Expert consensus on the clinical diagnosis and targeted therapy of HER2 breast cancer (2023 edition)

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Abstract: Human epidermal growth factor receptor 2 (HER2) is an important driver gene and prognostic indicator of breast cancer and also a key predictor of HER2-targeted therapies. The emerging anti-HER2 drugs have greatly changed the diagnosis and treatment modalities of breast cancer and dramatically improved the prognosis of HER2-positive breast cancer patients. To optimize the treatment of HER2 breast cancer an update of expert consensus on HER2 positive breast cancer was made to adjust the different recommendation levels from early stage to metastatic stage. Meanwhile, antibody-drug conjugate (ADC) like trastuzumab deruxtecan (T-Dxd) has been shown to have great efficacy in HER2-positive and HER2 low expression breast cancer patients. Clinically, on the basis of the original definition for HER2-negative breast cancer, patients with HER2 immunohistochemistry (IHC) 1+ or IHC 2+ and in-situ hybridization (ISH)-negative are defined as low HER2 expression (HER2-low). As both the low expression and the positive expression of the HER2 protein is clinically significant for disease treatment and prognosis, we added a new chapter of HER2 low to recommend a proper regimen for this kind of patients. In this consensus, we also talk about the importance of clinical research, real world evidence, biosimilars and so on. In addition, the whole-course management of HER2 breast cancer is even more critical during pandemic of coronavirus disease 2019 (COVID-19). An approach that gives preference to "low-toxicity regimens and oral preparations" are also recommended.

Keywords: Human epidermal growth factor receptor 2 (HER2); breast cancer; consensus; low expression

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Introduction

Human epidermal growth factor receptor 2 (HER2) is an important driver gene and prognostic indicator of breast cancer and also a key predictor of HER2-targeted therapies. The anti-HER2 drug, trastuzumab, which represents a major breakthrough in targeted therapy for breast cancer, has greatly changed the diagnosis and treatment modalities of breast cancer and dramatically improved the prognosis of HER2-positive breast cancer patients. In recent years, a series of new anti-HER2 drugs, including tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates (ADCs) have entered the market, which have been shown to have good efficacy in the treatment of HER2-positive breast cancer and changed clinical practice.

After a careful review of the latest evidence, the Breast Cancer Expert Committee of the Chinese Society of Clinical Oncology (CSCO BC) and the Chinese Anti-Cancer Association, Committee of Breast Cancer Society (CACA-CBCS) released this updated consensus document on the basis of the last version of HER2 consensus previously published in Chinese (1). We updated the latest progress in HER2 positive patients and adjusted the recommendation levels for different stages. Meanwhile, we also further added three new chapters to discuss HER2-low expression, coronavirus disease 2019 (COVID-19) vaccines and biosimilars for these patients. We hope it will be of benefit to optimize the diagnosis and treatment of HER2 breast cancer, to make up for the lack in recommending those regimens with poor evidence or accessibility in the guidelines (2), and ultimately achieve the goal of "feasible regimens at proper times for appropriate population".

Methods

Professor Zefei Jiang, Vice President and Secretary General of the Chinese Society of Clinical Oncology (CSCO) and Chairman designate of Chinese Anti-Cancer Association, Committee of Breast Cancer Society, took the lead in formulating an expert consensus on HER2 breast cancer. On the 31st July 2022, the consensus expert group held an online meeting to define the consensus on the diagnosis and treatment of HER2 from the detection, neoadjuvant, adjuvant, treatment after metastasis, low expression of HER2, clinical research versus real-world evidence, biosimilars, treatment during public-health emergencies eight aspects, and written by the experts. Finally, the CSCO expert consensus on the diagnosis and treatment of HER2 was formed through discussion and summary of several

online meetings.

Results and discussions

The standardized detection of HER2 (3)

The proper detection and assessment of HER2 protein expression and gene amplification in breast cancer patients are crucial to the clinical treatment and prognostic prediction of patients. Under this circumstance, HER2 testing is required for all newly diagnosed invasive breast cancers and is recommended for recurrent or metastatic lesions whenever it is possible to harvest tumor tissues. Re-testing is particularly valuable if the development of the disease is not characteristics of a HER2-positive breast cancer.

HER2 should be detected with standard immunohistochemistry (IHC) or in-situ hybridization (ISH) in a quality-assured pathological laboratory that places special emphasis on the standardized collection of tissue specimens, the timely and adequate fixation of the specimens in 4% neutral formaldehyde solution, and other standard detection procedures. A HER2 positive status can be either IHC 3+ or fluorescence in-situ hybridization (FISH) positive. For IHC 2+ patients, HER2 gene amplification by ISH or other methods should be further performed. The currently available ISH methods include FISH, chromogenic in-situ hybridization (CISH), and silver-enhanced in-situ hybridization (SISH). Patients with a score of 0 or 1+ are considered HER2 negative.

ISH can also be used to determine HER2 status. The results of a dual-probe ISH can be interpreted as follows: (I) for breast cancers with a HER2/centromere enumerator probe 17 (CEP17) ratio of ≥2.0 and an average HER2 copy number of ≥4.0 signals per cell, the cancer can be considered HER2-positive; (II) for breast cancers with a HER2/CEP17 ratio of <2.0 and an average HER2 copy number of <4.0 signals per cell, the cancer can be considered HER2-negative; (III) for breast cancers with a HER2/CEP17 ratio of <2.0 and an average HER2 copy number of ≥6.0 signals per cell, it is recommended that the number of cells counted be increased, and if the result remains unchanged, the cancer can be considered FISH-positive; (IV) for breast cancers with a HER2/CEP17 ratio of <2.0 and an average HER2 copy number of <6.0 signals per cell but ≥4.0 signals per cell, it is recommended that the signals in at least 20 cell nuclei be re-counted. If the results change, a more comprehensive judgment can be made based on the findings of these 2 counting sessions. If the results remain unchanged, a note should be made in the FISH report that any judgment of the HER2 status for such patients should also consider the IHC findings, such that if the IHC result is 3+, the cancer can be considered HER2-positive, and if the IHC results is 0, 1+, or 2+, the cancer can be considered HER2-negative; (V) for breast cancer with a HER2/CEP17 ratio of ≥2.0 and an average HER2 copy number of <4.0 signals/cell, it is recommended that the number of cells for counting in such cases be increased, if the result remains unchanged, the cancer can be considered FISH negative, and the report should include the following notation, "The evidence from the currently available clinical trials is not sufficient to demonstrate that this group of patients can benefit from HER2-targeted therapies, which warrants further investigations."

Clinically, on the basis of the original definition for HER2-negative breast cancer, patients with HER2 IHC 1+ or IHC 2+ and ISH-negative are defined as low HER2 expression (HER2-low). As both the low expression and the positive expression of the HER2 protein is clinically significant for disease treatment and prognosis, it is recommended that positive and negative controls be added to each staining procedure.

Neoadjuvant treatment for HER2-positive breast cancer

Anti-HER2-based therapies have become the standard treatment for early stage HER2-positive breast cancer. Effective neoadjuvant therapy can achieve a higher pathological complete response (pCR), and pCR patients have longer disease-free survival (DFS) and overall survival (OS) period than non-pCR patients. HER2-positive breast cancer patients who undergo neoadjuvant treatment with trastuzumab plus chemotherapy have significantly higher pCR rates than those who undergo chemotherapy alone. Consequently, trastuzumab has become a basic agent in the neoadjuvant setting. Additionally, expert suggests that dual HER2-target therapy with trastuzumab and pertuzumab combined with chemotherapy further increases the pCR rate of patients with HER2-positive breast cancer.

The NeoSphere study (4), confirmed that adding pertuzumab to trastuzumab and chemotherapy (TH) further increased the pCR rate of HER2-positive patients. The PEONY study (5), validated the NeoSphere findings in an Asian population. The KRISTINE study (6), showed the efficacy and safety of the paclitaxel and carboplatin combined with trastuzumab and pertuzumab (TCbHP)

regimen in a neoadjuvant setting. The PHEDRA study revealed that the total pathologic complete response (tpCR) rate was 41% in the pyrotinib combined with trastuzumab and docetaxel group compared to only 22% in the control group, and the difference between the 2 groups was statistically significant.

As more HER2-positive breast cancer patients receive preoperative neoadjuvant treatment, the subsequent treatments are no longer based on the findings of research on postoperative adjuvant therapy alone. The KRISTINE study showed that patients who achieved a pCR with neoadjuvant TCbHP therapy continued to complete dual HER2-targeted therapy for 1 year after surgery, and their 3-year invasive disease-free survival (iDFS) rate reached 97.5%, while that of patients who did not achieve a pCR was 84.2%. In the KATHERINE study (7), regardless of whether neoadjuvant dual or single HER2-targeted therapy was used, the efficacy of the adjuvant trastuzumab emtansine (T-DM1) therapy was superior to that of trastuzumab in non-pCR patients, and the results of the Chinese subgroup were consistent with those of the general population. Notably, the proportion of patients who received dual HER2-targeted combination chemotherapy before surgery was not high in this study. Additionally, there is a lack of head-to-head studies comparing the efficacy of T-DM1 to that of trastuzumab with pertuzumab (HP) dual HER2-targeted adjuvant therapies. In the ExteNET study (8), the administration of adjuvant treatment with oral neratinib for 1 year within 2 years of completing adjuvant trastuzumab further prolonged patients' iDFS.

Recommendations

(I) Trastuzumab-containing regimens are preferred in the preoperative neoadjuvant therapy for HER2-positive breast cancer. Experts generally believe that dual HER2-targeted therapy with pertuzumab and trastuzumab should be considered for the neoadjuvant treatment of all patients for whom single HER2-targeted therapies are suitable.

(II) Taxane chemotherapy combined with dual HER2-targeted therapy (e.g., 6 cycles of the TCbHP regimen) is preferred. However, 6 cycles of taxane + trastuzumab + pertuzumab (THP) therapy may be appropriate for some patients, such as those aged >60 years with a small tumor load and those who are generally intolerant to platinum-based combination regimens. A clinical study explored another protocol under which surgery was performed after 4 cycles of neoadjuvant treatment with THP, followed by a sequential 3-cycle fluorouracil, epirubicin, cyclophosphamide (FEC) program; however, the clinical feasibility of this protocol (5), remains questionable. The acceptance rate of AC-THP [(anthracyclines + cyclophosphamide) followed by THP] is low among the experts.

(III) There is a lack of head-to-head studies comparing the efficacy of TKI and pertuzumab in neoadjuvant setting. The panel recommends that HP should be the 1st choice for patients receiving neoadjuvant therapy. Based on clinically approved indications, the panel is also of the view that trastuzumab with pyrotinib is an optional regimen in neoadjuvant setting.

(IV) Researchers are encouraged to design clinical studies that meet scientific and ethical requirements [e.g., for the research and development (R&D) of anti-HER2 ADCs].

(V) The pre-planned treatment cycles must be completed during the neoadjuvant therapy for HER2-positive breast cancer. A decision to administer postoperative adjuvant treatment should be made based on the pathological results (i.e., whether the patient achieves or does not achieve a pCR) after completing the standard treatment course and administering the HER2-targeted drugs during the neoadjuvant therapy.

(VI) For patients who received anti-HER2 neoadjuvant therapy before surgery, the postoperative adjuvant therapy strategy should be determined according to the neoadjuvant therapy protocol and the postoperative pathological results. The recommendations are as follows:

  (i) For patients who achieve a pCR with neoadjuvant therapy and use dual HER2-targeted therapy before surgery, the Chinese experts are generally of the view that dual HER2-targeted therapy should be continued after surgery. For patients who only use trastuzumab before surgery, trastuzumab monotherapy may be continued; however, dual HER2-targeted therapy can also be considered based on the results of some clinical studies on postoperative adjuvant therapy.

  (ii) For patients who have not achieved a pCR, if only trastuzumab is used during preoperative anti-HER2 therapy, dual HER2-targeted therapy or T-DM1 can be considered; if dual HER2-targeted therapy has already been used before surgery, T-DM1 is preferred for postoperative adjuvant therapy, during which dual HER2-

targeted therapy can also be considered.

(iii) For patients who do not achieve a pCR after neoadjuvant therapy, HP or T-DM1 is preferred in adjuvant targeted therapy. Sequential neratinib can be considered after the completion of adjuvant targeted therapy with HP; however, there is still a lack of head-to-head clinical data on whether sequential neratinib is feasible in patients who choose T-DM1.

Adjuvant treatment for HER2-positive breast cancer

The addition of trastuzumab to postoperative adjuvant therapy for early stage HER2-positive breast cancer can significantly reduce the risk of recurrence and death, and thus has become a standard targeted therapy for adjuvant treatment of early stage HER2-positive breast cancer. Studies have shown that, in addition to the trastuzumab-containing regimen, concurrent pertuzumab or sequential neratinib within 1 year of trastuzumab therapy can further improve the therapeutic response of some patients.

The HERA study (9), demonstrated that the addition of trastuzumab to chemotherapy significantly improved patient prognosis. The NSABP B-31/NCCTG-9831 study (10), confirmed that anthracycline combined with cyclophosphamide followed by sequential taxanes combined with trastuzumab (AC → TH) was superior to conventional AC → T. The BCIRG 006 study (11), revealed that the TCbH regimen was also superior to AC → T. The APT study (12), reported that patients with small HER2-positive tumors treated with a weekly paclitaxel with trastuzumab (TH) regimen had a 3-year DFS rate of up to 98.7%. For dual HER2-targeted adjuvant therapy, the APHINTY study (13), confirmed for the 1st time that in HER2-positive breast cancer patients at high risk of recurrence, pertuzumab combined with trastuzumab further prolonged iDFS, especially in the node-positive subgroup. The ExteNET study (8), suggested that after 1 year of trastuzumab therapy, sequential neratinib therapy for 1 year improved the iDFS of patients with stage II–III HER2-positive breast cancer; however, the incidence of diarrhea was high, and there was a lack of data on the use of adjuvant therapy with pertuzumab plus trastuzumab for 1 year.

Recommendations

(I) The combination of trastuzumab and pertuzumab with chemotherapy increases cardiotoxicity, and thus its concurrent use with anthracyclines is not recommended; however, it can be used in combination with taxanes or with adjuvant radiotherapy and adjuvant endocrine therapy.

(II) For patients with positive lymph nodes, dual HER2-targeted therapy with pertuzumab plus trastuzumab for 1 year is preferred. AC → THP or TCbHP may be used in adjuvant chemotherapy.

(III) For patients with negative lymph nodes, in principle, single HER2-targeted therapy, such as AC → TH and TCbH should be selected. However, in patients with other high-risk factors (e.g., a tumor >5 cm, negative hormone receptor, and/or a high Ki67 index), dual HER2-targeted adjuvant therapy can also be considered.

(IV) TC+H or a wTH regimen is recommended for patients at low risk of recurrence (e.g., lymph node-negative and a tumor ≤2 cm).

(V) For hormone receptor-positive breast cancer patients who do not need or cannot tolerate chemotherapy, trastuzumab combined with endocrine therapy is an option.

(VI) Dual HER2-targeted therapy is preferred for patients who require an intensified targeted therapy (the panel unanimously agrees on this approach). After standard trastuzumab therapy is completed, sequential neratinib should be administered to high-risk patients. If dual HER2-targeted therapy has been applied in the adjuvant setting, subsequent intensified therapy with neratinib can also be considered.

Treatment of HER2-positive recurrent/metastatic breast cancer

Anti-HER2 therapy has been shown to have significant benefits in patients with recurrent/metastatic HER2-positive breast cancer or patients with stage IV disease at diagnosis, which suggests that anti-HER2-based therapies should be the mainstay of treatment of these patients. A rational combination of targeted therapies should be selected according to each patient's previous medications, hormone receptor status, and general physical performance status.

Trastuzumab-based anti-HER2 therapies

The H0648g and M77001 studies (14), showed that trastuzumab combined with taxane-based chemotherapy significantly prolonged progression-free survival (PFS) and OS, which further validated the role of trastuzumab plus

taxanes as the standard 1st-line therapy for HER2-positive breast cancer. The CHAT study (15), confirmed that, for patients who could tolerate dual-drug chemotherapy, trastuzumab combined with docetaxel plus capecitabine was more efficient than trastuzumab combined with docetaxel, especially in patients requiring maintenance treatment. In the CLEOPATRA study (16), the combination of docetaxel with dual HER2-targeted therapy with trastuzumab and pertuzumab was more effective than the combination of docetaxel with single HER2-targeted therapy with trastuzumab in prolonging PFS and OS. In Monarch HER study (17), it also suggested that a chemotherapy-free regimen might potentially be an alternative treatment option for patients with hormone receptor-positive, HER2-positive advanced breast cancer. In the HOPES study (18), inetetamab plus vinorelbine significantly prolonged PFS in trastuzumab-naïve patients with HER2-positive advanced breast cancer compared to those treated with vinorelbine alone. Clinical studies have shown that a trastuzumab biosimilar (see definition below), which has been approved in China, has the same clinical efficacy as trastuzumab and thus can be used as an anti-HER2 monoclonal antibody in clinical settings.

Anti-HER2 therapy after trastuzumab failure

Several studies (19) confirmed that T-DM1 yielded significant superior benefits in terms of both the PFS and OS compared to lapatinib and capecitabine. The PHENIX study (20) showed that pyrotinib combined with capecitabine was more effective in patients who failed the treatment with taxanes and trastuzumab than capecitabine monotherapy in increasing the overall response rate (ORR) and PFS; however, the patients in the placebo plus capecitabine group who received pyrotinib monotherapy sequentially after disease progression still experienced good benefits. Similarly, the PHOEBE study (21) showed that pyrotinib combined with capecitabine significantly increased PFS compared to lapatinib combined with capecitabine. In the PERMEATE study (22), the ORR of central nervous system lesions reached 74.6% after pyrotinib plus capecitabine treatment in patients with HER2-positive breast cancer brain metastases without local radiotherapy, and in patients with brain metastases that had progressed again after local radiotherapy, pyrotinib plus capecitabine achieved an ORR of up to 41.2%. According to the NALA study (23), neratinib plus capecitabine significantly prolonged PFS compared to lapatinib plus capecitabine in patients with metastatic HER2-positive breast cancer who had undergone ≥2 previous targeted therapies, especially for patients with brain metastasis.

In the DESTINY-Breast01study (24), the anti-HER2 ADC trastuzumab deruxtecan (T-Dxd) produced notable clinical benefits in patients with advanced breast cancer, especially when used in later-line settings. According to the DESTINY-Breast03 study (25), T-Dxd significantly improved PFS and reduced the risk of disease progression or death by 72% compared to T-DM1 after trastuzumab failure, confirming the role of T-Dxd as a 2nd- and later-line treatment after trastuzumab failure. In the SOPHIA study (26), patients receiving margetuximab and chemotherapy had a median increase of 1.8 months in OS compared to those receiving trastuzumab and chemotherapy. The HER2CLIMB study (27), showed that tucatinib combined with trastuzumab plus capecitabine significantly prolonged PFS and OS; in particular, it significantly reduced the risk of disease progression or death in patients with brain metastases.

In the SYSUCC-002 study (28), trastuzumab combined with endocrine therapy was non-inferior to trastuzumab combined with chemotherapy in patients with HR+/HER2+ advanced breast cancer, and had fewer toxicities. Research has also shown that HER2-targeted therapy combined with endocrine therapy + CDK4/6 inhibitors (cyclin-dependent kinases) have certain efficacy.

Recommendations

(I) All patients with HER2-positive recurrent/metastatic breast cancer should be adequately informed of the efficacy and necessity of timely HER2-targeted therapy.

(II) Trastuzumab-based therapy is preferred for trastuzumab-responsive patients. A reasonable combination treatment protocol should be selected according to each patient's hormone receptor status and previous neoadjuvant/adjuvant therapies. The panel preferentially recommends THP however, trastuzumab plus chemotherapy and pyrotinib plus capecitabine are also options.

(III) For patients with a previous history of trastuzumab use, the efficacy of trastuzumab should be assessed. Trastuzumab or its biosimilars may be used if: (i) the previous neoadjuvant therapy was effective; (ii) the tumor recurs 1 year after the completion of adjuvant therapy; and/or (iii) the drug is discontinued after salvage therapy.

(IV) For patients who have failed to respond to trastuzumab

treatment, pyrotinib plus capecitabine is preferred. ADCs, such as T-DM1 and T-Dxd, are options, and other TKIs combined with chemotherapy can also be considered. For pertuzumab-naïve patients, some experts also agree to switch to dual HER2-targeted therapy with trastuzumab and pertuzumab.

(V) As there is currently no clinical standard for the later-line anti-HER2 treatments for patients who have failed to respond to trastuzumab and TKI therapies, the panel suggests a rational decision be made based on the previous use of targeted drugs and their benefits. The options include: (i) T-Dxd; (ii) T-DM1; (iii) a switch to another TKI; (iv) H+P dual HER2-targeted therapy combined with other chemotherapy; and (v) the use of other HER2-targeted drugs that have not been used.

(VI) For HER2-positive/HR-positive recurrent and metastatic breast cancer, anti-HER2 drugs combined with chemotherapy can be considered. For patients for whom chemotherapy is not suitable or for those who have slow disease progression, combinations with endocrine therapy or CDK4/6 inhibitors can also be considered. For patients who have achieved stable disease after HER2-targeted therapy combined with chemotherapy, chemotherapy may be discontinued, and anti-HER2 drugs combined with maintenance endocrine therapy can be considered.

(VII) The anti-HER2 therapy plus chemotherapy should continue for at least 6–8 cycles when it is effective. Based on the therapeutic response and the patient's tolerance to chemotherapy, the chemotherapy may be discontinued and the anti-HER2 drug (antibodies or TKIs) can be used as maintenance therapy. Considering the availability of these drugs in China, the panel recommends that anti-HER2 therapy should not be discontinued arbitrarily.

(VIII) Brain metastases may occur during the treatment of HER2-positive advanced breast cancer. If the extracranial lesions do not progress, the original targeted therapy can be continued after effective local treatment; if necessary, a switch to TKIs can be considered (29).

Low-level expression of HER2 (HER2-low)

In a special subpopulation, HER2-low is associated with specific biological features, and HER2-low patients has shown differences in responses to treatment and prognosis, especially in their treatment resistance and hormone receptor negativity. With the advent of ADCs, more treatment options have become available to patients with HER2-low tumors.

In a phase-I clinical study (24), patients with HER2-low (IHC 2+/ISH– or IHC 1+) advanced breast cancer who had previously received multiple anti-cancer therapies (median: 7.5 therapies) and were then treated with T-Dxd treatment achieved an ORR of 44.2%, a disease-control rate (DCR) of 79.1%, a duration of response (DOR) of 9.4 months, and a median PFS of 7.6 months.

The Destiny-Breast 04 study (30) showed that regardless of hormone receptor status, T-Dxd significantly improved PFS and OS in patients with HER2-low metastatic breast cancer compared to treatment of the physician's choice (TPC). The PFS of the T-Dxd group and TPC group was 10.1 and 5.4 months, respectively. T-Dxd reduced the risk of disease progression or death by 49% in patients with HR-positive/HER2-low metastatic breast cancer. In HR-positive patients, T-Dxd reduced the risk of death by 36% compared to chemotherapy.

Recommendations

For patients with HER2-low disease, standard treatments should be offered according to their hormone receptor status. For hormone receptor-positive patients, endocrine therapy combined with CDK4/6 inhibitor is recommended first. For hormone receptor-negative patients, rational and risk-stratified treatment can be performed according to breast cancer gene (BRCA) status. ADCs can be considered after standard therapy.

The time at which T-Dxd treatment should be initiated in patients with HER2-low lesions remains controversial due to the limited data and inaccessibility of T-Dxd at this moment. However, the panel generally agrees to use T-Dxd treatment in line with the Destiny-Breast 04 study.

Clinical research and real-world evidence

The development of clinical research has greatly optimized the clinical practice for HER2-positive breast cancer and improved the prognosis and survival of patients. Thus, the panel encourages patients at all stages to actively participate in rigorously designed clinical trials.

However, not all clinically questions can be solved by clinical trials. For example, no sponsors will support to design such a randomized clinical trial to compare the use of

T-DM1 versus pyrotinib versus T-Dxd for advanced breast cancer, or the use of dual HER-targeted therapy versus T-DM1 for the treatment of non-pCR patients following neoadjuvant therapy. Thus, the panel is also of the view that clinicians should actively conduct real-world research on HER2-positive breast cancer to help address scientific issues that do not require randomization or are difficult to randomize in clinical settings.

Biosimilars

A biosimilar is a biological product for therapeutic use that is similar in quality, safety and efficacy to a licensed reference medicine (mainly the innovator drugs). It is subject to strict regulatory oversight at the time of marketing, which requires complete pharmaceutical, non-clinical and clinical data to demonstrate its similarity. Thus, there is no clinically significant difference between a biosimilar and its reference medicine in terms of quality, safety, and efficacy. The application of biosimilars can, to a certain extent, increase the availability of drugs and reduce medical costs (31).

Diagnosis and treatment of HER2-positive breast cancer during public-health emergencies

The whole-course management of HER2 breast cancer is even more critical during public-health emergencies. Patients in low-risk areas should adhere to standard treatment regimens. Conversely, treatment plans for patients in high-risk areas should be adjusted reasonably according to local control measures. Currently, a strict "dynamic clearing" policy for COVID-19 pandemic is in place in China. The quiet and rapid spread of the Omicron variant has resulted in scattered COVID-19 outbreaks in many provinces. The community-based control approach for COVID-19 is currently short-term, multi-centered, and unpredictable. Thus, in the event of a public-health emergency, an approach that gives preference to "low-toxicity regimens and oral preparations" should be adopted. HER2 positive breast cancer patients could receive oral preparations like pyrotinib combined capecitabine rather than chemotherapy with dual target therapy during the quarantine. Additionally, modern communication technology and network service platforms (including the CSCO BC artificial intelligence decision-making system, network hospitals, drug transportation cloud platforms, and patient case management system) are essential in ensuring that patients receive standard treatment during home isolation (32).

Conclusions

In the era of precision medicine, the diagnosis and treatment of HER2-positive breast cancer have advanced greatly. The continuously upgraded HER2 detection technology and standardized reading techniques provide a solid foundation for anti-HER treatment. The R&D of new anti-HER2 drugs and advances in clinical research have provided more treatment options and improved patient survival. We have updated this consensus document on the diagnosis and treatment of HER2 breast cancer based on the currently available evidence. The regimens added in HER2 positive especially in metastatic settings and the newly chapter added for HER2 low expression patients give these patients more options compared with last version consensus and guidelines. Yet, the disparities of medical recourses in China, the hard accessibility to novel target drugs and heavy burden of standardized treatment limit the promotion of guidelines and consensuses. With the joint efforts of clinical departments (including pathology and medical imaging departments), scientific and rational multi-discipline treatment may be achieved based on standard tissue and molecular pathology results and clinical experience. Oncologists must follow the treatment guidelines and respect patients' wishes before making treatment decisions at different stages to improve the quality of life of patients and increase their survival rates.

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Footnote

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References

1. CSCO BC, CACA-Breast cancner. Expert consensus on the clinical diagnosis and targeted therapy of HER2 breast cancer(2021 version). Zhonghua Yixue Zazhi 2021;101:1226-31.
2. Jiang Z, Li J, Chen J, et al. Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines 2022. Transl Breast Cancer Res 2022;3:13.
3. Breast Cancer Expert Panel of HER2 testing. Guidelines for Her2 testing of breast cancer (2019). Zhonghua Binglixue Zazhi 2019;48:169-75.
4. 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.
5. Shao Z, Pang D, Yang H, et al. Efficacy, Safety, and Tolerability of Pertuzumab, Trastuzumab, and Docetaxel for Patients With Early or Locally Advanced ERBB2-Positive Breast Cancer in Asia: The PEONY Phase 3 Randomized Clinical Trial. JAMA Oncol 2020;6:e193692.
6. Hurvitz SA, Martin M, Jung KH, et al. Neoadjuvant Trastuzumab Emtansine and Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Three-Year Outcomes From the Phase III KRISTINE Study. J Clin Oncol 2019;37:2206-16.
7. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617-28.
8. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016;17:367-77.
9. 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.
10. 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.
11. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-83.
12. Tolaney SM, Guo H, Pernas S, et al. Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. J Clin Oncol 2019;37:1868-75.
13. Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol 2021;39:1448-57.
14. Rayson D, Lutes S, Walsh G, et al. Trastuzumab beyond progression for HER2 positive metastatic breast cancer: progression-free survival on first-line therapy predicts overall survival impact. Breast J 2014;20:408-13.
15. Wardley AM, Pivot X, Morales-Vasquez F, et al. Randomized phase II trial of first-line trastuzumab plus docetaxel and capecitabine compared with trastuzumab plus docetaxel in HER2-positive metastatic breast cancer. J Clin Oncol 2010;28:976-83.
16. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:519-30.
17. Tolaney SM, Wardley AM, Zambelli S, et al. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised,

open-label, phase 2 trial. Lancet Oncol 2020;21:763-75.
18. Bian L, Xu BH, Di LJ, et al. Phase III randomized controlled, multicenter, prospective study of recombinant anti-HER2 humanized monoclonal antibody (Cipterbin) combined with vinorelbine in patients with HER2 positive metastatic breast cancer: the HOPES Study. Zhonghua Yi Xue Za Zhi 2020;100:2351-57.
19. Beck A, Goetsch L, Dumontet C, et al. Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov 2017;16:315-37.
20. Yan M, Bian L, Hu X, et al. Pyrotinib plus capecitabine for human epidermal growth factor receptor 2-positive metastatic breast cancer after trastuzumab and taxanes (PHENIX): a randomized, double-blind, placebo-controlled phase 3 study. Transl Breast Cancer Res 2020;1:13.
21. Xu B, Yan M, Ma F, et al. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22:351-60.
22. Yan M, Ouyang Q, Sun T, et al. Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases (PERMEATE): a multicentre, single-arm, two-cohort, phase 2 trial. Lancet Oncol 2022;23:353-61.
23. Saura C, Oliveira M, Feng YH, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol 2020;38:3138-49.
24. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020;382:610-21.
25. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med 2022;386:1143-54.
26. Rugo HS, Im SA, Cardoso F, et al. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol 2021;7:573-84.
27. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med 2020;382:597-609.
28. Hua X, Bi XW, Zhao JL, et al. Trastuzumab Plus Endocrine Therapy or Chemotherapy as First-line Treatment for Patients with Hormone Receptor-Positive and HER2-Positive Metastatic Breast Cancer (SYSUCC-002). Clin Cancer Res 2022;28:637-45.
29. Yan Y, Li Q, Li J. Round table discussion: strategies for the treatment of HER2-positive advanced breast cancer in the rising age of antibody-drug conjugates. Transl Breast Cancer Res 2022;3:18.
30. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 2022;387:9-20.
31. Mysler E, Azevedo VF, Danese S, et al. Biosimilar-to-Biosimilar Switching: What is the Rationale and Current Experience? Drugs 2021;81:1859-79.
32. Ge R, Li J, Jiang Z. Key points of breast cancer management under public health emergencies. Transl Breast Cancer Res 2022;3:25.

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