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Superiority of Enhertu: A Question to be answered

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ABSTRACT

Approximately 20% of metastatic breast cancers are characterized by overexpression or amplification of human epidermal growth factor receptor 2 (HER2). Trastuzumab emtansine is the standard treatment for patients with HER2 –positive metastatic breast cancer whose disease progresses after treatment with a combination of anti-HER2 antibodies and a taxane. The recent approval of trastuzumab deruxtecan (Enhertu) based on phase 3, multicenter, open-label, randomized trial which compared the efficacy and safety of trastuzumab deruxtecan (a HER2 antibody-drug conjugate) with trastuzumab emtansine. In the present mini-review, we discuss recent findings of clinical studies concerning the pros and cons of Enhertu.

Key words: Metastatic breast cancer, Trastuzumab emtansine, Trastuzumab deruxtecan

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INTRODUCTION

In 2020, there were 685,000 breast cancer deaths worldwide and 02.3 million new cases among women. Breast cancer is the most common cancer in the world, affecting 7.8 million women alive as of the end of 2020. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life [1].

In general, treatment modalities include surgery, chemotherapy, radiation, molecular targeted therapy, and most recently immunotherapy. However, many of the current therapies used within the clinic today cannot target tumor cells specifically and therefore are administered in large doses to eliminate residual breast cancer cells. Unfortunately, this approach usually leaves the patient with poor quality of life due to harmful off-target side effects resulting from a lack of treatment specificity. Trends for research and development of novel therapeutics have shifted from conventional targeting of cancer cells with cytotoxic agents to a more targeted approach that relies on the concept of oncogene addiction [2] and the development of antibody-drug conjugates composed of a cytotoxic agent and a monoclonal antibody carrier [3].

Metastatic breast cancer and treatment

Up to 20 percent of women with breast cancer have tumors that have high levels of a protein called human epidermal growth factor receptor 2 (HER2), which is involved in the growth of cancer cells, that can be aggressive and associated with an increased risk of both recurrence and death from breast cancer [4]. However, the prognosis of HER2-positive breast cancers has improved substantially with the use of chemotherapy and targeted treatment against HER2. In a large population-based cohort study reported that late breast cancer recurrence appears less aggressive and is associated with a better prognosis than early recurrence [5].

In the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial, the combination of trastuzumab, pertuzumab, and docetaxel resulted in a median duration of progression-free survival and overall survival of 18.7 months and 56.5 months, respectively [6]. Standard second-line therapy is the antibody-drug conjugate trastuzumab emtansine (T-DM1), which was associated with an objective response of 43.6% and a median duration of progression-free survival of 9.6 months when the drug was administered after trastuzumab and a taxane [7]. No uniformly accepted standard of care has been defined after the administration of T-DM1, and the currently available options have limited benefits, with response rates of approximately 9 to 31% and duration of progression-free survival of approximately 3 to 6 months for third-line therapy [8].

Enhertu and its development

In 2019, Enhertu (fam-trastuzumab deruxtecan-nxki, T-DXd) received accelerated approval based on tumor response rate and response duration from the phase

2 DESTINY-Breast01 trial for adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. In the trial, T-DXd (at a dose of 5.4 mg per kilogram) had durable antitumor activity in patients with HER2-positive metastatic breast cancer who had undergone extensive previous treatment, with a confirmed overall response rate of 60.9%, a median duration of progression-free survival of 16.4 months, and median response duration of 14.8 months. These results validate earlier observations from a phase 1 study (DS8201-A-J101), which showed a response of 59.5% in a similar patient population [9].

Later, on May 4, 2022, the FDA approved fam-trastuzumab deruxtecan-nxki, T-DXd (Enhertu, Daiichi Sankyo, Inc.) with recent changes on the indications, dosage, and warning. T-DXd got regular approval for adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy. The efficacy is based on DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized trial assigned 524 patients, an overall response (a complete or partial response) occurred in 79.7% (95% CI, 74.3 to 84.4) of the patients who received T-DXd and in 34.2% (95% CI, 28.5 to 40.3) of those who received T-DM1 (Table 1). Patients were randomized 1:1 to receive either T-DXd or T-DM1 by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumors shrank or disappeared completely on imaging tests in about 80% of patients who received T-DXd, compared with 34% who were treated with T-DM1. The incidence of drug-related adverse events of any grade was 98.1% with T-DXd and 86.6% with T-DM1 [10]. The most common adverse reactions (incidence >30%) in patients receiving T-DXd were nausea, fatigue, vomiting, alopecia, constipation, anemia, and musculoskeletal pain. Serious adverse reactions in >1% of patients who received T-DXd were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection [11]. The drug-related interstitial lung disease or pneumonitis occurred in 10.5% of the patients in the T-DXd group and 1.9% of those in the T-DM1 group [10].

Table 1: Efficacy results in destiny breast 03.

Efficacy parameter	Enhertu (5.4 mg/kg)	Ado-trastuzumab emstansine (3.6 mg/kg)
Progression-free survival		
N	261	263
No. of events (%)	87 (33.3)	158 (60.1)
Median, months(95%CI)	NR (18.5, NE)	6.8 (5.6, 8.2)
Hazard ratio (95%CI)	0.28 (0.22,0.37)	
P-value	P<0.0001	
Confirmed objective response rate per BICR		
N	248	241
n (%)	205 (82.7)	87(36.1)
95% CI	(77.4,87.2)	(30.0,42.5)
Complete response n (%)	39 (15.7)	20(8.3)
Partial response n (%)	166 (66.9)	67 (27.8)
	79.7	34.2
CI=confidence interval		
NR=not reached		
NE=not estimable		
BICR=blinded independent central review		
*Analysis was performed based on the patients with measurable disease assessed by BICR at baseline		

CONCLUSION

Although T-DXd had a high level of clinical activity in patients with HER2-positive metastatic breast cancer who had undergone extensive previous therapies. But it was associated with a substantial risk of interstitial lung diseases, which require attention to pulmonary symptoms and careful monitoring. However, as the phase III trial was an international study, they include patients with different genetic variations, but this drug's rare side effects are now unknown. Despite phenomenal and long-lasting responses to T-DXd, metastatic breast cancer eventually does progress and it's important to understand why tumors stop responding. Further studies will be needed to ensure the efficacy of Enhertu in breast cancer as well as other cancers. Is it worthy to go for prescribing Enhertu for a patient with metastatic breast cancer? Still, it is a question to answer.

CONFLICT OF INTEREST

The author declares no competing interests.

ETHICAL APPROVAL

None.

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