short review

memo (2023) 16:237–241
https://doi.org/10.1007/s12254-023-00924-y

memo
magazine of european medical oncology

Second-line treatment of HER2-positive advanced gastroesophageal adenocarcinoma

Past, present and future

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Received: 4 September 2023 / Accepted: 8 October 2023 / Published online: 19 October 2023

Summary There is an unmet need for the treatment of patients with HER2-positive gastroesophageal tumors whose disease progressed on a first-line trastuzumab-based regimen. Several prospective trials took a targeted approach and evaluated various HER2-targeted agents as second-line therapy. However, these trials failed to demonstrate a survival benefit and were negative in primary endpoints. Recently, the antibody–drug conjugate trastuzumab deruxtecan has shown promise as a second-line treatment in patients with HER2-positive metastatic gastroesophageal tumors, with a remarkable overall response rate and a relevant prolongation of prognostic outcome. Several clinical trials will introduce more targeted therapy approaches with novel structures, which will hopefully further extend patients' survival. This mini-review briefly summarizes the past practice of second-line treatment of HER2-positive gastroesophageal tumor patients, describes current knowledge based on recently published studies, and provides a short overview on the novel anti-HER2 compounds that are currently being clinically investigated and could yield positive results in the near future.

Keywords Anbibody drug conjugate · Targeted therapy · HER2 · Gastric cancer · Chemotherapy

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Introduction

Assessment of epidermal growth factor receptor 2 (HER2) is part of the routine pathologic evaluation of patients with gastroesophageal adenocarcinoma when systemic treatment for advanced or metastatic disease is proposed [1]. If positivity is confirmed, patients with an appropriate general condition should be offered anti-HER2 treatment with trastuzumab [2]. In some countries, the addition of immunotherapy to trastuzumab-based chemotherapy has already become standard [3]. A significant proportion of patients with initial HER2 positivity progress on trastuzumab-based chemotherapy, requiring the implementation of second-line treatment.

This mini-review briefly summarizes the previous practice of second-line treatment of HER2-positive gastroesophageal patients, describes current knowledge based on the recently published studies, and provides a brief overview of the novel anti-HER2 compounds that are currently being clinically investigated and could yield positive results in the near future.

Historical development of second-line treatment

Patients with advanced or metastatic gastric and esophagogastric junction tumors who have received standard first-line chemotherapy and have progressed or are intolerant to this therapy could be offered subsequent systemic treatment based on performance score. The European Society for Medical Oncology (ESMO) and German Onkopedia Guidelines updated the treatment recommendations in 2022, incorporating a biomarker-based approach to the second-line treatment algorithm [1, 4].

Chemotherapy options that could be used in this situation include paclitaxel, docetaxel, and irinotecan [1]. Although there is no direct comparison of these

compounds, the effectiveness seems to be quite similar. However, careful attention should be paid to the toxicity profile of each substance, since patients' quality of life may already be impaired after first-line therapy. In the majority of patients, peripheral polyneuropathy can still be a serious problem, which may limit the use of paclitaxel, as it is associated with additional polyneuropathy [5].

The phase III RAINBOW study showed that the anti-vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody ramucirumab, in addition to paclitaxel, was shown to prolong overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) [6]. Ramucirumab was further evaluated in the phase III REGARD trial as monotherapy versus placebo in patients with reduced condition, however with modest efficacy in improving OS [7]. Therefore, ramucirumab has been approved by several medical authorities with or without paclitaxel as a second-line treatment option for patients with advanced or metastatic gastroesophageal tumors.

A biomarker test for microsatellite instability was proposed in the 2022 version of the ESMO guidelines [1]. This recommendation is based on the KEYNOTE-158 study, which showed that the anti-PD-1 monoclonal antibody pembrolizumab is active in patients with previously treated advanced MSI-H gastric cancer and had induced an ORR of 45.8% and PFS of 11 months (OS had not yet been reached at the time of data reporting) [8]. Pembrolizumab has therefore been approved by several authorities as a tissue-agnostic treatment of MSI-H tumors in second-line therapy.

HER2-positive tumors in second line

No additional HER2 assessment or specific anti-HER2 treatment for second-line treatment of gastroesophageal tumors was proposed in the updated ESMO guidelines from 2022. However, an online amendment was made to the 2022 guidelines based on HER2 positivity in July 2023.

A post hoc analysis of the pivotal RAINBOW study evaluated patients with initial HER2-positive tumors who had previously received trastuzumab-based treatment [9]. In this study population, 20 patients treated with ramucirumab plus paclitaxel and 19 patients in the paclitaxel arm could be identified. In patients with prior trastuzumab treatment, a numerical benefit in OS and PFS was observed when treated with second-line ramucirumab and paclitaxel. Due to the limited sample size of the post hoc assessment, no statistical significance could be established.

Another real-world study revealed an analysis of a nationwide tumor registry in Korea that reported the efficacy of ramucirumab and paclitaxel as second-line therapy in patients with gastroesophageal adenocarcinoma [10]. Of the almost 1000 patients, 16.4% were initially HER2 positive. This patient population had a significantly higher ORR compared to the HER2-negative population. However, mean PFS and OS were comparable (4.3 vs. 3.7 months, $p = 0.054$ and 9.8 vs. 10.1 months, $p = 0.564$), respectively.

Additional treatments with specific anti-HER2 agents in the second-line setting were evaluated in patients with prior trastuzumab treatment. GATSBY was a phase III study evaluating the antibody–drug conjugate trastuzumab-emtansine as a second-line therapy versus a taxane [11]. In another phase III study, TyTAN, patients were randomized to either the tyrosine kinase inhibitor lapatinib plus paclitaxel or paclitaxel alone [12]. Both studies showed no significant improvement in outcome in the experimental arms.

The Japanese T-ACT study aimed to answer the question of whether trastuzumab treatment along with second-line chemotherapy improves outcome beyond progression [13]. In this study, HER2-positive patients were initially randomized to receive either trastuzumab beyond progression plus paclitaxel or paclitaxel alone. Both PFS and OS have not been improved. It is important to note that ramucirumab was not standard of care at the time the T-ACT study was designed. Interestingly, a recent Korean study followed a similar approach, but selected ramucirumab plus paclitaxel as the baseline treatment to represent the current standard [14]. This single-arm study showed mean PFS and OS of 7.1 and 13.6 months, respectively, with an ORR of 45%. Compared to historical data, the combination of ramucirumab and paclitaxel with trastuzumab therapy beyond progression showed a clinically relevant improvement in efficacy and prolongation of PFS and OS.

The new era of DESTINY

Trastuzumab deruxtecan is an antibody–drug conjugate consisting of a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload via a cleavable tetrapeptide-based linker [15]. After internalization by tumor cells, the linker is cleaved by lysosomal enzymes. The cytotoxic payload, which is cell membrane permeable after intracellular cleavage, has a bystander antitumor effect, allowing tumor cell killing in the neighborhood of HER2-expressing tumor cells.

The efficacy and safety of trastuzumab deruxtecan in gastric or gastroesophageal junction adenocarcinoma was evaluated in patients from Japan and South Korea with HER2-positive locally advanced or metastatic HER2-positive gastroesophageal adenocarcinoma that had progressed after at least two prior lines of therapy, which should include trastuzumab [16]. In this study, trastuzumab deruxtecan demonstrated a significant benefit in ORR and OS over the physician's chosen standard of care. This led to approval of trastuzumab deruxtecan in several countries,

including the US, although patients of Caucasian descent were not included in this study.

A number of factors, including diet, smoking status, *Helicobacter pylori* infection, or different screening strategies, could lead to different outcomes in patients of Asian or Caucasian ethnicity [17, 18]. Therefore, a confirmatory study evaluating trastuzumab deruxtecan diverse patient population was required. The DESTINY-Gastric02 study was a single-arm phase II study with patients from the United States and Europe [19]. Patients who were initially HER2 positive and received first-line trastuzumab-containing therapy were evaluated and rebiopsied to evaluate the maintenance of HER2 positivity. These patients then received 6.4 mg/kg trastuzumab deruxtecan every 3 weeks. The study's primary endpoint, confirmed ORR, was reported for 42% of the patient population (5% complete response and 37% partial response). Mean OS and PFS improved compared to historical data (12.1 months versus 5.6 months, respectively). There were no unexpected adverse events, the adverse event of special interest pneumonitis/interstitial lung disease was observed in 10% of the patient population (grade 1 in 2 patients [2.5%], grade 2 in 4 patients [5.1%], grade 5 in 2 patients [2.5%]). Careful monitoring and patient's awareness of symptoms could lead to early diagnosis and treatment of this adverse event. Based on these data, trastuzumab deruxtecan was approved by the European Medicines Agency (EMA) for the treatment of patients with gastroesophageal adenocarcinoma who have been previously treated with trastuzumab, irrespective of treatment line. According to this label, a new biopsy of the tumor is not mandatory.

Emerging clinical trials targeting HER2 as second-line therapy

Because DESTINY-Gastric02 was a single-arm, phase II study with no control arm, a phase III study, DESTINY-Gastric04 was designed as a confirmatory trial [20]. In this study, the similar patient population studied in DESTINY-Gastric02 will be randomized to receive either trastuzumab deruxtecan or ramucirumab plus paclitaxel treatment. Recruitment is ongoing.

There are other anti-HER2 approaches being tested in second-line treatment in HER2-positive patients. Tucatinib, a tyrosine kinase inhibitor, is currently being evaluated in the MOUNTAINEER-02 trial along with trastuzumab [21]. In addition, the bispecific monoclonal antibody zanidatamab is part of other combination approaches with the immune checkpoint inhibitor tislelizumab (NCT05270889). Mergetixumab, a novel investigational Fc-derived anti-HER2 monoclonal antibody, has been combined with pembrolizumab and evaluated as a second-line treatment for refractory or relapsed HER2-positive gastroesophageal adenocarcinoma [22]. Preliminary results showed a synergistic antitumor activity of this combination, which will be further investigated in different settings.

Discussion

There is an unmet need for the treatment of patients with HER2-positive gastroesophageal tumors whose disease has progressed on first-line trastuzumab-based therapy. The pivotal RAINBOW study, which evaluated ramucirumab and paclitaxel as second-line therapy, enrolled patients regardless of biomarker profiling [6]. The post hoc analyses of this study and large real-world data indicate that the HER2-positive patient population may benefit from treatment with ramucirumab and paclitaxel to a similar extent compared to HER2-negative patients [9, 10]. Therefore, this treatment has been adopted and widely accepted as the standard second-line treatment for patients with gastroesophageal tumors, including the HER2-overexpressing subgroup.

Further prospective studies followed a targeted approach and evaluated different HER2-targeted agents as second-line therapy [11, 12]. However, these studies failed to demonstrate a survival benefit and were mostly negative. The reason for this failure is potentially multidimensional, with the main focus being the lack of confirmation of HER2 positivity in the second-line setting. Various reports suggest that HER2 positivity is lost in up to 60% of patients, which could possibly explain the failure of subsequent HER2-targeted treatments [13, 23, 24]. Originally, a similar scoring system was used for gastroesophageal tumors as for breast cancer [25]. However, recent data revealed a new subclassification of HER2-positive breast cancer, as HER2 2x-positive and in situ hybridization (ISH)-negative and HER2 1x-positive patients were classified as "HER2-low" [26]. Initial ground-breaking clinical evidence in breast cancer demonstrated a relevant benefit of trastuzumab deruxtecan as second-line therapy in the HER2 subgroup, in both hormone receptor-positive and triple-negative cases [27]. Whether gastric cancer also has a "HER2-low" subgroup is currently controversial. Only a small patient cohort of "HER2-low" gastroesophageal adenocarcinoma patients was treated with trastuzumab deruxtecan in the DESTINY Gastric01 trial, showing encouraging, although modest, results [28].

To address this issue, the DESTINY Gastric02 study required a rebiopsy and treated patients in this single-arm study with the antibody–drug conjugate trastuzumab deruxtecan [19]. The study results show promising numerical values that are almost comparable to first-line treatment of patients with metastatic gastroesophageal cancer. Whether this success is related to the confirmation of HER2 status according to the study protocol is not known. It is noteworthy that biopsy of a gastroesophageal tumor patient at the time of progression to trastuzumab is not always fea-

sible in clinical practice for several reasons, including but not limited to the patient's reduced clinical condition, site of metastasis (e.g., peritoneal carcinoma), and informed consent of the patient. In addition, the assessment of HER2 with immunohistochemistry (IHC) also needs improvement, as in addition to spatial and temporal discrepancies, differences in the assessment of HER2 between central and local assessments have been reported, which influenced the outcome of trastuzumab treatment [29, 30]. Other techniques include liquid biopsy could help to solve this problem [31]. However, current data are not sufficient to support the use of liquid biopsy in everyday clinical practice.

Nonetheless, both the US Food and Drug Administration (FDA) and EMA have approved trastuzumab deruxtecan without mandatory rebiopsy at the time of progression. However, such a practice could be encouraged as the expression of HER2 could be lost and the initial clinical study also required a repeated biopsy [4].

In summary, since trastuzumab was first established as a HER2-targeted treatment in first-line treatment, antibody–drug conjugates have evolved into further promising anti-HER2 treatments in second-line treatment and beyond in patients with HER2-positive metastatic gastroesophageal tumors. Further clinical investigations will introduce several targeted therapeutic approaches with novel structures that will hopefully further prolong patient survival. Today, gastroesophageal cancer is a rapidly changing field that requires continuous education of clinicians.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest A. Ilhan-Mutlu declares following potential conflict of interests: participation in advisory boards organized by MSD, Servier, Daiichi Sankyo, BMS and Astellas, lecture honoraria from Eli Lilly, Servier, BMS, MSD, Astellas and Daiichi Sankyo, consulting for Astellas, MSD, Amgen and Astra Zeneca, travel support from BMS, Roche, Eli Lilly and Daiichi Sankyo. E. Wöll declares following potential conflict of interests: lecture honoraria and advisory roles for Astellas Pharma, Astra Zeneca, BMS, Calgen, Daiichi Sankyo, Ebewe, Eisai, Eli Lilly, Elsevier, Janssen Cilag, Merck, MSD, Novartis, Pierre Fabre, Pfizer, Ratiopharm, Roche, Sanofi Aventis, Servier, Takeda.

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