-DM1 | Median PFS: G1 vs. G2: 9.2 months vs. 14.2 months (HR=0.59, P =0.035) ORR: G1 vs. G2: 58.0% vs. 64.2% | Grade ≥3: G1 vs. G2: 90.9% vs. 46.4% Serious AEs: G1 vs. G2: 20.3% vs. 25.8% G1: neutropenia, alopecia, diarrhea G2: thrombocytopenia, increased aminotransferase levels, headache |
| TH3RESA (2014) (58) | III   | Patients (n=602) with HER2-positive advanced breast cancer who had received two or more HER2-directed regimens in the advanced setting, including trastuzumab and lapatinib, and previous taxane therapy in any setting | G1: physician’s choice (68.5% chemotherapy plus trastuzumab) G2: T-DM1 | Median PFS: G1 vs. G2: 3.3 months vs. 6.2 months (HR=0.528, P<0.0001) OS: G1 vs. G2: 22.7 months vs. 15.8 months (HR=0.68, P=0.0007) | Grade ≥3: G1 vs. G2: 47% vs. 40% Serious AEs: G1 vs. G2: 22% vs. 25% G1: neutropenia, diarrhea G2: thrombocytopenia |
| MARIANNE (2017) (59) | III   | Patients (n=1,095) with HER2-positive, advanced breast cancer and no prior therapy for advanced disease | G1: trastuzumab plus taxane G2: T-DM1 plus placebo G3: T-DM1 plus pertuzumab | Median PFS: G1 vs. G2 vs. G3: 13.7 months vs. 14.1 months vs. 15.2 months (G2 and G3 are not superior to G1) (P>0.05) ORR: G1 vs. G2 vs. G3: 67.9% vs. 59.7% vs. 64.2% | Grade ≥3: G1 vs. G2 vs. G3: 54.1% vs. 45.4% vs. 46.2% G1: alopecia, diarrhea G2: T-DM1: thrombocytopenia, increased aminotransferase, diarrhea |

Table 1 (continued)
Concerning AEs, the occurrence rate of grade $\geq 3$ AEs in disease after NAC when T-DM1 is unavailable. HER2-overexpressing breast cancer patients with residual trastuzumab might be used as an alternative therapy for Therefore, additional chemotherapy combined with trastuzumab might be used as an alternative therapy for HER2-overexpressing breast cancer patients with residual disease after NAC when T-DM1 is unavailable. Concerning AEs, the occurrence rate of grade $\geq 3$ AEs in the chemotherapy plus trastuzumab group was relatively higher than that in the T-DM1 group, but the side effects observed in both groups were acceptable. Although frequent AEs, such as nausea, alopecia, and diarrhea, in T-DM1 group were improved compared with those in the chemotherapy plus anti-HER2 group, T-DM1 has specific AEs such as thrombocytopenia and increased amino-transferase levels, which cannot be neglected. Although T-DM1 has been recommended as the preferred treatment because of its clinical advantages in patients with residual disease after neoadjuvant therapy, its high price and low availability limit its application. Many experts have performed cost-effectiveness analyses of T-DM1 in developed countries, and even though the cost varied by different regimens, regions and willing-to-pay (WTP) thresholds, the conclusions were consistent: T-DM1 was not cost-effective. Almost all the clinical effectiveness data were taken from the EMILIA study [T-DM1 vs. lapatinib plus capecitabine (LC)]. In the United States (62), researchers constructed four possible Markov models to estimate the overall cost-effectiveness by taking the mean of total costs and quality-adjusted life years (QALY). The results showed that the incremental cost-effectiveness ratio (ICER) for T-DM1 compared with LC was $183,828/QALY and $220,385/QALY from the perspective of US society and the payer, respectively. The probability of cost-effectiveness for T-DM1 vs. LC was just
28.1% from the societal perspective. So, the researchers had to admit that T-DM1 was not cost-effective when comparing to the LC combination therapy. According to the 2015 import price of T-DM1 in Spain (63), T-DM1 had a cost per QALY of over 120,000 €, and at least a 50% reduction in the price was needed to place T-DM1 close to the threshold of what is usually considered cost-effectiveness. The National Institute for Health and Care Excellence (NICE) of England concluded that T-DM1 could not be recommended for treating HER2-positive advanced or metastatic breast cancer patients who were previously treated with trastuzumab and taxane, because the patient access scheme analysis suggested that T-DM1 had a 0% probability of being cost-effective at an ICER of £30,000 per QALY gained (64). The list price for T-DM1 was £1,641.01 for a 100 mg vial and £2,625.62 for a 160 mg vial in 2017, and it was estimated that the average cost of a course of treatment was over £90,000, according to the list price (65). Similarly, a final recommendation from the pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) demonstrated that the average cost per 28-day course of T-DM1 was $8,426.88 according to 2013 list price, and this assessment did not take the wastage into consideration. By contrast, the cost of capecitabine in combination with lapatinib or trastuzumab just was approximately half that of T-DM1 (66). In brief, given current acquisition costs, there is no possibility that T-DM1 can be cost-effective for HER2-positive advanced breast cancer, even in developed countries. We have to admit that all of the above cost-effective analyses were based on treatment for unresectable advanced breast cancer patients whose life expectancy was relatively short. If the analysis was performed for the treatment of early breast cancer, the ICER may be closer to the WTP threshold. Nevertheless, in low- and middle-income developing countries and regions, such as sub-Saharan Africa and Iran (67,68), trastuzumab, the most basic targeted agent for early HER2-positive breast cancer, does not appear to be cost-effective. Although the remarkable efficacy of T-DM1 has been confirmed, it met challenge of demonstrating its cost-effectiveness to payers around the globe. Therefore, application of T-DM1 to HER2-positive residual cancer seems to be economically unfeasible in most countries and regions. Moreover, in May 2019, the FDA approved T-DM1 for patients with HER2-positive early breast cancer with residual disease after neoadjuvant therapy in the adjuvant treatment setting (69). However, in many countries, especially developing countries, such as China, T-DM1 has not been approved for treatment of patients with HER2-positive advanced breast cancer. Thus, T-DM1 is also difficult to obtain, even for patients who can afford it.

Although T-DM1 can significantly improve the prognosis of patients with HER2-positive residual breast cancer, it is unavailable in many countries, especially some low- and middle-income regions, not only because of the high cost but also due to policy constraints. We recommend additional chemotherapy in combination with trastuzumab-based targeted therapy as an alternative for treatment with T-DM1 considering the similar effect of these two approaches in HER2-positive breast cancer patients with residual disease after NAC and the high cost of T-DM1.

**Future perspective**

In some countries and regions where T-DM1 is unavailable, we need to further investigate the efficacy of adding additional chemotherapy to trastuzumab for patients with HER2-overexpressing residual breast cancer after NAC and select appropriate chemotherapeutic drugs. A prospective clinical trial with three experimental groups should be conducted, and the three groups can be designed to receive trastuzumab with or without pertuzumab, T-DM1, and trastuzumab plus chemotherapeutic drugs. Moreover, the selection of the cytotoxic drugs can be guided by the pathological response to NAC, and to avoid severe adverse reactions, oral chemotherapeutic drugs such as capecitabine or metronomic chemotherapy (70) may be considered. At the same time, we are waiting for publication of the results of two ongoing trials (KAITLIN and ATEMPT) to confirm the efficacy of T-DM1 in early breast cancer and further clarify the possibility of replacing T-DM1 with chemotherapy combined with trastuzumab-based targeted therapy. We are also looking forward to a reduction in the acquisition cost of T-DM1 and supports of national policies. Under the current circumstances, according to the results of published studies and rational derivations, administering chemotherapy along with the current single anti-HER2 therapy is a reliable and efficacious alternative regimen for HER2-overexpressing breast cancer patients with residual disease, particularly those with positive lymph nodes, after NAC when T-DM1 is unavailable. This approach may reduce the death and recurrence risk and improve the prognosis and quality of life of these patients.
Conclusions

Despite the advantages of NAC, the majority of patients received NAC fail to experience pCR. Residual disease, particularly positive lymph nodes, after NAC is a high-risk factor for recurrence and death, and the correlation is the strongest for patients with aggressive breast cancer, such as the HER2-overexpressing and triple-negative subtypes. Approximately a quarter of HER2-overexpressing breast cancer patients who receive surgery and standard systemic treatments are at risk of relapse after 8–10 years. Therefore, the treatment regimens for patients with residual disease after NAC need to be optimized to improve outcomes of patients. Compared with the systemic treatment of patients that receive surgery directly or those with recurrent lesions, adding chemotherapy to treatment regimens for patients with residual disease after NAC is rational. Furthermore, the CREATE-X study has confirmed that administering capecitabine to HER2-negative patients with residual invasive cancer can significantly prolong patient survival. In addition, due to tumor heterogeneity, HER2-negative and triple-negative tumor cells are present in HER2-overexpressing breast cancer, and these cells are sensitive to chemotherapy. Hence, it is reasonable to infer that the efficacy of additional chemotherapy plus trastuzumab would be superior to HER2 directed therapy alone for HER2-overexpressing residual breast cancer. Although the efficacy of T-DM1 in patients with residual invasive HER2-positive breast cancer has been verified in the KATHERINE study, the high cost and low accessibility of T-DM1 limit its use, especially in low- and middle-income countries and regions. Furthermore, previous studies have demonstrated that chemotherapy in combination with trastuzumab-based targeted therapy was not inferior to T-DM1. Therefore, administering additional chemotherapy to the currently used pure targeted therapy for HER2-overexpressing breast cancer patients with residual disease, particularly those with positive lymph nodes after NAC is a potentially efficacious alternative regimen to T-DM1, but further clinical research is highly warranted to explore which chemotherapeutic agents and administration routes are the most efficacious and the safest.

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Footnote

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

References

1. Pruneri G, Bonizzi G, Vingiani A. Biomarkers for the identification of recurrence in human epidermal growth factor receptor 2-positive breast cancer patients. Curr Opin Oncol 2016;28:476-83.
2. Mohd Sharial MS, Crown J, Hennessy BT. Overcoming resistance and restoring sensitivity to HER2-targeted therapies in breast cancer. Ann Oncol 2012;23:3007-16.
3. Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene 2007;26:6469-87.
4. Parise CA, Bauer KR, Brown MM, et al. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) among women with invasive breast cancer in California, 1999-2004. Breast J 2009;15:593-602.
5. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 2014;32:3744-52.
6. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years’ follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet 2017;389:1195-205.
7. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet 2013;382:1021-8.
8. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 2017;377:122-31.
9. Wolmark N, Wang J, Mamounas E, et al. 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.

10. van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224-37.

11. Asselain B, Barlow W, Bartlett J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018;19:27-39.

12. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005;97:188-94.

13. Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. Surg Oncol Clin N Am 2014;23:505-23.

14. Bonnefoi H, Litiere S, Piccart M, et al. Pathological complete response after neoadjuvant chemotherapy is an independent predictive factor irrespective of simplified breast cancer intrinsic subtypes: a landmark and two-step approach analyses from the EORTC 10994/BIG 1-00 phase III trial. Ann Oncol 2014;25:1128-36.

15. Houssami N, Macaskill P, von Minckwitz G, et al. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Cancer 2012;48:3342-54.

16. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796-804.

17. Corben AD, Abi-Raad R, Popa I, et al. Pathologic response and long-term follow-up in breast cancer patients treated with neoadjuvant chemotherapy: a comparison between classifications and their practical application. Arch Pathol Lab Med 2013;137:1074-82.

18. Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. J Clin Oncol 2007;25:2650-5.
neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-84.

29. Rimawi MF, Mayer IA, Forero A, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol 2013;31:1726-31.

30. Gianni L, Bisagni G, Colleoni M, et al. Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, phase 2 study. Lancet Oncol 2018;19:249-56.

31. Bear HD, Anderson S, Smith RE, 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 2006;24:2019-27.

32. Mougalian SS, Hernandez M, Lei X, et al. Ten-year outcomes of patients with breast cancer with cytologically confirmed axillary lymph node metastases and pathologic complete response after primary systemic chemotherapy. JAMA Oncol 2016;2:508-16.

33. Bear HD, Anderson S, Brown A, et al. 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;21:4165-74.

34. Arsenault D, Hurley J, Takita C, et al. Predictors of locoregional outcome in HER2-overexpressing breast cancer treated with neoadjuvant chemotherapy. Am J Clin Oncol 2015;38:348-52.

35. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007;25:4414-22.

36. Ogston KN, Miller ID, Payne S, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. Breast 2003;12:320-7.

37. Zhao Y, Dong X, Li R, et al. Evaluation of the pathological response and prognosis following neoadjuvant chemotherapy in molecular subtypes of breast cancer. Onco Targets Ther 2015;8:1511-21.

38. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. 2011;365:1273-83.

39. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809-20.

40. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007;18:1133-44.

41. Dall P, Koch T, Göhler T, et al. Trastuzumab without chemotherapy in the adjuvant treatment of breast cancer: subgroup results from a large observational study. BMC Cancer 2018;18:51.

42. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol 2016;17:791-800.

43. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Breast Cancer (Version 1. 2019). Available online: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

44. Dominici LS, Negron Gonzalez VM, Buzdar AU, et al. Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. Cancer 2010;116:2884-9.

45. Fisher CS, Ma CX, Gillanders WE, et al. Neoadjuvant chemotherapy is associated with improved survival compared with adjuvant chemotherapy in patients with triple-negative breast cancer only after complete pathologic response. Ann Surg Oncol 2012;19:253-8.

46. Mountfort K. Treatment De-escalation in Women
with Metastatic HER2-positive Breast Cancer – The PERNETTA Trial. Available online: https://touchoncology.com/insight/treatment-de-escalation-in-women-with-metastatic-her2-positive-breast-cancer-the-pernetta-trial/

47. Hsiao YH, Chou MC, Fowler C, et al. Breast cancer heterogeneity: mechanisms, proofs, and implications. J Cancer 2010;1:6-13.

48. Martelotto LG, Ng CK, Piscuoglio S, et al. Breast cancer intra-tumor heterogeneity. Breast Cancer Res 2014;16:210.

49. Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? Nat Rev Cancer 2012;12:323-34.

50. Zou M, Jin R, Au KF. Revealing tumor heterogeneity of breast cancer by utilizing the linkage between somatic and germline mutations. Brief Bioinform 2018.

51. Brooks MD, Burness ML, Wicha MS. Therapeutic implications of cellular heterogeneity and plasticity in breast cancer. Cell Stem Cell 2015;17:260-71.

52. Yu T, Di G. Role of tumor microenvironment in triple-negative breast cancer and its prognostic significance. Chin J Cancer Res 2017;29:237-52.

53. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. 2018;36:2105-22.

54. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784-95.

55. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376:2147-59.

56. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.

57. Hurvitz SA, Dirix L, Kocsis J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 2013;31:1157-63.

58. Krop IE, Kim SB, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician’s choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:689-99.

59. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: Primary results from the phase III MARIANNE study. J Clin Oncol 2017;35:141-8.

60. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KTRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncology 2018;19:115-26.

61. Yan H, Yu K, Zhang K, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in the treatment of HER2-positive metastatic breast cancer (MBC): a meta-analysis of randomized controlled trial. OncoTarget 2017;8:102458-67.

62. Le QA, Bae YH, Kang JH. Cost-effectiveness analysis of trastuzumab emtansine (T-DM1) in human epidermal growth factor receptor 2 (HER2): positive advanced breast cancer. Breast Cancer Res Treat 2016;159:565-73.

63. Miranda Romero P, Marín Gil R. Trastuzumab emtansine in locally advanced or metastatic HER2 positive breast cancer; GENESIS-SEFH drug evaluation report. Farm Hosp 2015;39:171-5.

64. Squires H, Stevenson M, Simpson E, et al. Trastuzumab Emtansine for Treating HER2-Positive, Unresectable, Locally Advanced or Metastatic Breast Cancer After Treatment with Trastuzumab and a Taxane: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics 2016;34:673-80.

65. National Institute for Health and Care Excellence. Final appraisal determination -- Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane. Available
Final Recommendation for Trastuzumab Emtansine (Kadcyla) for Metastatic Breast Cancer. PAN-CANADIAN ONCOLOGY DRUG REVIEW. Available online: https://www.cadth.ca/sites/default/files/pcodr/pcodr-kadcyla-mbc-fn-rec.pdf

Gershon N, Berchenko Y, Hall PS, et al. Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer. Cost Eff Resour Alloc 2019;17:5.

Ansaripour A, Uyl-de Groot CA, Redekop WK. Adjuvant Trastuzumab Therapy for Early HER2-Positive Breast Cancer in Iran: A Cost-Effectiveness and Scenario Analysis for an Optimal Treatment Strategy. Pharmacoeconomics 2018;36:91-103.

FDA Approves Genentech’s Kadcyla for Adjuvant Treatment of People With HER2-Positive Early Breast Cancer With Residual Invasive Disease After Neoadjuvant Treatment. Available online: https://bit.ly/2UYWOVN

Cazzaniga ME, Dionisio MR, Riva F. Metronomic chemotherapy for advanced breast cancer patients. Cancer Lett 2017;400:252-8.

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