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Current Management and Future Perspectives in Metastatic *HER2*-Positive Breast Cancer

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ABSTRACT

Objective: Metastatic *HER2*-positive breast cancer remains a significant clinical challenge with a poor prognosis. The introduction of anti-*HER2* therapies has significantly improved survival in early and advanced stages. However, patients with metastatic *HER2*-positive breast cancer eventually experience progression due to de novo or acquired resistance. This review article comprehensively analyzes the current management of metastatic *HER2*-positive breast cancer, addressing the complexities in determining the optimal *HER2*-targeted therapy sequence.
Data Sources: Discussion of selected peer-reviewed articles and expert opinion.
Conclusions: We explore the actual standard of care and the emerging therapeutic options that hold promise for further improving patient care and survival in this aggressive breast cancer subtype. This article highlights vital toxicities linked to anti-*HER2* therapies, emphasizing their recognition across treatments as interstitial lung disease, diarrhea, or left ventricular dysfunction.
Implications for Nursing Practices: Oncology nurses have a key role to play in detecting potential adverse effects of anti-*HER2* therapies. The development of new drugs, as antibody–drug conjugates, with a distinct toxicity profile makes it necessary for us to be updated on the management of these new toxicities.

Introduction

The authors discuss the significant advancements in treatments for *HER2*-positive metastatic breast cancer (MBC), focusing on targeted therapies and antibody–drug conjugates (ADCs). Various clinical trials and studies, such as DESTINY-Breast01 and DESTINY-Breast03, are highlighted to demonstrate the impact of novel therapies on patient outcomes. We also discuss the use of classic *HER2* therapy and the newer-generation ADCs and their unique mechanisms of action in the context of *HER2*-positive MBC treatment. The text contributes by summarizing and contextualizing recent clinical trial findings, providing a comprehensive overview of the evolving treatment landscape for *HER2*-positive MBC. It emphasizes the need for ongoing research to understand resistance mechanisms, identify new therapeutic targets, and explore combination therapies and immunotherapy approaches. The text underscores the essential role of oncology nurse specialists in the care of *HER2*-positive breast cancer (BC) patients, highlighting their involvement in patient education, emotional support, and treatment coordination.

BC is the most prevalent malignancy in females, with approximately 13% of women at risk of diagnosis during their lifetime.[1] About 15–20% of BC cases exhibit overexpression of human epidermal growth factor receptor 2 (HER2), a transmembrane receptor tyrosine kinase.[2] This BC subtype is clinically and biologically heterogeneous, with around 50% of cases also expressing estrogen and/or progesterone receptors (ER/PR).[3] Before the development of anti-*HER2* therapies, this disease was associated with an increased risk of systemic and brain metastases, leading to poor overall survival (OS) as it is associated with worse prognosis compared to other metastatic sites.[4] Despite significant treatment advances, approximately 15–24% of *HER2* BC patients will develop metastatic disease after completing curative-intent treatment, and 3–10% will present with de novo metastatic disease.[5,6] The incorporation of anti-*HER2* therapies trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1), and lapatinib in the metastatic setting has resulted in a median OS of approximately 5 years, with nearly 30-40% of patients achieving 8 years of survival.[7]

The dual blockade with trastuzumab and pertuzumab as first line remains the standard of care in the metastatic setting.[8] The introduction of novel *HER2*-targeted monoclonal antibodies, tyrosine kinase inhibitors (TKI), and ADCs has led to a dramatic shift in the clinical outcomes for *HER2*-positive advanced BC (ABC) patients in recent

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years, revolutionizing the treatment paradigm for the disease. Significantly, the emergence of new-generation ADCs has yielded unparalleled outcomes in comparison to T-DM1, establishing trastuzumab deruxtecan (T-DXd) as the new second-line standard of care.

This review explores current and emerging treatments for *HER2*-positive ABC and the role of nurse's role in this context. It examines existing management strategies and promising future perspectives to improve patient care and outcomes, with a special emphasis on anti-*HER2* drugs with high intracranial activity that has represented one of the major improvements.

Current Management of Advanced *HER2*-Positive Breast Cancer

In cancer treatment, first-line chemotherapy is the primary course of therapy prescribed initially to fight the disease, while second-line chemotherapy is a secondary treatment used if the cancer does not respond or if it returns after the initial treatment.

First-Line

Trastuzumab, pertuzumab plus taxane

The triplet of pertuzumab, trastuzumab, and chemotherapy (usually a taxane) is the standard first-line treatment for most patients with *HER2*-positive ABC, based on the results of the CLEOPATRA trial.[8] This phase III trial compared trastuzumab and docetaxel with pertuzumab or placebo as first-line treatment in *HER2*-positive ABC. The pertuzumab group demonstrated a statistically significant progression-free survival (PFS) increase (Table 1). Notably, with over 8 years of follow-up, the dual *HER2* blockade led to a significant increase in OS, with a median OS of 57.1 months in the pertuzumab group vs. 40.8 months in the placebo group. Pertuzumab group reported higher toxicities like diarrhea (67%), febrile neutropenia (14%), or rash (34%). Despite pertuzumab not increasing the risk of left ventricular dysfunction, even in the long-term analysis, adherence to guidelines and regular cardiac monitoring remain crucial.[8-10]

Paclitaxel is also a valid alternative for these patients, supported by the PERUSE trial, a phase IIIb study comparing either docetaxel, paclitaxel, or nab-paclitaxel with trastuzumab and pertuzumab[11] (Table 1).

It is important to highlight that despite 10% of patients included in the CLEOPATRA trial receiving trastuzumab in early disease, the efficacy of the regimen did not appear to be compromised in those patients, even in early relapses.[8] However, there is a lack of data regarding the benefit of this triple therapy in patients who received prior pertuzumab or TDM-1 in the adjuvant setting.

Another important consideration is that the CLEOPATRA trial did not allow maintenance endocrine therapy. In HR-positive BC, *HER2*-positivity is known to be associated with endocrine resistance.[12] However, emerging evidence suggests that inhibiting the *HER2* pathway can potentially restore hormone sensitivity.[13] The dual *HER2* blockade in combination with endocrine therapy has been explored in the PERTAIN and ALTERNATIVE trials,[14,15] and it is considered as a reasonable maintenance therapy after completion of chemotherapy or even a first-line treatment option for patients who are not candidates for chemotherapy.[16]

Second-Line

Trastuzumab deruxtecan (T-DXd)

T-DXd is a stable ADC in plasma, linking an *HER2*-targeting antibody to a topoisomerase I inhibitor, deruxtecan, through a cleavable tetrapeptide-based linker. This yields a high drug:antibody ratio of 8. The payload can cross the cell membrane and diffuse to neighboring cancer cells, intensifying its cytotoxic impact through the bystander effect.[17]

Initially tested in heavily pretreated *HER2*-positive ABC patients, the single-arm phase II study DESTINY-Breast01 led to worldwide regulatory approvals.[18] In phase III DESTINY-Breast02, T-DXd notably enhanced PFS as a third-line therapy post T-DM1 progression compared to capecitabine + lapatinib or capecitabine + trastuzumab in *HER2*-positive ABC.[19] After highlighting third-line benefits, DESTINY-Breast03 compared T-DXd to T-DM1 in second-line after first-line trastuzumab, pertuzumab, and taxane–based chemotherapy (62% were previously treated with pertuzumab), achieving substantial improvements in PFS, objective response rates (ORR), and OS in the second interim analysis (Table 1).[20,21] The most common adverse events grade 3 or higher were neutropenia (20.7%), anemia (8.7%), and nausea (7.6%). Twenty-five patients (13.6%) experienced T-DXd–associated interstitial lung disease (ILD). Although the majority of these ILD cases were of grade 1 or 2 severity, it is important to note that there were four deaths (2.2% of patients) attributed to ILD.[20,21]

Later Lines and Future Perspectives

A diverse range of drugs are available for patients with trastuzumab, pertuzumab, and ADC–pretreated *HER2*-positive ABC. All these drugs are accessible in the US, but, regrettably, not in Europe and the UK. The disparities in the availability of *HER2* BC drugs arise from a variety of factors, including regulatory procedures, pricing, and reimbursement policies.

TDM-1

Until 2021, T-DM1, the first approved ADC, was the *HER2*-positive ABC standard second-line treatment. Its structure merges trastuzumab and an average 3.5 maytansine molecules per antibody linked via a stable thioether linker.[22] T-DM1's approval derived from the EMILIA trial, a phase III study comparing it with lapatinib + capecitabine in *HER2*+ ABC patients pretreated with trastuzumab and taxanes.[23] This trial demonstrated a statistically significant PFS and OS improvement (Table 1). The ORR was also greater for TDM-1: 43.6% vs. 30.8% for the control arm.[24] The most common grade 3 or greater adverse effects of T-DM1 include thrombocytopenia and elevated aminotransferases. Thrombocytopenia usually occurs in the first two cycles and can be managed with dose adjustments. The rate of bleeding is higher in T-DM1 compared to capecitabine and lapatinib, but serious bleeding events are rare (1–2%).[18] Significant cardiotoxicity is also infrequent in patients treated with T-DM1.[23,24]

In the TH3RESA trial, T-DM1 significantly improved treatment of physician's choice (TPC) in terms of PFS and OS in *HER2*-positive ABC pretreated with ≥2 anti-*HER2* lines[25,26] (Table 1). The study enrolled patients with treated and asymptomatic central nervous system (CNS) metastases, also favoring increased outcomes in this subset.[25,26] In the first-line setting, the phase III MARIANNE trial found that neither T-DM1 monotherapy nor its combination with pertuzumab showed superiority in terms of PFS compared to the trastuzumab plus taxane chemotherapy combination.[27] (Table 1). A limitation of this trial is its 2009 design, when trastuzumab and taxane was standard vs. the current dual blockade with taxane.[8,27]

Tucatinib

Tucatinib, a potent reversible HER2 tyrosine kinase inhibitor, was tested in the phase II HER2CLIMB trial, comparing it with placebo, along with trastuzumab and capecitabine. This included *HER2*+ ABC patients previously treated with trastuzumab, pertuzumab, and T-DM1. Patients with brain metastases were eligible except for those requiring immediate local intervention. There was a significant

TABLE 1
Efficacy of *HER2*+ Drugs in Prospective Clinical Trials in ABC and Brain Metastases Across.

Trial	Phase	Drug	Line	Treatment	Study Population	Brain Metastases	ORR	mPFS	mOS
CLEOPATRA[8]	3	P	First line metastatic	Docetaxel + T + P vs docetaxel + T	808	Not included	80%	18.5 vs. 12.4 months (HR 0.62; 95% CI: 0.51−0.75; $P < .001$)	57.1 vs. 40.8 months (HR 0.69; 95% CI: 0.58−0.82; $P < .0001$).
PERUSE[11]	3b	P	First line metastatic	Taxane (A: docetaxel, B: paclitaxel, or C: nab-paclitaxel) + T + P	1436	Treated	79%	19.4 (95%CI: 16.9−22.1), 23,2 (95% CI: 19.6−25.6), and 19.2 (95% CI: 11.7−37.1) months, respectively	66.5 (95% CI: 61.7−77.3), 64 (95% CI: 56.6−72.2), 70.9 (95% CI: 39.7−NE) months, respectively
PERTAIN[14]	2	P	First line metastatic	Taxane + T + P- > AI vs taxane+ T- > AI	129	Treated	63.3%	20.6 vs. 15.8 months (HR 0.67; 95% CI: 0.50−0.89; $P = .006$).	60.2 vs. 57.2 months (HR 1.05; 95% CI: 0.73−1.52; $P = .78$).
MARIANNE[27]	3	T-DM1	First line metastatic	Taxane + T vs. T-DM1 vs. T-DM1 + P	1095	Not included	82.6% for T-DM1	13.7, 14.1, and 15.2 months for the T + taxane, T-DM1 (HR 0.91; 97.5% CI 0.73−1.13; $P = .31$), and T-DM1 + P groups (HR 0.87; 97.5% CI: 0.69−1.08; $P = .14$).	50.9, 53.7, and 51.8 months for the T + taxane, T-DM1 (HR 0.93; 97.5% CI 0.73−1.20), and T-DM1 + P groups (HR 0.86; 97.5% CI: 0.67−1.11).
EMILIA(23)	3	T-DM1	Second line metastatic	T-DM1 vs. L + C	991	95 (45 T-DM1/50 L+C)	43.6%	9.6 vs. 6.4 months (HR 0.65; 95% CI: 0.55−0.77; $P < .001$)	29.9 vs. 25.9 months (HR 0·75; 95% CI: 0.64−0.88)
TH3RESA[26]	3	T-DM1	Third line metastatic or more	T-DM1 vs. TPC	602	67 (40 T-DM1/27 TPC)	31%	6.2 vs. 3.3 months (HR 0.528; 95% CI: 0.42−0.66; $P < .0001$)	22.7 vs. 15.8 months (HR 0.68; 95% CI: 0.54−0.85; $P = .0007$)
DESTINY BREAST 03[21]	3	T-DXd	Second line metastatic	T-DXd vs. T-DM1	261	82 (39 T-DM1/43 T-DXd)	79%	28.8 vs. 6.8 months (HR 0.33; 95% CI: 0.26−0.43; $P < .0001$)	Data not mature
HER2CLIMB[28]	2	Tu	Third line metastatic or more	C + T + Tu vs C + T	612	291 (198 C + T-Tu/93 C + T)	40.6%	7.6 vs. 4.9 months (HR 0.57; 95% CI: 0.47−0.70; $P < .00001$)	24.7 vs. 19.2 months (HR 0.73; 95% CI: 0.59−0.90; $P .004$)
NALA[30]	3	N	Third line metastatic or more	N + C vs. L + C	621	101 (51 N + C/50 L + C)	32.8%	8.8 vs. 6.6 months (HR 0.76; 95% CI: 0.63−0.93; $P = .0003$)	24 vs 22.2 months (HR 0.88; 95% CI: 0.72−1.07; $P = .2098$)
SOPHIA[31]	3	M	Third line metastatic or more	Ch + M vs Ch + T	536	Treated	22%	5.8 vs, 4.9 months (HR 0.76; 95% CI: 0.59−0.98; $P = .033$)	21.6 vs. 21.9 months (HR 0.95; 95% CI: 0.77−1.17; $P = .62$)

Abbreviations: AI, aromatase inhibitor; C, capecitabine; Ch, chemotherapy; L, lapatinib; M, margetuximab; ORR, median overall response rate; mOS, median overall survival; N, neratinib; NE, not estimable; P, pertuzumab; T, trastuzumab; TD, trastuzumab duocarmazine; Tu, tucatiniband; TPC, treatment of physician's choice.

increase in median PFS and OS for the experimental arm (Table 1).[28] Among the patients with brain involvement at inclusion, tucatinib-based arm showed 25% 12-month PFS, compared to 0% in the control arm. The triplet was well tolerated, displaying minimal discontinuation due to adverse events.[28] At the 2023 ASCO Congress, a retrospective cohort study was presented, in which tucatinib, trastuzumab, and capecitabine show significant efficacy for patients with *HER2*-positive ABC previously exposed to T-DXd.[29]

Neratinib

Neratinib is an irreversible pan-HER tyrosine kinase inhibitor (HER1, HER2, and HER4). The approval in the US was based on the NALA trial, a phase III trial designed to compare neratinib vs. lapatinib both in combination to capecitabine, in patients who received at least two prior anti-*HER2* regimens.[30] There was a modest improvement in PFS and substantial toxicity without OS benefit (Table 1). The most common grade 3 or 4 adverse events were diarrhea (24.4%), which was most common during cycle 1, nausea (4.3%), and vomiting (4%).[30]

Margetuximab

Margetuximab is a fragment crystallizable engineered anti-HER2 receptor monoclonal antibody evaluated in the phase III SOPHIA trial. The trial compared the clinical efficacy of margetuximab vs. trastuzumab, each with TPC in patients pretreated with ≥2 anti-*HER2* lines. There was a modest improvement in PFS without significant OS benefit (Table 1).[31]

Future Perspectives

While *HER2*-positive breast cancer management has advanced remarkably in the past few decades, challenges like treatment resistance, side effects, and costs persist. Future research should unravel resistance mechanisms, find new targets, and explore combination therapies and immunotherapy. Implementing precision medicine and biomarker-guided strategies could significantly enhance outcomes.

Nursing Implications

Nurses play a key role providing comprehensive care to *HER2*-positive ABC patients, from diagnosis to long-term survival, by collaborating with a multidisciplinary team, coordinating the treatment plan, and ensuring timely and appropriate care.[32]

Specialist nurses must provide patients with information about their disease and treatment. They assist both the patient and their family in understanding the illness and making informed decisions about their care. This continuous education empowers the patient to manage their health better through ongoing dialogue between the nurse and the patient. The approach should enable full patient participation as partners in their own care, capable of weighing options and making important decisions.[33]

The introduction of new ADCs for the treatment of *HER2*-positive ABC has heightened our awareness of treatment associated toxicities. For example, in the T-DXd clinical trials, the most common adverse events included nausea, vomiting, alopecia, diarrhea, left ventricular dysfunction, and thrombocytopenia.[18] Notably, approximately 10−12.5% of patients receiving T-DXd developed ILD, a diverse group of pulmonary disorders characterized by lung inflammation and/or fibrosis. ILD onset typically occurred 5−6 months after treatment initiation, with an overall fatality rate of 1.9−2.2%.[18,34] We consider this adverse event very significant as it can lead to an early treatment discontinuation.

Several risk factors for T-DXd−induced ILD have been identified, such as advanced age (≥60 years), preexisting lung disease, concurrent radiation, smoking, renal failure, and specific genetic predispositions, notably among individuals of East Asian ethnicity, particularly in Japan.[35-37]

Dyspnea is the most common manifestation, often accompanied by symptoms like cough, discomfort, chest pain, hypoxemia, and fever.[38] These clinical symptoms correlate with abnormal pulmonary function test results and radiological findings of unilateral or bilateral pulmonary infiltrates on thoracic imaging.[38,39]

Regular monitoring during clinic visits is essential, including oxygen saturation (SpO_2) measurement and symptom assessment. Patient education regarding risk factors and symptom recognition should be emphasized. Oncology nurses should encourage self-monitoring for new-onset cough or change in exercise tolerance. Patients with a decrease in SpO_2 at rest of 2−4% for 1−3 days measured as a continuous variable at home, or a decrease in SpO_2 after exertion of 2−5% for 1−7 days, should be examined for ILD.[40] Long-term potential complications of ILD encompass the development of pulmonary fibrosis, pulmonary hypertension, small airways disease, or congestive heart failure.

Gastrointestinal toxicity, manifesting as diarrhea, is a common side effect of anti-*HER2* therapies. Diarrhea management involves distinct approaches based on onset. Early-onset diarrhea, linked to cholinergic response, can be addressed with atropine. For late-onset diarrhea, a progressive loperamide regimen, from 4 mg to a maximum of 16 mg, is effective. Otherwise, if not resolved in 48 hours from loperamide assumption, octreotide is a recommended intervention.

Additionally, the nurse provides emotional support to both the patient and their family, as a cancer diagnosis can be emotionally overwhelming. Patients' quality of life can be affected physically, physiologically, and functionally.[41] Issues such as depression and anxiety can arise due to the distress of the diagnosis, fear of disease progression, and death.

Conclusion

The management of *HER2*-positive metastatic breast cancer remains an area of active investigation. As research advances, promising new approaches for both prevention and treatment are emerging, alongside the need to identify and manage new adverse events. Oncology nurse specialists in breast cancer play a crucial role in the care of *HER2*-positive breast cancer patients by providing comprehensive care, education, emotional support, and coordination of their care process.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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