Therapies for Treating HER2-Positive Advanced Breast Cancer

Subjects: Oncology

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The advent of anti-HER2 targeted therapies has dramatically improved the outcome of HER2-positive breast cancer; however, resistance to treatment in the metastatic setting remains a challenge, highlighting the need for novel therapies. The arrival of new treatment options and clinical trials examining the efficacy of novel agents may improve outcomes in the metastatic setting, including in patients with brain metastases. In the first-line setting, the researchers can potentially cure a selected number of patients treated with pertuzumab + trastuzumab + taxane. In the second-line setting, clinical trials show that trastuzumab deruxtecan (T-DXd) is a highly effective option, resulting in a shift from trastuzumab emtansine (T-DM1) as the previous standard of care. Moreover, the researchers now have data for patients with brain metastases to show that tucatinib + trastuzumab + capecitabine can improve survival in this higher-risk group and be an effective regimen for all patients in the third-line setting. Finally, the researchers have a number of effective anti-HER2 therapies that can be used in subsequent lines of therapy to improve patient outcomes.

breast cancer HER2 oncology human epidermal growth factor receptor 2

1. Canadian Perspective and Recommendations

Based on the clinical trial evidence to date and considering the Canadian landscape, the researchers propose a practical treatment sequencing algorithm (**Figure 1**) for metastatic HER2-positive breast cancer in Canada. These recommendations should be seen as suggestions only, and clinical judgment should always be considered. Moreover, it is noted that any relevant Canadian clinical trials should always be considered as an option for all patients with metastatic HER2-positive breast cancer.

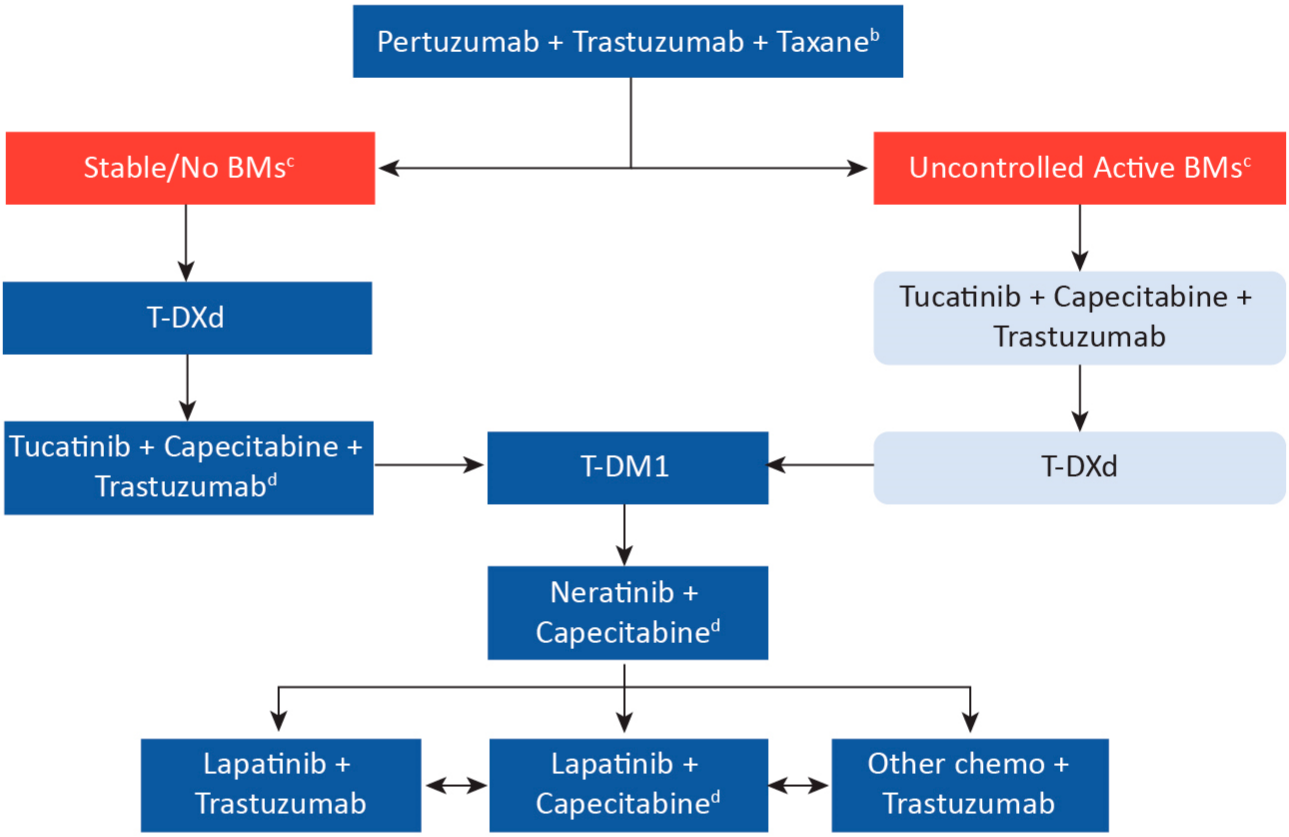

Figure 1. Suggested Treatment Sequence Algorithm for Metastatic HER2-Positive Breast Cancer in Canada Based on Clinical Trial Data [a]. [a] Arrows represent treatment sequencing upon disease progression or toxicity and are suggestions only; clinical judgment must always be considered. Note that clinical data is based on historical treatment sequencing, and there remain data gaps in sequencing (e.g., use of T-DM1 following T-DXd). However, despite gaps in data, continual suppression of HER2 is considered critical. [b] Consider the response length if pertuzumab was used in the neoadjuvant setting. [c] Prior review with radiation oncology should be completed. As per the ASCO 2018 guidelines, patients with symptoms or a history of brain metastases should undergo imaging for brain metastases. However, the researchers would consider baseline brain imaging also for untreated asymptomatic patients. Where local intervention with radiotherapy and/or surgery is not indicated, patients with uncontrolled BMs, or in the minority of patients with BMs and no visceral disease, the researchers recommend tucatinib + capecitabine + trastuzumab. All patients should also be considered for clinical trials. [d] If no previous exposure to capecitabine. BM, brain metastases; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

With improvement to systemic therapies for patients with HER2-positive breast cancer resulting in longer survival, the incidence of brain metastases has increased, developing in up to half of the patients during the course of their disease [1][2][3][4]. Moreover, patients with HER2-positive breast cancer are close to three times as likely to be diagnosed with brain metastases [5]. However, the role of brain imaging in a patient with recurrent disease is controversial, and there is no consensus. According to the ASCO 2018 guidelines for the treatment of patients with HER2-positive metastatic breast cancer, clinicians should not perform routine surveillance for brain metastases without a previous history or indicative symptoms [6]. However, these recommendations are now four years old and

precede the newer evidence from HER2CLIMB, where approximately 50% of all HER2-positive metastatic breast cancer patients had brain metastases at baseline, based on mandated brain magnetic resonance imaging (MRI) screening, with 23% being untreated (unknown) [7][8]. The most recent ESMO guidelines suggest that brain imaging in patients with asymptomatic metastatic HER2-positive breast cancer may be justified if it will alter the treatment course [9]. As the finding of CNS disease may impact both local and systemic therapy, the authors of this manuscript recommend brain imaging at the time of the diagnosis of advanced disease or disease progression to have more comprehensive staging and help tailor treatment. In addition, because of the poor prognosis of patients with brain metastases, it is important to monitor for symptoms throughout the disease course.

2. First-Line Treatment

Based on the results of the CLEOPATRA trial, the researchers recommend that pertuzumab + trastuzumab + a taxane remain the standard of care for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease [10]. However, if patients were previously exposed to pertuzumab in the neoadjuvant/adjuvant setting, it is important to consider the disease-free interval (DFI) when deciding whether to repeat treatment with pertuzumab with evidence of recurrent disease. A DFI of less than 6 months may not warrant re-treatment with trastuzumab + pertuzumab, and the subsequent line of treatment can then be considered. First-line treatment for patients with brain metastases will remain pertuzumab + trastuzumab + a taxane, given the lack of studies examining this patient population in the first-line setting.

3. Second-Line Treatment

T-DM1 was considered the standard of care in the second-line setting in Canada based on the EMILA study [11]. However, T-DM1 is also indicated in the adjuvant setting in Canada for patients who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment [12][13]. Given the results of the DESTINY-Breast03 trial, which reported a significant, large improvement in median PFS with T-DXd over T-DM1, the researchers now recommend T-DXd as the preferred treatment option in the second-line setting.

Patients with Brain Metastases

Penetration of antibody-based anti-HER2 agents, such as trastuzumab, pertuzumab, and ADCs across an intact blood-brain barrier is thought to be limited [14]. However, tucatinib and its metabolites have been shown to effectively distribute to the cerebrospinal fluid [15]. It is of note that HER2CLIMB demonstrated effective treatment with only systemic therapy alone, including tucatinib + trastuzumab + capecitabine, rather than standard local therapies, such as neurosurgical resection and stereotactic (or whole-brain) radiation therapy [7]. This is an area of active research, with novel therapeutics leading to CNS penetrance and effective therapy for brain metastases. As a result of the improvement in outcomes for patients with brain metastases in the HER2CLIMB trial [7][8], the researchers recommend that tucatinib + trastuzumab + capecitabine be favored as second-line treatment in patients with metastatic HER2-positive breast cancer with uncontrolled active brain metastases.

4. Third-Line Treatment

Third-line treatment of metastatic HER2-positive breast cancer and beyond is complicated by a lack of studies examining the efficacy of treatment following novel therapies such as T-DXd, as they were not used in earlier lines of therapy at the time of historical clinical trials. However, the importance of continual HER2 blockade has been established in clinical trials demonstrating the benefit of using trastuzumab beyond progression [16][17]. The researchers believe that, when available, all lines of therapy for metastatic HER2-positive breast cancer should include anti-HER2 agents to maintain ongoing suppression of the HER2 pathway signaling. The availability of five new trastuzumab biosimilars may allow for potential ongoing HER2 blockade in these later line settings [18].

The demonstrated OS improvement with the addition of tucatinib to trastuzumab + capecitabine was documented in the HER2CLIMB trial, which included patients previously exposed to T-DM1 [7][8]. The researchers believe it reasonable to extrapolate from these results to suggest that this combination should be the preferred option in the third-line setting in patients not previously exposed to capecitabine, and previously exposed to an ADC, whether T-DM1 or T-DXd (**Figure 1**). In addition, results from the EMILIA [11] and TH3RESA [19][20] trials suggest that T-DM1 also remains a reasonable option in the third-line setting. However, in patients progressing after T-DXd, the triplet tucatinib + capecitabine + trastuzumab may be preferable to T-DM1, prioritizing a regimen with a different mechanism of action while still leaving T-DM1 for later lines of therapy.

Patients with Brain Metastases

T-DXd is a reasonable third-line option in metastatic patients with active brain metastases who received tucatinib + capecitabine + trastuzumab as second-line therapy.

5. Subsequent Treatments

Based on the results of the TH3RESA trial in metastatic patients with two or more previous lines of therapy, T-DM1 is a reasonable option in this setting [19] (**Figure 1**). Neratinib is preferred over lapatinib in combination with capecitabine based on a demonstrated PFS benefit in the NALA trial, which included metastatic patients with two or more previous lines of therapy [21]. However, other options may be preferable in patients previously exposed to capecitabine. Margetuximab also demonstrated an improvement in PFS over trastuzumab in the SOPHIA trial [22]. As margetuximab is not available in Canada, for patients previously exposed to capecitabine, the researchers would recommend either novel therapies available through clinical trials or continuous trastuzumab combined with other chemotherapies (such as vinorelbine) [23].

6. Summary

In recent years, the development of a number of effective anti-HER2 targeted treatments has revolutionized the treatment landscape in HER2-positive metastatic breast cancer. In the first-line setting, pertuzumab + trastuzumab + taxane provides a durable benefit in a significant proportion of patients. In the second-line setting, clinical trials

show T-DXd is a highly effective option, resulting in a shift from T-DM1 as the previous standard of care. Moreover, the researchers now have data in a subgroup of these patients with brain metastases to show that tucatinib + trastuzumab + capecitabine can improve survival in this higher-risk group and be an effective regimen for all patients in the third-line setting. In addition, the researchers have a number of effective anti-HER2 therapies that can be used in subsequent lines of therapy to improve patient outcomes.

In the future years, the researchers expect to see continued improvements in outcomes with the development of novel anti-HER2 agents, such as the bispecific antibody ZW25 (zanidatamab) and its corresponding ADC, ZW49 (zanidatamab linked with a cytotoxin), as well as the novel ADC, ARX788 (ACE-Breast03; NCT04829604) [24][25]. There are also ongoing trials combining HER2-targeting agents with atezolizumab immunotherapy either in all comers (e.g., NCT03199885) or in patients selected for PD-L1 positive disease (e.g., KATE3; NCT04740918). The researchers are also making strides in their understanding of various HER2-positive subtypes, such as estrogen receptor-positive patients, who may benefit from other types of therapy. For example, results of the monarcHER study demonstrated promising efficacy in this subgroup with abemaciclib, a potent oral cyclin-dependent kinase 4 (CDK4) and 6 (CDK6) inhibitor, combined with trastuzumab + fulvestrant to produce an effective chemotherapy-free regimen [26].

Given the rapid change to the treatment landscape for HER2-positive breast cancer, it has become a priority to accelerate drug approval and access to therapies for patients in Canada. However, it is also critical that clinical trials be designed to produce meaningful outcomes, allowing for more rapid worldwide access. The researchers hope that as newer data emerges, Canadians can access these promising novel agents to provide the best outcomes for patients with metastatic HER2-positive breast cancer.

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