Review Article

Strategies for the treatment of HER2$^+$ advanced breast cancer based on clinical practice in Chinese patients: a roundtable discussion

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Abstract: Human epithelial growth factor receptor 2-positive (HER2$^+$) breast cancer is easy to relapse and metastasize in the early stage, and usually has more aggressive clinical behavior and worse patient survival outcomes as compared with estrogen receptor-positive (ER$^+$), HER2-negative (HER2$^-$) breast cancer. The HER2$^+$ breast cancer has been significantly enhanced by trastuzumab and other multiple novel HER2 anti-tumor drugs. The dual combination regimen of trastuzumab + pertuzumab has been established as the standard first-line therapy for advanced HER2$^+$ patients, and pyrotinib with capecitabine is the preferred second-line treatment in Chinese patients. However, no third- or later-line regimens are currently recommended, and thus, the treatment needs of these patients remain unmet. Margetuximab is a human/mouse chimeric anti-HER2 immunoglobulin G1 (IgG1) monoclonal antibody (mAb) based on the murine precursor of trastuzumab, has shown greater efficacy than trastuzumab in terms of its natural killer (NK) cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) effect and may become the preferred solution for HER2$^+$ metastatic breast cancer (mBC) following progression on second-line therapy with small molecule tyrosine kinase inhibitors (TKIs). This paper explores discussion of therapeutic strategies of anti-HER2 drugs based on Chinese clinical practice, and summarizes the consensus and controversy in the post-anti-HER2 TKIs guideline recommendations, so as to provide certain guidance to HER2$^+$ mBC patients pretreated with TKIs in the third or later lines.

Keywords: Metastatic breast cancer (mBC); human epithelial growth factor receptor 2-positive (HER2$^+$); margetuximab; SOPHIA trial

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Introduction

Human epithelial growth factor receptor 2-positive (HER2$^+$) breast cancer refers to HER2 protein overexpression and/or *HER2* gene amplification and accounts for 15–20% of all breast cancers (1). It is one of the most aggressive subtypes of breast cancer, easy to relapse and metastasize in the early stage, and usually has poor outcomes (2). The first HER2-targeted drug, trastuzumab, changed the HER2$^+$ breast cancer landscape. In the past 20 years, more novel anti-HER2 drugs have emerged, such as pertuzumab,

trastuzumab-emtansine (T-DM1), and small molecule tyrosine kinase inhibitors (TKIs) [including lapatinib, pyrotinib, niratinib, etc.] (3). These treatments have enhanced the therapeutic options for HER2$^+$ advanced breast cancer and largely extended the overall survival (OS) of patients (4). Higher 5-year OS rates have been achieved, with approximately 30–40% of patients being able to live for more than 8 years without disease progression (5). HER2$^+$ breast cancer tends to be a chorionic disease, and treatment is aimed at relieving symptoms, improving quality of life, and extending OS.

Trastuzumab based anti-HER2 therapies (such as trastuzumab-pertuzumab-taxane) is currently the standard first-line treatment for HER2$^+$ advanced breast cancer, and T-DM1 is recommended as a second-line therapy by authoritative guidelines (6-8). The DESTINY-Breast03 study showed that trastuzumab deruxtecan (T-DXd, DS-8201) is a superior second-line treatment compared to T-DM1 (9), thus European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) clinical practice guidelines have recommended T-DXd as a future second-line choice (6,8,10). However, in Chinese clinical practice, prices and the lack of approval have resulted in access issues for these two antibody drug conjugate (ADC) drugs, and they are recommended by the Chinese Society of Clinical Oncology (CSCO; 2022) guidelines only in level II (7). TKIs, such as pyrotinib, combined with capecitabine have been approved and recommended as second-line standard treatments for HER2$^+$ breast cancer in China (11). However, for the third and later lines of therapy, there is currently no unified recommendation. The commonly agreed opinion is that anti-HER2 therapy should be continued during the entire treatment process for HER2$^+$ breast cancer, and the specific drugs should be chosen according to the patient's baseline characteristics, prior therapy, drug-specific toxicity, domestic indication approved, etc. (11). In addition to the above-mentioned anti-HER2 antibodies, ADCs (T-DXd), and TKIs (lapatinib, pyrotinib, and neratinib), a novel anti-HER2 monoclonal antibody (mAb), margetuximab, is an effective third- and later-line therapy for HER2$^+$ advanced metastatic breast cancer (mBC).

On July 14, 2022, more than 10 top experts in breast cancer gathered for a roundtable discussion with Professor Zefei Jiang, aiming to explore optimized third- and later-line anti-HER2 therapies based on current clinical practices in Chinese patients. In this paper, we discussed all of the anti-HER2 treatment strategies based on Chinese clinical practice to provide a reference for the optimization of third- and later-line therapies for HER2$^+$ breast cancer.

Discussion of therapeutic strategies of anti-HER2 drugs based on Chinese clinical practice

Difference in anti-HER2 therapy choice between China and Western countries

Trastuzumab was adopted in China in 2002 for advanced HER2$^+$ breast cancer and changed the prognosis of this disease. Subsequently, the CLEOPATRA study published in 2015 established dual-targeted trastuzumab + pertuzumab as the first-line standard therapy for advanced HER2$^+$ patients (12). However, in Chinese clinical daily practice, the anti-HER2 therapy landscape is different from that in Western countries. Owing to the relatively high price or cost of targeted therapy, many advanced patients cannot receive trastuzumab or dual-targeted drugs. To optimize anti-HER2 therapy and better guide current clinical practice in China, the CSCO exerted great efforts to update the different versions of breast cancer guidelines according to the real-world Chinese experience, which fully considered the huge disparities from different provinces or regions, differences in novel drug access, and different treatment choices of physicians.

Owing to the higher costs of dual-targeted therapy, single-targeted Trastuzumab with chemotherapy is still recommended by the CSCO guidelines as the preferred regimen (IA) (7). According to the EMILIA and DESTINY-Breast03 studies, TDM-1 and T-DXd are currently both recommended as second-line treatment by international guidelines (6,8). However, in China, good efficacy data from phase III clinical studies [PHENIX (13) and PHOEBE (14)] and better accessibility have made pyrotinib with capecitabine the preferred second-line choice for HER2$^+$ advanced breast cancer. Yet, no standard regimens are currently recommended for third- or later-line therapy. Continuous anti-HER2 therapy is crucial throughout the entire treatment process of HER2$^+$ advanced breast cancer patients. Also, choosing the best regimen post-anti-HER2 TKIs has tended to be a challenge in Chinese clinical practice.

Possibility of post-anti-HER2 TKIs treatment in HER2$^+$ mBC

Tumor cells may undergo clonal evolution under drug

pressure (15). Most tumor clones from naive patients are wild strains, but some mutant clones (with drug-resistant clones) will emerge under drug pressure, which is a dynamic process. If a patient stops first-line regimen treatment for some time, the tumor clones may return to the original wild-type and become re-sensitized to the primary therapy (16,17). This dynamic tumor clonal evolution has been confirmed in other solid tumors. Siravegna *et al.* found that if colorectal cancer patients discontinued anti-EGFR targeted therapy, drug-resistant clones would decline while drug-sensitive clones would re-emerge due to the clonal growth competition. Also, patients may return to a status that is very similar to naïve foci (18), which means that anti-EGFR therapy can be re-challenged. Perera *et al.* also proposed "intermittent treatment" to deal with the drug resistance problem (19).

There is also an indication of clonal evolution in the HER2 pathway. The HER2 family involves extracellular protein overexpression and intracellular point mutations, both of which can activate the downstream pathway. Primary resistance to the dual-targeted drugs, trastuzumab + pertuzumab, can be partially reversed by TKIs such as lapatinib, pyrotinib, and neratinib (20). TKIs inhibit multiple targets of the human epidermal growth factor receptor family intracellularly and also help regulate cell growth, differentiation, migration, and apoptosis. Thus, TKIs may reverse anti-HER2 drug resistance to a near naïve clone status (20). Preclinical studies have shown that lapatinib could induce the stabilization and accumulation of inactive HER2 receptors on the cellular membrane and may become sensitive to trastuzumab again (21). Gori *et al.* found that lapatinib with capecitabine could enhance the efficacy of re-challenged trastuzumab in HER2$^+$ mBC patients after progression (22). This may provide theoretical and practical evidence for the re-challenging of trastuzumab.

HER2 remains an ideal and effective therapeutic target (even after disease progression with trastuzumab therapy) because HER2 protein overexpression remains stable in HER2$^+$ mBC (22). So, a more potent anti-HER2 antibody post-anti-HER2 TKIs may maximize patient survival in the third or later lines. Margetuximab is a novel HER2 mAb, which exhibits a similar HER2 binding domain and anti-proliferative effects to trastuzumab (Herceptin). However, it has modified affinity with the Fcγ receptor (FcγR) and more potent antibody-dependent cell-mediated cytotoxicity (ADCC) effects than trastuzumab (23).

Optimized treatment strategy of post-anti-HER2 TKIs in HER2$^+$ mBC

TKIs, such as pyrotinib, are mainly second-line treatments in Chinese clinical practice. The PHENIX phase III clinical trial (n=279) was presented by Professor Zefei Jiang at the 2019 ASCO annual meeting. Pyrotinib plus capecitabine showed a significantly better median progression-free survival (mPFS) (11.1 *vs.* 4.1 months, P<0.001), and a markedly higher objective response rate (ORR) (68.6% *vs.* 16.0%, P<0.001) (13) in HER2$^+$ mBC patients who were previously treated with trastuzumab. Another phase III PHOEBE study with Professor Binghe Xu as principle investigator (PI) aimed to assess the efficacy and safety of pyrotinib plus capecitabine after prior trastuzumab therapy for HER2$^+$ mBC (n=267). It showed a significantly longer mPFS than with pyrotinib *vs.* lapatinib [12.5 *vs.* 6.8 months, hazard ratio (HR) =0.39, 95% confidence interval (CI): 0.27–0.56, P<0.0001] at interim analysis, but no significant benefit in median OS (mOS) in the trastuzumab-resistant population was observed (34.5 *vs.* 29.7 months, HR =0.94, 95% CI: 0.48–1.58) (14). Key domestic guidelines, including the Standardized Diagnosis and Treatment of Advanced Breast Cancer in China 2020, CSCO Breast Cancer (CSCO BC) 2022, and Committee of Breast Cancer Society (CBCS) 2021 recommend pyrotinib plus capecitabine as the preferred second-line regimen in level I (IA) (7,24,25).

Cancer Discovery recently published Chang *et al.* paper, which found that two types of drug-tolerant persisters (DTPs) emerged after anti-HER2 TKI treatment and that the mTORC1 pathway was reactivated, which could potentially restart cell proliferation and neoplasm generation. TKI drug resistance appeared through this mechanism (26). However, in clinical practice, there is a lack of follow-up for HER2$^+$ mBC patients who failed after TKIs, and only a few studies have shown limited data on drug selection post-anti-HER2 TKIs. The TH3RESA study (27) enrolled HER2$^+$ mBC patients who experienced failure with trastuzumab and lapatinib and then received T-DM1. In the HER2CLIMB study (28), tucatinib demonstrated a survival benefit in the intention to treat (ITT) analysis population, in which 5.6% of enrolled patients failed prior lapatinib treatment. Both of these studies lacked strong stratified data on the post-anti-HER2 TKIs population. Also, since the prior regimen was mainly lapatinib, they did not present evidence for other TKIs beyond lapatinib. Both studies also showed that more attention should be paid to the adverse

events (AEs) of T-DM1 and tucatinib; 7% of patients discontinued T-DM1 therapy due to severe AEs, with ≥G3 thrombocytopenia being significantly higher with T-DM1 *vs.* chemotherapy (5% *vs.* 2%); and 5.7% of patients stopped tucatinib due to grade 3 or higher AEs including diarrhea (12.9%) and palmar-plantar erythrodysesthesia syndrome (13.1%).

In the SOPHIA-China study (29) 72.4% of HER2$^+$ mBC patients enrolled had previously been treated with pyrotinib and then received margetuximab therapy. This was the first study to show that margetuximab can reduce the risk of progression by 42% (HR =0.58, P=0.038) in post-anti-HER2 TKI patients, with a manageable safety profile. Margetuximab may become another option for post-TKI third- or later-line therapy for patients in China.

Consensus and controversy in the post-anti-HER2 TKIs guideline recommendations

The NCCN Clinical Practice Guidelines 2022 (6) recommend anti-HER2 mAbs such as margetuximab or trastuzumab for third- or later-line therapy in HER2$^+$ mBC. However, the optimal treatment sequence and information on how to treat post-TKIs patients are not mentioned.

In China, TKIs such as pyrotinib and lapatinib are recommended as second-line options for HER2$^+$ mBC patients. Yet, most patients will ultimately be refractory to second-line TKIs, and the subsequent options remain unclear, leading to significant unmet medical needs. The CSCO added a TKI-resistant patient stratification in their recently published Breast Cancer Guidelines 2022 (7). Several regimens have been recommended for level II, including anti-HER2 ADC drugs (T-DXd or T-DM1), dual-targeted HP, switching to another type of TKI, or participating in clinical studies. Moreover, an important new update is that other unused anti-HER2 targeting agents are recommended for level III. The Chinese Anti-Cancer Association Committee of Breast Cancer Society (CACA-CBCS) 2021 guidelines (25) also recommend unused anti-HER2 therapy after the second line.

There is little evidence-based data or clear recommendation on post-TKI choices in third- or later-line therapy in HER2$^+$ mBC both in China and globally. At present, no large or randomized trials in China can provide valuable information on patients who failed second-line therapy with an anti-HER2-TKI (pyrotinib), so the subsequent treatment choice of these patients remains a considerable challenge in daily clinical practice.

Margetuximab may become the preferred third-line option for HER2$^+$ MBC

Margetuximab is a human/mouse chimeric anti-HER2 immunoglobulin G1 (IgG1) mAb modified from the murine precursor of trastuzumab. The variable domain of margetuximab is identical to that of trastuzumab and is derived from the mouse precursor 4D5, which can bind to the HER2 extracellular domain IV. The Fc region is modified with five replaced amino acids from wild-type IgG1 (L235V, F243L, R292P, Y300L, and P396L). Margetuximab has increased affinity for activating the FcγR CD16A (FcγRIIIa) and decreased affinity for inhibitory FcγR CD32B (FcγRIIb), which will enhance both the innate and adaptive immunity (30). Three FcγRs (CD16A, CD32A, and CD32B) in immune effector cells regulate cellular activation by antibodies (31), and CD16A triggers ADCC via innate immune cells (32,33). There are two types [valine (V)/phenylalanine (F)] of amino acid 158 on CD16A, and numerous trials of trastuzumab have shown that patients with genotype F benefit less from trastuzumab than those with genotype CD16A-158VV, and the disease-free survival (DFS) with trastuzumab therapy is significantly lower in patients with the CD16A-158FF genotype than that in patients with 158VV/158FV. Patients with the FF/FV genotype account for 85–90% of HER2$^+$ breast cancer patients (34,35). Preclinical studies have shown that, compared to trastuzumab, margitoximab does not alter HER2 receptor binding, but increases the affinity for Fc segment CD16A by 4.7–6.6-fold, decreases the affinity for CD32B by 8.4-fold, and provides greater natural killer (NK)-mediated ADCC effects (23). In addition, with the release of cytotoxic particles such as granzyme and perforin, pro-inflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) are released, and the pro-inflammatory environment can regulate other immune cell populations to produce a "vaccine" effect (36,37).

A phase I study indicated that single-agent margetuximab was well tolerated. with promising activity in patients with HER2-overexpressing tumors; 64% of 60 patients evaluable for a tumor response achieved stable disease (52%) or a partial response (12%). The mPFS was 4.5 months among breast cancer patients (38). The confirmatory, randomized, open-label, phase III SOPHIA study (NCT02492711) comparing margetuximab plus chemotherapy *vs.* trastuzumab plus chemotherapy "head-

to-head" in patients with HER2$^+$ mBC was initiated in 2015 and the results were published in January 2021 in the Journal of American Medical Association (JAMA) Oncology and San Antonio Breast Cancer Symposium (SABCS) 2021 (39). All patients were pretreated with at least two anti-HER2 regimens (including pertuzumab and 1–3 lines of systemic therapy) for HER2$^+$ mBC. Patients were randomized 1:1 to receive margetuximab (n=266) or trastuzumab (n=270) along with capecitabine, eribulin, gemcitabine, or vinorelbine, as per the investigator's choice, and the primary endpoints of the study were PFS and OS.

As of the 10th of October 2018, a total of 137 patients remained on treatment, 79 of whom were in the margetuximab group and 58 in the trastuzumab group. Margetuximab showed significantly prolonged PFS *vs.* trastuzumab (5.8 *vs.* 4.9 months, HR =0.76, 95% CI: 0.59–0.98, P=0.033). Furthermore, the anti-tumor responses were also higher in patients in the experimental arm (ORR: 22% *vs.* 16%, P=0.06).

In terms of safety, the combination of margetuximab and chemotherapy was relatively well tolerated, with adverse reactions comparable to those in the trastuzumab group. Grade 3 or above AEs occurred in 53.8% and 52.6% of patients treated with margetuximab and trastuzumab, respectively, with a low discontinuation rate due to AEs (3% *vs.* 2.6%); serious AEs (SAEs) occurred in 16.3% and 18.4% of patients, respectively, and common SAEs (≥5%) in the two groups included neutropenia, anemia, and fatigue.

On the 16th of December 2020, margetuximab was approved by the U.S. Food & Drug Administration for pretreated HER2$^+$ mBC (40) and was subsequently recommended by the U.S NCCN and the ESMO for the same indication in 2021 (8,41).

Margetuximab may be a valuable addition to the treatment options for pretreated HER2$^+$ mBC patients in China. However, due to the differing landscapes of anti-HER2 therapy between China and Western countries, the efficacy and safety data of margetuximab (especially in the third or later lines) need to be verified. A randomized, open-label, multicenter, phase II, bridging study was conducted to evaluate the efficacy and safety of margetuximab plus chemotherapy *vs.* trastuzumab plus chemotherapy in Chinese patients with pretreated HER2$^+$ mBC, and confirm whether the results are consistent with the clinical benefit observed in the global population of SOPHIA (29,42). From February 4, 2020, to February 23, 2021, a total of 173 patients were screened, and 123 Chinese patients were enrolled at 33 centers and randomly assigned (1:1) to receive either margetuximab plus chemotherapy (n=62) or trastuzumab plus chemotherapy (n=61). Prior treatments of patients enrolled in this study were highly reflective of the current treatment options for HER2$^+$ mBC patients in China and thus differed from those in the SOPHIA study. All patients were pretreated with trastuzumab and 83.7%, 25.2%, and 11.4% of the patients were pretreated with TKIs, pertuzumab, and T-DM1, respectively, the majority of whom (72.4%) also received pyrotinib at baseline. Meanwhile, almost all patients in the SOPHIA study had been previously treated with trastuzumab and pertuzumab, and more than 91% of the patients had received T-DM1 for prior anti-HER2 therapy.

The results showed that the SOPHIA-China trial met the consistency criterion (HR <0.88) for bridging success. Blinded independent central review-assessed mPFS was better in the margetuximab arm than in the trastuzumab arm (5.5 *vs.* 4.1 months, HR =0.69, 95% CI: 0.43–1.12, P=0.128). Median OS was not yet reached. Moreover, both the ORR and clinical benefit rate were greater in the margetuximab arm (25.5% *vs.* 12.5%; 32.7% *vs.* 14.3%). Notably, the PFS risk was reduced by 42% (HR =0.58, P=0.038) in patients who had previously received TKIs, which was better than 31% in the ITT population, so margetuximab may be considered a treatment option for patients post-TKIs treatment.

The safety results showed that drug-related infusion related reactions (IRRs) were more common in the margetuximab arm (12.9%) than in the trastuzumab arm (1.7%). Most IRRs were of grades 1–2 and all of the patients recovered after symptomatic treatment. Grade ≥3 treatment-emergent AEs (TEAEs) occurred in 45.2% and 41.7% of patients in the margetuximab and trastuzumab arms, respectively. The proportions of patients with grade ≥3 study drug (margetuximab or trastuzumab)-related TEAEs were 21.0% and 15.0%, respectively. The common SAEs (≥5%) in both groups included neutropenia, decreased white blood cell count, anemia, and decreased lymphocyte count. TEAEs leading to study drug discontinuation occurred in 16.1% and 10.0% of patients in the margetuximab and trastuzumab arms, respectively. The discontinuation rates for all drugs due to AEs were significantly lower in the margetuximab arm (1.6% *vs.* 10.0%). No death due to TEAEs was observed.

In China, patients pretreated with TKIs account for the main population among HER2$^+$ mBC patients in the third or later lines but subsequent treatment options

remain controversial. In the SOPHIA-China trial, patients pretreated with pyrotinib or lapatinib seemed to benefit more from margetuximab treatment than those who were not. Among the treatment recommendations in the CSCO BC 2022 guidelines for patients who failed trastuzumab, a level III recommendation has added margetuximab + chemotherapy (2B) (7), suggesting that margetuximab may also be a suitable treatment option for patients pre-treated with TKIs.

The positive results obtained by the SOPHIA and SOPHIA-China trials in advanced breast cancer patients encourage more trials to explore the early setting of breast cancer. A newly-designed phase II, open-label, single-arm study (MARGARTE) is currently ongoing to evaluate the efficacy and safety of margetuximab plus tucatinib and capecitabine for HER2$^+$ mBC. Also, another phase II study (ClinicalTrials.gov ID: NCT04425018-MARGOT) is currently comparing the activity of margetuximab plus pertuzumab and paclitaxel to the standard-of-care treatment (trastuzumab, pertuzumab, and paclitaxel) in the neoadjuvant setting for HER2$^+$ breast cancer patients. Also, other pharmacokinetic studies of margetuximab in Chinese patients with HER2$^+$ mBC are ongoing (NCT04398108). We hope to see more comprehensive results from these trials in the future.

Conclusions

HER2$^+$ breast cancer is an aggressive subtype of breast cancer that is easy to relapse and metastasize in the early stage and has a poor overall prognosis. Trastuzumab, as the first anti-HER2 targeted antibody, has largely improved the prognosis of HER2$^+$ breast cancer. The dual-targeted therapy of trastuzumab + pertuzumab is currently recognized as the standard first-line treatment for HER2$^+$ advanced breast cancer. Pyrotinib, as a highly potent anti-HER2 TKI has been the standard second-line therapy in China. However, third- or later-line treatments, especially post-TKIs, pose a major challenge in Chinese daily clinical practice.

Novel ADCs have exhibited good efficacy and safety profiles and may change the treatment landscape of HER2$^+$ mBC in the future. T-DM1 is recommended by several authoritative guidelines and is a consensus for second-line therapy; the Destiny-Breast03 showed that T-DXd had better efficacy *vs.* T-DM1. The ESMO MBC 2021 (8), NCCN 2022 (6), and ASCO 2022 (10) guidelines all recommend that T-DXd be added as a new second-line treatment for HER2$^+$ advanced breast cancer. Thus, we will have T-DXd, pyrotinib, and T-DM1 as second-line therapy options. However, for third and subsequent-line treatment regimens, there is no unified standard treatment, resulting in a huge unmet need for the treatment of post-TKIs patients in China.

According to the evolution mechanism of tumor clones under treatment pressure and the data from the SOPHIA and SOPHIA-China trials, margetuximab provides a stronger ADCC effect and offers another ideal treatment option for TKI-resistant patients in the local clinical setting, which is expected to provide a new model of breast cancer treatment based on clinical practice in China. This may help to achieve better long-term survival outcomes for HER2$^+$ mBC patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-22-49/coif). XW serves as an unpaid editorial member of *Translational Breast Cancer Research* from December 2020 to November 2022. QZ serves as an unpaid editorial member of *Translational Breast Cancer Research* from March 2022 to April 2024. The other authors have no conflicts of interest to declare.

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