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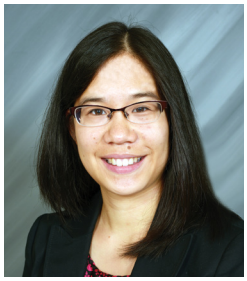

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From Intractable to Treatable: Milestones and Horizons in the Management of HER2+ Breast Cancer

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Introduction

The human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family that initiates various signalling pathways that control cell proliferation and tumourigenesis.[1,2] Historically, approximately 15% of breast cancers have been characterized by overexpression or amplification of HER2, known as "HER2+" breast cancers. This subtype has been associated with an adverse prognosis, along with a high risk of recurrence and worse survival outcomes. However, with the discovery and subsequent development of HER2-targeted therapies, the clinical course of HER2+ breast cancers has fundamentally changed. Optimizing therapeutic strategies using existing and emerging HER2-targeted therapies to build upon these advances remains a major priority for clinical development and treatment delivery.

In 1998, the American Food and Drug Administration (FDA) and Health Canada approved trastuzumab, the first HER2-targeted therapy. Trastuzumab, a monoclonal antibody that binds to the HER2 receptor, has demonstrated clinical activity and improved outcomes in patients with metastatic HER2+ breast cancer when combined with chemotherapy. Following soon after, the first trial of adjuvant trastuzumab (HERA) demonstrated improvements in outcomes when combined with chemotherapy for early HER2+ breast cancer.[3] More than 25 years after its first approval, trastuzumab retains a central role in the treatment of both early and advanced HER2+ breast cancer and has provided a backbone for both new therapeutic combinations (eg. with small molecule inhibitors of HER2) and new classes of therapeutic agents (antibody drug conjugates [ADC]). These successors of trastuzumab are currently redefining the HER2+ treatment landscape in both advanced and early breast cancer.

Metastatic HER2+ Breast Cancer

The current first line treatment of metastatic HER2+ breast cancer, dual antibody therapy with trastuzumab and pertuzumab in combination with a taxane, was established by the CLEOPATRA trial. This study, which was the initial basis for approval of pertuzumab in 2012, demonstrated a significant improvement in both progression-free survival (PFS) and overall survival (OS) with the addition of pertuzumab to trastuzumab and docetaxel, with modest increases in treatment toxicity.[4,5] Shortly thereafter, the ADC trastuzumab-emtansine (T-DM1) displaced lapatinib (a HER2 tyrosine kinase inhibitor [TKI]) and capecitabine in the second line setting, and held this position for nearly a decade (**Figure 1**).

In 2019, a new ADC trastuzumab-deruxtecan (T-DXd) was approved by the FDA after the DESTINY-Breast02 trial showed markedly improved PFS and OS in metastatic HER2+ breast cancer patients who had already received and were resistant to T-DM1 compared to other chemotherapy treatments of physician's choice (PFS 17.8 months for those treated with T-DXd versus 6.9 months for those who received treatments of physician's choice, hazard ratio [HR] 0.36; OS 39.2 months for those treated with T-DXd versus 26.5 months for those who received treatments of physician's choice, HR 0.66).[6] The efficacy of T-DXd, which delivers a topoisomerase I inhibitor payload, was particularly noteworthy, especially given that this class of cytotoxic agent previously had no established

role in the treatment of breast cancer. T-DXd was associated with pneumonitis occurring at a rate of approximately 10% with two reported grade 5 deaths; thus, although T-DXd is certainly a potent treatment agent, its use requires careful monitoring.

T-DXd was then compared to the second line standard T-DM1 in patients who had progressed on a trastuzumab- and taxane-containing regimen in the DESTINY-Breast03 trial, which subsequently led to the approval of T-DXd as a second line treatment. Updated results showed a PFS of 28.8 months with T-DXd and 6.8 months with T-DM1 (HR 0.33), which is the longest reported PFS in the second-line setting.[7]

The DESTINY-Breast03 trial excluded patients with active brain metastases but did include 15% of patients with clinically inactive brain metastases or stable brain metastases that were previously treated and were no longer symptomatic. Within this subgroup, a substantial PFS advantage favouring T-DXd was observed (15 months for those treated with T-DXd versus 5.7 months for those receiving other treatments, HR 0.38), suggesting that T-DXd has intracranial activity in patients with stable brain metastases.[7] These findings, complemented by data from smaller trials, have underscored the significant central nervous system (CNS) activity of this agent. Such an outcome might have been unexpected for a large molecule therapy, given the challenges posed by the blood-brain barrier. This is particularly noteworthy in the context of CNS metastases, which have historically been a challenge for HER2 antibody therapies. Furthermore, preliminary evidence suggests that T-DXd has CNS efficacy in patients with active brain metastases, however, data generation is ongoing.

During the intervening decade, a number of other HER2-directed therapies were evaluated, including both small molecule TKIs (eg. neratinib, tucatinib, lapatinib) and monoclonal antibodies (eg. margetuximab). Among these, tucatinib, when used in combination therapy, has become part of the standard treatment regimen, for its overall efficacy and for its notable effectiveness in patients with brain metastases, as demonstrated in the HER2CLIMB trial. The patients enrolled in this study were heavily pre-treated (a median of four prior lines of therapy) and were randomized to receive tucatinib or placebo in combination with trastuzumab and capecitabine. At one year, the PFS was 33% among patients receiving the tucatinib combination compared to 12% among patients not receiving tucatinib. Specifically, among patients with brain metastases, the 1-year PFS rate was 25% in the group treated with tucatinib compared to 0% without tucatinib.[8]

These data can be viewed in the context of previous examinations of HER2 TKIs including neratinib and lapatinib, which demonstrated some intracranial activity in combination with capecitabine in small single-arm phase II trials. Response rates were variable, although some patients did achieve a prolonged clinical benefit. Most of these patients were previously treated with trastuzumab (not T-DM1) and other chemotherapy agents. Although prospective trials of T-DM1 excluded patients with active brain metastases, at least some intracranial activity has also been reported in subsequent case series and trials. Therefore, the intracranial activity of neratinib and lapatinib when used after T-DM1 and tucatinib is not known. Moreover, the intracranial activity of tucatinib, neratinib, and lapatinib have never been directly compared.

The most recently reported phase III trial for advanced HER2+ breast cancer is the HER2CLIMB-02 trial, which evaluated T-DM1 against T-DM1 in combination with tucatinib as a second-line treatment. Primary results presented at the 2023 San Antonio Breast Cancer Symposium (SABCS) showed an improvement in PFS that met the primary endpoint. However, the initial data for OS, while immature, demonstrate a numerical advantage for the placebo arm.[9] Considering these findings and the established role of T-DXd in the second-line setting, the major application of tucatinib is likely to remain in combination with trastuzumab and capecitabine following T-DXd. However, in selected situations, such as for patients with active brain metastases, limited extracranial disease burden, or contraindications to T-DXd, this combination may serve as an alternative to the general approach.

Advancements in systemic treatments for CNS involvement are reshaping clinical management strategies for brain metastases, which have traditionally relied on surgery and radiation therapy (either stereotactic or whole-brain). The optimal integration of these approaches, however, necessitates the generation of prospective evidence to inform evidence-based guidelines. Meanwhile, the prognosis of patients with leptomeningeal disease (LMD) has not changed significantly over the last decade, which calls for increased attention. Limited data

Figure 1. Approval of anti-HER2 therapies; *courtesy of Meredith Li, MD and David W. Cescon, MD*

exist for both T-DXd and tucatinib combinations in LMD. The CLIMB-LMD trial (NCT06016387) is a Canadian investigator-initiated study evaluating the efficacy of radiation therapy followed by tucatinib, trastuzumab, and capecitabine in patients with HER2+ LMD in any line of treatment.

Looking Forward

Despite these developments, there is still a significant amount of work required to refine clinical management with existing agents and to develop the numerous new agents currently under investigation. Several trials are currently underway to challenge the first-line standard treatment of trastuzumab, pertuzumab and taxane. The DESTINY-Breast09 trial (NCT04784715) is evaluating T-DXd with or without pertuzumab in this context. Given the proven efficacy of T-DXd in later lines of treatment, this trial is important. However, the potential tolerability benefits of maintenance therapy with trastuzumab and pertuzumab need to be balanced against the more toxic profile of T-DXd. Additionally, while the primary endpoint is PFS, understanding the impact on OS, and ensuring adequate delivery of second-line T-DXd in the study population, will be crucial to assess the true impact of this strategy. Alternative maintenance regimens following induction with taxane, trastuzumab, and pertuzumab are also being evaluated, such as the addition of tucatinib in the HER2CLIMB-05 trial (NCT05132582), the phosphatidylinositol 3-kinase (PI3K) inhibitor inavolisib for PI3K-p100α (PIK3CA) mutated disease in the INAVO122 trial (NCT04191499), or novel endocrine agents.

At the other end of the spectrum, there are a large number of investigational anti-HER2 therapies being evaluated principally for drug resistant disease. Understanding the mechanisms of resistance to established agents and how to prioritize the development of new agents based on identifiable biomarkers is likely to be important for this increasingly complex therapeutic arena.

Early HER2+ Breast Cancer

The evolution of systemic therapy for early HER2+ breast cancer has followed a general approach of de-escalating therapy for low-risk patients and escalating therapy for higher-risk patients. Identification of low-risk disease has principally been based on anatomic stage (small tumour size and node negativity), while escalation strategies have taken advantage of response assessment to neoadjuvant therapy and the prognostic value of residual disease after pre-operative antibody-based chemotherapy combinations.

In the single arm phase II APT trial, patients with resected small (<3 cm) node-negative HER2+ cancers were treated with single-agent paclitaxel rather than multiagent chemotherapy and trastuzumab to complete one year of treatment. After a median follow-up of 10 years, the safety profile remained excellent, and breast cancer specific survival was a remarkable 98.8%, confirming this de-escalated regimen as the standard of care for patients with low-risk/node negative disease.[10]

The phase II NeoSphere trial included patients with higher risk (>2cm or node positive) HER2+ early breast cancer. The findings indicated that dual HER2 blockade with trastuzumab and pertuzumab in combination with chemotherapy significantly improved the rate of pathologic complete response (pCR) compared to trastuzumab and chemotherapy (45.8% vs 29% in the trastuzumab group).[11] Consistent with the recognized prognostic association of pCR in HER2+ breast cancer, patients from any treatment group who achieved a pCR had a longer PFS than those who did not achieve a pCR. Notably, PFS was numerically improved at five years (HR 0.69). However, this difference was not statistically significant because the study was not powered to definitively assess this secondary endpoint.[12]

The improvements in pCR rates achieved with neoadjuvant dual HER2 blockade allows for

the avoidance of an adjuvant course of T-DM1, which is currently the standard treatment for patients with residual disease. This approach was established by the KATHERINE trial, which demonstrated improved outcomes compared to completing adjuvant trastuzumab for patients who had residual invasive cancer following neoadjuvant therapy. The trial found that T-DM1 reduced the risk of invasive disease recurrence at 3 years by 50% compared to trastuzumab (invasive disease-free survival [iDFS] was 88.3% in the T-DM1 group and 77% in the trastuzumab group). Furthermore, distant recurrence as the first invasive disease event occurred in 10.5% of patients in the T-DM1 group compared to 15.9% in the trastuzumab group.[13] Based on these results from the KATHERINE trial, T-DM1 was approved for adjuvant use by the FDA and Health Canada in 2019, establishing this adjuvant regimen and solidifying the neoadjuvant approach necessary for its delivery.

Within the framework of neoadjuvant response-guided use of adjuvant T-DM1, several unanswered questions remain, particularly concerning the role of pertuzumab in patients who achieve a pCR. The APHINITY trial compared 1 year of adjuvant pertuzumab and trastuzumab with trastuzumab alone in patients with node-positive or high-risk node-negative HER2+ breast cancer. The trial demonstrated an improved iDFS at six years (91% versus 88%, respectively).[14] The benefit was mostly driven by the node-positive cohort; the node-negative cohort derived no benefit. The interim survival analysis also did not reach statistical significance for benefit. Whether the impact of an adjuvant course of pertuzumab can be extrapolated to the subset of patients who achieve a pCR with neoadjuvant therapy who continue with trastuzumab is unknown.

Ongoing Development of Adjuvant Therapy for Residual Disease

Given the improvements observed with newer HER2 therapies for metastatic disease, there has been substantial interest in evaluating these agents in early breast cancer. In particular, T-DXd and tucatinib have been a focus of such efforts, with ongoing phase III trials underway. In addition to improving overall outcomes with the delivery of more effective therapy, the CNS activity of these agents offers the hope that CNS recurrences, which comprise 7% of distant recurrences,[15] can be reduced.

While residual disease has been useful to identify patients for treatment with adjuvant T-DM1, this strategy nevertheless results in overtreatment of a considerable proportion of patients, especially considering that the distant recurrence-free survival at 7 years for participants treated with adjuvant trastuzumab was 78.5%. An update of the KATHERINE trial presented at the SABCS 2023 showed that the subgroup of patients with small residual disease up to ypT1b and ypN0 (<1 cm and negative axillary lymph nodes) did have a meaningfully improved iDFS at 7 years with T-DM1 (85.7%, T-DM1 versus 76.7%, trastuzumab), though no difference in OS has been observed in this exploratory subset.[15] Escalating beyond T-DM1 creates further potential overtreatment. Therefore, improving outcomes necessitates identification of the subpopulations at higher risk. The extent of residual disease, as discussed earlier, remains strongly prognostic and other clinical features such as ER (estrogen receptor) status (iDFS 83.1% for ER+ versus 75.0% for ER- disease), and HER2 score (iDFS 82.8% for IHC 3+ versus 72.4% for IHC 2+) are associated with outcomes following adjuvant T-DM1.[15] Diagnostic tools employing tumour-based gene expression analysis, similar to those employed

for ER+/HER2-negative disease, are currently under development.[16] and may offer an additional opportunity to refine risk estimates.

Recent advances in technologies for the detection of circulating tumour DNA (ctDNA) in "liquid biopsies" present an additional opportunity to individualize treatment escalation for adjuvant therapy.[17] Highly sensitive and specific ctDNA tests, designed expressly for this purpose, can detect ctDNA "molecular residual disease" (MRD) in patients prior to clinical recurrence. Retrospective analyses have demonstrated that such detection may risk stratify individuals with residual disease, and that the detection of ctDNA (in the absence of a subsequent change in therapy) is associated with an extreme risk of recurrence. Such assays thus enable the development of strategies to identify and "intercept" recurrences with treatment escalation and can also provide a measurable surrogate of disease that may reflect treatment response.

We are actively exploring this question through the KAN-HER2 MRD (NCT0538814) trial, a phase II study enrolling patients with pathological residual disease following neoadjuvant therapy who are recommended standard adjuvant T-DM1 therapy. In the initial 4 to 6 cycles of T-DM1 therapy, participants are monitored using ctDNA surveillance via a tumour-informed assay. If MRD is detected, their treatment regimen is intensified by adding neratinib (for up to one year) alongside T-DM1 therapy. The primary efficacy outcome for this proof-of-concept study is the clearance of ctDNA, with secondary outcomes of invasive breast cancer-free and distant metastasis-free survival. The findings from this trial are expected to yield significant insights into the effectiveness of this therapeutic combination as well as the feasibility and performance of ctDNA monitoring in this patient population.

Summary

Once a breast cancer subtype linked with a poor prognosis, HER2-positive breast cancer has become highly treatable over the past two decades owing to the advent of HER2-targeted therapies. It is crucial to note, however, that HER2+ breast cancer is a heterogeneous disease in today's clinical context. Therefore, future treatment strategies must be tailored to each individual's disease biology and the clinical behaviour of their disease. Achieving optimal clinical outcomes while minimizing treatment-related toxicities calls for the development and application of precise diagnostic tools to accurately assess each individual's risk, and the selection among available therapies requires a refined understanding of predictive biomarkers for these treatments. Finally, ongoing development of new therapeutic agents necessitates a deeper insight into tumour evolution and resistance mechanisms, advancing the groundwork laid by the introduction of trastuzumab.

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Financial Disclosures

M.L.: None declared.
D.C.: None declared.

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