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Editorial

The Field Of Her-2-Positive Tumors Is Constantly Changing In The Study Of Cancer.

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INTRODUCTION

The United States of America (USA) licensed trastuzumab, a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2), about 25 years ago for the treatment of patients with metastatic HER2-positive breast cancer. Since then, patients with HER2-positive breast cancer have benefited greatly from HER2-targeted treatment in a number of ways: (i) double targeting with pertuzumab and trastuzumab has been introduced into both the metastatic and neoadjuvant treatment settings; (ii) HER2-targeted therapy has transitioned from the palliative to the adjuvant and then to the neoadjuvant treatment settings; (iii) Patients with metastatic illness are now being treated with tyrosine kinase inhibitors including lapatinib, tucatinib, and neratinib, sometimes in conjunction with trastuzumab. allowing HER2-directed treatment in multiple treatment lines; (iv) antibody–drug conjugates, specifically trastuzumab emtansine and trastuzumab deruxtecan, have been approved for the treatment of breast cancer; and (v) the latter medication has also demonstrated significant efficacy in patients whose tumors do not meet the "classical" criteria for HER2 positivity (i.e., HER2 3+ and HER2 2+ with ISH positivity). When trastuzumab deruxtecan was administered as a second-line treatment for patients with so-called HER2-low tumors (i.e., HER2 1+ or HER2 2+, ISH negative), it was demonstrated that these patients had a considerable survival advantage over previous standard therapies. Consequently, this medication is currently authorized to treat these patients.he development of HER2-targeted medical treatment for various HER2-positive malignancies was modeled after the successful evolution of HER2-positive breast cancer. First, the main ToGA trial in 2010 showed a significant survival improvement when trastuzumab was added to platinum/5-fluorouracil-based treatment for metastatic gastric cancer [1]. However, in the JACOB research, double targeting with pertuzumab and trastuzumab did not statistically improve survival when compared to the ToGA regimen [2]. Furthermore, additional randomized studies employing trastuzumab emtasine [4] and lapatinib [3] also produced unfavorable outcomes. However, based on phase II trials, trastuzumab deruxtecan is currently licensed as a second-line treatment [5].However, because gastric cancer tumor cells exhibit more HER-2 heterogeneity than breast cancer, determining HER2 expression in gastric cancer remains a challenge. Due to a larger percentage of tumors testing as false positives locally, the VARIANZ research recently showed that only patients with centrally confirmed HER2 positivity seemed to benefit from a trastuzumab-based treatment [6]. Regarding the histological examination of tumor tissue, it is well known that there are distinct standards for HER2 positive in breast and gastric cancer. Valtorta and colleagues provided an alternative scoring system for colorectal cancer, the third entity in which HER2 targeted treatment was studied [7]. In individuals with metastatic colorectal cancer (mCRC) that is HER2-positive, Promising overall and progression-free survival rates were shown in a number of phase II trials, primarily in patients who had received extensive pretreatment. Tucatinib with trastuzumab, for example, produced a 38% response rate and an 8.2 month PFS in 84 patients with mCRC who had received at least two lines of pretreatment in a recent phase II trial [8]. In the meantime, the USA has granted this combination a license to treat mCRC. Many individuals with metastatic biliary tract cancer (BTC), particularly gallbladder and extrahepatic BTC, are found to be HER2-positive. Two phase II trials that were recently presented at the ASCO 2023 meeting showed the efficacy of HER2-targeted treatments in this hitherto challenging-to-treat population [9, 10].For example, a phase II trial that used the bispecific monoclonal antibody zanidatamab, which targets two domains of the HER2 receptor, revealed a length of remission of almost one

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year, a median PFS of 5.5 months, and a response rate of 41% [9].Five articles in the current Special Issue of Cancers deepen our knowledge of HER2-positive cancer diagnosis and treatment. Morales and colleagues conducted a thorough evaluation of the mechanism of action and outcomes of HER2-directed medications, including recently licensed medications [11]. To improve efficacy and/or stop escape mechanisms, novel medication combinations that target HER2 on one side and other targets on the other are being investigated in various tumor types.Xu and colleagues aimed to evaluate the effectiveness of a double targeting approach using an ovarian cancer xenograft model that expressed EpCAM and HER2. When compared to monotherapy or no treatment, they showed that the combination could maximize tumor reduction and increase survival [12].Very few (randomized) trials have looked into the combination of radiotherapy and HER2-targeted treatments. Unfortunately, there was no advantage observed when trastuzumab was used in conjunction with conventional radiation therapy for HER2-positive locally advanced adenocarcinomas of the gastro-esophageal junction [13]. In a thorough analysis of breast cancer patients, Debbi and colleagues talked about the history, safety, and possible drawbacks of this combination.While they cautioned against combining tyrosine kinase inhibitors and antibody drug conjugates with radiation, they came to the conclusion that monoclonal antibodies and checkpoint inhibitors can be safely used with radiation [14].The neoadjuvant treatment of breast cancer is the subject of two articles in this Special Issue. The long-term outcomes of the five-arm randomized phase II Neo-Lath Study were published by Tokunaga and associates [15]. This study reported on the 5-year outcomes and aimed to evaluate the advantages of long-term neoadjuvant HER2 targeted treatment. A biomarker analysis of patients with HER2-positive early breast cancer who were part of the neoadjuvant WSG-ADAPT HER2 research was conducted by Harbeck and colleagues.Following neoadjuvant therapy and tumor resections, patients with treatment-induced CD8 protein-expressing cells that do not have a PIK3CA mutation may be eligible for less rigorous treatment, according to this data [16]. In conclusion, we face a wide and sequential use of various HER2-targeted medications in patients with gastric cancer and breast cancer, including in those with HER2-low tumors, 25 years after trastuzumab was approved for the treatment of metastatic breast cancer. Phase II trials demonstrated that HER2-targeted treatment for various gastrointestinal malignancies produced positive outcomes, expanding the range of available treatments for patients with these tumors.While the prognosis for patients with HER2-positive malignancies in both early and late stages has significantly improved because to HER2-targeted therapy,Two significant challenges in the treatment strategy of HER2-positive malignancies are acquired resistance to trastuzumab brought on by ERr2 depletion and increased heterogeneity of HER2 gene expression. To address these issues, new HER2-targeted medications were created, including tyrosine kinase inhibitors, antibody–drug conjugates, and bispecific antibodies. In addition, future less invasive real-time evaluation and monitoring of anti-HER2 therapy may be made possible by new screening techniques like ctDNA and novel imaging agents (89Zr-Trastuzumab PET/CT).

Conflicts Of Interest

No conflicts of interest are disclosed by the writers.

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