Oncology
and Radiotherapy©
18(7) 2024: 001-007 • RESEARCH ARTICLE

HER2-positive gastric cancer: Consequences for targeted therapy

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ABSTRACT

Objective: The anti-drug combination known as trastuzumab deruxtecan is composed of a cytotoxicity topoisomerase I inhibitor, a cleavable tetrapeptide-based linker, and an anti-HER2 (Human Epidermal Growth Factors Receptor 2) antibody. This combination is designed to combat cancer. Patients diagnosed with advanced HER2-Positive Gastric Cancer (PSC) may benefit from the use of this medication.

Materials and Methods: Participants in our phase 2 trial with cancerous HER2-positive gastric cancer were allocated at random to receive the treatment trastuzumab-deruxtecan or chemotherapy, and we compared the two treatments. Trastuzumab deruxtecan (T-DXd) or the doctor's choice of chemotherapy was randomly distributed to patients with centralized proven HER2-positive gastric cancer the connection had received at least two previous treatments for their developed adenocarcinoma, such as trastuzumab. According to the impartial central review's results, the objective response was the main goal. Secondary end objectives were response duration, progression-free survival, verified response, and safety in addition to general survival.

Results: Out of 187 patients who got treatment, 125 obtained T-DXd and 62 chemotherapy treatments. In the T-DXd group, 49% of patients reported a realistic response in contrast to 18% of patients in the Doctors' selection association. T-DXd improved overall survival compared to chemotherapy. An independent committee determined that a total of 12 individuals experienced interstitial lung illness or pneumonitis caused by T-DXd. In the T-DXd group, there was one drug-related fatality; there were none in the Doctors' Preference Group.

Conclusion: When compared to those who received standard therapy, persons who had chemotherapy for HER2-positive gastric cancer treated with T-DXd demonstrated significantly better responses and overall survival. Interstitial lung disease and a weakened immune system were the most noticeable negative effects.

Keywords: HER2, Trastuzumab deruxtecan, positive gastric cancer

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Word count: 4533 **Tables:** 03 **Figures:** 05 **References:** 30

Received: 14 June, 2024, Manuscript No. OAR-24-141015
Editor Assigned: 17June, 2024, Pre-QC No. OAR-24-141015(PQ)
Reviewed: 05 July, 2024, QC No. OAR-24-141015(Q)
Revised: 12 July, 2024, Manuscript No. OAR-24-141015(R)
Published: 22 July, 2024, Invoice No. J-141015

INTRODUCTION

The third most common cause of cancer-related fatalities in men and the fifth most common in women globally is advanced Gastric Cancer (GC). Although many chemotherapeutic drugs, that include anthracyclines, 5-fluorouracil, and taxanes, have been researched to enhance the prognosis of metastatic GC, the clinical results of advanced GC remain poor with an average Overall Survival (OS) of a year or fewer [1]. The most common option for the management of GC is full surgical removal with regional lymph node dissection, although a considerable proportion of patients have recurrence after curative resection, which results in a poor prognosis. Adjuvant chemo radiotherapy was made the norm in the treatment of GC after the Intergroup-0116 trial1 [2]. Early studies indicated that the addition of targeted substances to conventional cytotoxic chemotherapy may improve treatment reactions, and trastuzumab-based treatment with chemotherapy has become an established approach for HER2-positive GC after demonstrating an advantage in terms of survival in the ToGA trial. However, not every patient with positive for HER2 GC is responsive to trastuzumab-containing training regimes; Overall Response Rates (ORRs) vary from 48% to 67%, and the majority of patients develop resistance to trastuzumab [3, 4]. Age, gender, and race/ethnicity are only a few examples of the numerous non-modifiable risk factors for stomach cancer. Figure 1 shows the activation of HER2.

Smoking, eating a diet rich in nitrates and nitrites, and Helicobacter pylori infection are among other risk factors that may be managed. Several other very uncommon risk factors exist, including pernicious anaemia, prior stomach surgery, and mucosa-associated lymphoid tissue lymphoma. An additional risk factor is having a first-degree relative who has stomach cancer [5]. Even though specific deaths have decreased, GC, one of the most common cancers with over a million cases detected annually, persists as the subsequent leading cause of death from cancer worldwide, responsible for more than 780,000 mortalities annually.

The majority of GC patients had advanced incurable illnesses at the time of diagnosis. Systemic chemotherapy continues to be the most effective form of care for the treatment of advanced illness since therapeutic advancements for the management of the condition have been gradual [6]. To identify patients who would probably respond to therapy and to develop innovative approaches to treating drug resistance, it is essential to understand the

underlying molecular causes of innate and acquired trastuzumab resistance. Intense inherent molecular heterogeneity seen in GC may have a significant role in the development of resistance to targeted treatment. Furthermore, it might be challenging to collect cancer samples, and the genetic profiles of original tumours and metastasis are not necessarily the same [7, 8]. A topoisomerase I inhibitor payload is connected to a transtuzumab deruxtecan, a humanized anti-HER2 monoclonal antibody, is cleavable through a tetrapeptide-based intermediary (also known as T-DXd and DS-8201) [9]. Adult individuals suffering from metastases or incurable HER2-optimistic breast malignancy patients have had greater than two previous treatments known to inhibit-HER2-based therapies should receive this kind of medication is T-DXd. It is also being reviewed by regulatory authorities for HER2-positive metastatic breast cancer [10].

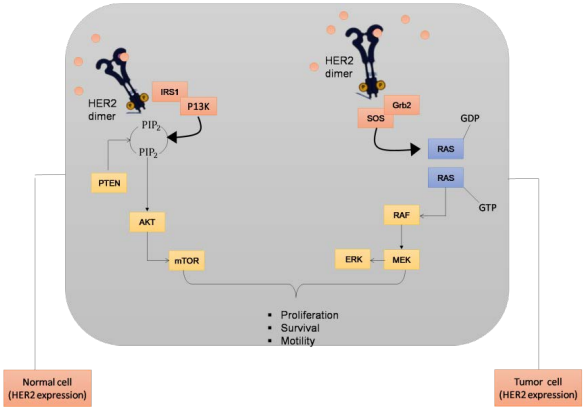

Fig. 1. HER2 activation

To locate Randomized Controlled Trials (RCTs) assessing the effects of treatment for removal on the development of PSC in gastric neoplasia. Pylori-positive patients having endoscopic mucosal resection and healthy H. pylori-positive individuals. The placebo or no-treatment group served as the control. Follow-up lasted around two years. In addition to evaluating the years of life with a handicap gained via assessments of the systematic review, we calculated the relative risk number required to treat [11]. Gastric Non-Helicobacter Pylori Helicobacter (NHPH) genetic analysis and culture methods are improving. Nodular gastritis, stomach MALT lymphoma, and moderate gastritis have all been linked to NHPH [12]. The paper used two suggested computational techniques to completely quantify the TME penetration patterns of gastric cancer patients and then methodically connect the TME phenotypes with genetic traits and clinicopathologic aspects of gastric cancer [13]. Principal component analysis procedures were used to create the TME score, which was based on the definition of three TME phenotypes. An arbitrary-effects framework is employed; the Confidence Intervals (CIs) and mutual EBV occurrence were calculated. For case-control studies, the pooling odds ratio and associated 89% CI were calculated to assess the relationship among EBV and stomach tumour. The pooled estimates of ORs were calculated using two different methods using case-control study information using mismatched and non-match pair's designs [14]. A random-effects framework was employed to forecast the aggregated EBV occurrence and ninety-five percent CIs. Pooled Odds Ratios (OR) and their 98% CI were estimated to evaluate the association between EBV and stomach cancer. To assess the pooled calculations of ORs, 2 dissimilar appraisals were performed on data engaging layouts for coordinated and non-coordinated pairings [15]. Gastric cancer linked to the Epstein - Barr virus (EBVaGC) is a usually malignant tumour linked to EBV infection. Based on gastric carcinoma's molecular recognition, EBVaGC was a unique group regarding cancer evolution and molecular landscapes [16]. RNA-sequencing was employed to address the transcription pattern of circRNAs in six sets of GC areas and neighbouring non-tumour tissues. In GC body portions and cell lines, the transcript level of circCCDC9 was assessed by quantitative real-time PCR.

The features of circCCDC9 on cancer growth and malignancy in the GC were examined utilizing functional validations showed both in vitro and in vivo [17]. The objective of the article examined the possible guidelines and procedures of IDO1 in the evolution of GC in vivo and in vitro employing Weighted Gene Co-expression the Network Analysis (WGCNA) evaluation of the transcriptome information through GC cell lines via the Can-cer Cell Line Encyclopaedia (CCLE) [18]. AGC patients experienc-ing systemic chemotherapy were retrospectively addressed. The time-varying features to evaluate the impacts of trastuzumab exposure throughout any form of chemotherapy to avoid a possible lead-time prejudice [19]. The Somatic Copy Number Variation (SCNV), somatic Single Nucleotide Variant (SNV), and somatic Structural Variation (SV) studies were carried out, and the whole genome was sequenced using Illumina HiSeq PE150 equipment [20].

MATERIALS AND METHODS

In this section we discuss in detail about HER2-Positive Gastric Cancer: Consequences for Targeted Therapy. HER2-PSC is a type of stomach cancer where the cancer cells produce an excessive amount of HER2 protein. HER2 is a protein that helps to regulate cell growth and division. In normal amounts, it has a significant impact on the creation and upkeep of healthy cells. However, in HER2-PSC, the overexpression of this protein leads to uncontrolled cell growth and division, which can cause the cancer to spread more quickly.

Trail design

Conducted a phase 2 randomized trial involving individuals with at least two previous trastuzumab-containing treatments and HER2-expressing, locally advanced, or metastatic gastric or gastro-oesophageal joint cancer. Both high and low HER2 levels have been determined. The main cohort, on which this research is focused, included individuals with high-grade HER2-positive ill-

ness. Two distinct exploratory cohorts of patients with low-grade HER2 disease were included; the data are not presented here. Patients were to be at least 20 years old and have an ECOG condition as well as efficiency rating of zero or one. If a patient possessed interstitial lung disorder or pneumonia, had a track record of not transmissible interstitial fluid lung illness or pneumonitis and that had been treated in the past with a group of hormones or had been suspected of having interstitial fluid lung illness or pneumonitis at screening but the diagnosis was not ruled out on imaging, they were disqualified from the study [21]. Patients were randomly assigned to receive either trastuzumab deruxtecan or the physician's decision a compound called paclitaxel in a 2:1 ratio. The use of randomized was stratified by nation, ECOG according to the accomplishment-status rating, status in HER2 with the guidelines.

Based on prior studies of pharmacokinetics, effectiveness, and safety, T-DXd was administered to individuals receiving a 6.5 mg dosage per kg of body weight of the person. Given intravenously every three weeks. Breast cancer patients typically get 4.9 mg/kg of human body mass. Patients in the doctor-selected category either received irinotecan monotherapy at a dosage of 145 mg/m^2 of total body surface area supplied every 2 weeks or paclitaxel treatment at a dose of 85 mg every square meter supplied on days 1, days 8, and days 15 for four weeks. Treatment was continued until intolerable side effects appeared, the sickness became worse or the patient withdrew consent.

Final points

The main outcome was the objective response, which was assessed using the assessment standards for responses in Consolidated Tumours, edition 1.1, by an impartial centralized review [22]. Generalized survival was a critical supplementary outcome that required determining if the significance of the main end objective was calculated and appraised hierarchically. Secondary end goals were the length of the reaction, advancement-free survival, and verified prevention of illness, validated objective reaction, verified objective response, and safety. Amongst the preliminary end targets were the length of response and the most promising percentage increase in the combined diameters of the measurable tumours.

Safety

A lowered neutrophil count was one of the most common severe adverse effects, based on the safety study, which also showed that significant side effects were common. This suggests a substantial influence on patients' immune systems, underscoring the significance of keeping an eye on and controlling these side effects while receiving therapy.

Analytical statistics

According to our calculations, a sample size of 180 patients would give the trial 96% ability to distinguish between the replies of the two distinct groups. The trial's 83% power to identify a hazard ratio of 0.61 at a significance level with two sides of 0.05 would need around 133 fatalities to take place. Cochran-Mantel-Haenszel analyses subdivided by area were used to compare responses between the therapy groups in the overall sample of patients whose responses could be evaluated. The Fisher's Exact Test (FET) was used to compare treatment groups as part of an unstratified sensitivity analysis. In the whole data set, the region was used as a stratification factor in stratified log-rank tests to analyse each therapy organization's overall effectiveness.

Patients were showed assessment able responses were compared between the therapy groups using Cochran-Mantel-Haenszel tests stratified by area [23]. The FET was used to compare treatment groups as part of an unstratified sensitivity analysis. In the whole analytic set, geographically divided record-rank tests as a stratified component were used to compare the general survival in every group receiving treatment.

The familywise type I error was maintained below the threshold at 0.06 for each of the main and supplementary effective objectives of unbiased reaction and general survivance utilizing a resolved-sequence testing approach. If the outcome of the hypothesis test for impartial responsiveness was meaningful at a symmetrical alpha level of 0.05, then overall survival was evaluated at the same level. The goal of the reaction evaluation and initial assessments of general survivance was completed after every one of the participants had undergone tumour evaluation at approximately 24 weeks or had terminated the trial; the final general survivance. It was planned to finish the evaluation after around 133 fatalities. Calculating statistically important values for the overall survivance analysis required the use of the Lan-DeMets alpha-spending functional and an O'Brien-Fleming border [24, 25]. Using Cox proportional-hazards models of regression stratified by area, hazard ratios with associated intervals of assurance of 95% were obtained for the studies of prolonged survival and progression-free survivance. There are also presented unadjusted ratios of hazard with matching 95% confidence intervals. The percentage of those who have shown illness tolerance is also provided. The spreading of event conclusion points throughout time for overall progression-free survivance and responsiveness length was calculated using the Kaplan-Meier method. With a both-sided assurance level of 95% interval, the median of these measurements was evaluated using the Brookmeyer and Crowley method [26].

RESULTS

In this section, we see the results of positive gastric cancer. A total of 187 patients got care; 125 obtained T-DXd and 62 obtained the doctor's recommended course of treatments (Figure 2). Due to an abnormal echocardiography performed before starting therapy, For the T-DXd category, a single patient was ineligible to start therapy. The individual parameters were comparable in both groups [27, 28].

Patients suffering from severe or metastatic illness had a baseline of two prior systemic therapies, and 31 patients (20%) had undergone at least four. Ramucirumab had been given to 69% of the patients before, and taxanes to 89%. People in the T-DXd category had a median interval from the last management of trastuzumab of 6 months, while patients in the healthcare provider's choice category had a typical interval of 6.7 months.

Total number of 28% of the individuals enrolled in the T-DXd category and 8% of the patients in the physician's selection category were still receiving therapy as of the information's cutoff date. In the T-DXd group, the average treatment time was 4.6 months, whereas it was just 2.8 months in the medical professional's decision category.

Efficacy

Compared to chemotherapy prescribed by the doctor, T-DXd

medication considerably increased the proportion of patients who had a favourable objective response (Tables 1 and 2). In 51 patients (45%) deruxtecan was associated with validated subjective reac-tions in the trastuzumab group, as opposed to 7 patients (14%), in the medical professionals' selection category. In this investiga-tion, more than a hundred patients who received T-DXd had a proven full response, but neither of the 56 patients who received the healthcare provider's recommended treatment had such an outcome. Most patients who received T-DXd had a decrease in tumour size, as opposed to around half of those who received che-motherapy of the doctor's choosing.

Tab. 1. Clinical and statistical features of the participants in the background

Characteristic	Trastuzumapderuxtecan	Chemotherapy Chosen by the Doctor
Median age (range) year	65	66
Female sex no. (%)	40	16
Region (%)		
Delhi	100	51
Bangalore	27	13
HER2 expression no. (%)	-	-
IHC 3+		
IHC 2+ or ISH-positive	95	45
Primary site no. (%)	3	16
IHC 2+ or ISH-positive	97	48
Stomach Gastroesophageal Junction		
Initial treatment	24	7
Therapy Containing Trastuzumab		
Therapy taxane	124	63
Therapy ramucirumab	95	42
Immune checkpoint inhibitor	9	6

Tab. 2. Overview of efficiency

Characteristic	Trastuzumapderuxtecan	Chemotherapy Chosen by the Doctor
Median age (range) year	65	66
Female sex no. (%)	40	16
Region (%)		
Delhi	100	51
Bangalore	27	13
HER2 expression — no. (%)		
IHC 3+		
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Stomach Gastroesophageal Junction		
Initial treatment	24	7
Therapy Containing Trastuzumab		
Therapy taxane	124	63
Therapy ramucirumab	95	42
Immune checkpoint inhibitor	9	6

In the T-DXd category, the median time to a verified objective reaction was 12 months, compared to 4 months in the Doctors' selection association. In both groups, the average reaction time was comparable. More patients who received medication with trastuzumab deruxtecan had verified improvement in their disease than those who received the chemotherapy of the doctor's choice.

The average prognostic period without progression for the T-DXd category was 5.6 months and for the medical professionals' selection category, it was 3.5 months. At 6 months, the expected rate of progression-free survival for the T-DXd group was 48%, compared to 28% for the healthcare provider's choice group. At 12 months, the predicted progression-free survival for the T-DXd group was 30% (Table 3). According to an independent central evaluation, 73 patients (60%) in the T-DXd category and 36 patients (58%) in the doctor's choice group passed away or had their illnesses advanced.

Subgroup analysis

In a predetermined subgroup evaluation, patients obtaining T-DXd had more patients who had a more favourable objective response than patients receiving the doctor's recommended chemotherapy, and the results were usually following every group receiving treatment throughout subgroups.

The proportion of patients who had an objective reaction among those who got T-DXd was greater amongst those who had a HER2 score of 3+ on immunohistochemically testing than within those who had a score of 2+ with positive in situ hybridization findings. In most subgroups, the median survival also tended to choose T-DXd over the doctor's choice of chemotherapy.

Safety

In the T-DXd group, all 125 patients were having at least one serious side effect (of any grade) during the trial's medication period, as opposed to 61 patients of 62 patients (98%) in the medical professional's choice category. In 51% of individuals receiving trastuzumab, a reduced neutrophil count was one of the most frequent grades 3 or greater side effects. Figures 2 and 3 shows the total of all of the longest dimensions of measurable tumours with the best percentage increase from the foundation.

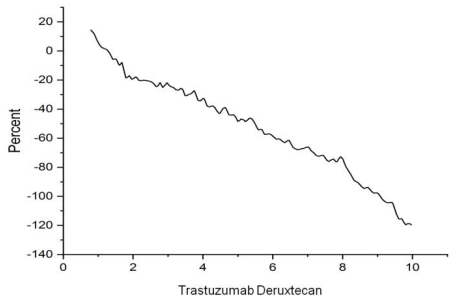

Fig. 2. Trastuzumab deruxtecan

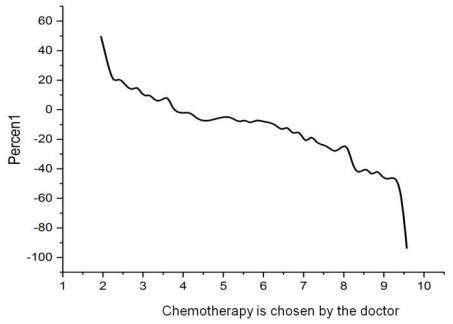

Fig. 3. Chemotherapy is chosen by the doctor

Tab. 3. At Least 30% of patients receiving trastuzumab deruxtecan experience adverse events

Preferred Term	T-DXd			Chemotherapy is Chosen by the Doctor		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Nausea	80	8	0	29	3	0
Decreased appetite	76	22	0	29	7	0
Neutrophil count decreased	78	25	49	22	11	6
Anemia	73	45	0	17	14	1
Platelet count decreased	51	13	3	5	2	2
Malaise	44	2	0	11	0	0
White-cell count decreased	51	27	0	24	6	8
Diarrhea	41	4	0	21	2	0
Constipation	31	0	0	11	0	0
Vomiting	34	0	0	6	0	0
Lymphocyte count decreased	29	9	7	2	0	1

Events

Patients in the T-DXd category were more likely than those in the physician's decision-making group to stop taking or disrupt therapy due to adverse events, but the proportion of patients who reduced their dose was comparable in the two categories. The researchers believed that one fatality in the T-DXd group was attributable to treatment (caused by pneumonia). The patient was

not neutropenic at the precise moment of the incident, and this death happened after cycle 6 had been administered. The cause of the pneumonia was not disclosed in full. In the doctor's choice group, no fatalities were thought to be caused by the medication. Figure 4 shows the total survival. Figure 5 shows the advancement of free survival.

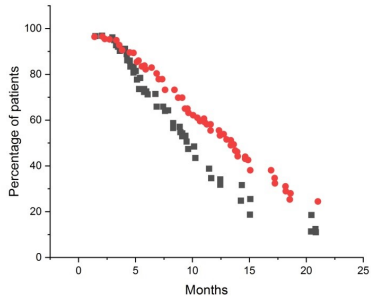

Fig. 4. Total survival

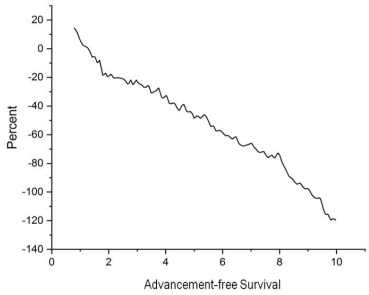

Fig. 5. Advancement-free survival

DISCUSSION

This research evaluated both the safety and efficacy of T-DXd to that of the patient's doctor-prescribed chemotherapeutic for individuals having HER2-PSC who are receiving third-line or later treatment. T-DXd greatly outperformed the physician's option in terms of the proportion of patients who had an objective reaction. These results support those from a phase 1 study of T-DXd in patients who have advanced HER2-positive gastric cancer.

In a subsection of individuals with the greatest degree of HER2 expression, trastuzumab deruxtecan was more effective than chemotherapy. The tiny patient population in this category, however, makes drawing firm conclusions challenging. Trastuzumab deruxtecan's topoisomerase I inhibitor payloads are also around a hundred times more powerful than SN-38, irinotecan's active metabolite [29]. Additionally, trastuzumab emtansine has a lesser drug-to-antibody ratio than trastuzumab deruxtecan. The different treatment results might be attributed to trastuzumab deruxtecan's superior linker and payload system.

Myelosuppression and interstitial pulmonary disease were the two major side effects of T-DXd in this study, and they were appropriately handled by dosage interruption or decrease. Even though the majority of gastrointestinal side effects were mild, T-DXd was more commonly associated with category 3 or higher hematologic side effects than chemotherapy. Dose adjustment was often used to alleviate these adverse consequences. Trastuzumab, one of the HER2-targeted treatments, has been linked to cardio toxic side effects, even though this has not been observed in our research.

The trial's limitations include its small sample size and restricted [30]. However, there was not a significant distinction in the course of therapy response between patients from nations and those from other areas in studies of other HER2-directed drugs. Although there weren't enough patients in this phase 2 study, it had enough power to find an extended overall survival under the predetermined statistical assumptions. To assess T-DXd in the context of second-line treatment, a single-group, phase 2 studies is now underway.

Overall, while treating patients with advanced gastric or gastro-esophageal junction cancer that was HER2-positive, T-DXd substantially increased the proportion of patients who had an objective reaction and increased lifespan compared to conventional chemotherapy.

CONCLUSIONS

HER2-PSC is a subtype of gastric cancer that overexpresses the HER2 protein, which can lead to more aggressive tumour growth and a worse outlook. Though, the development of targeted treatments such as trastuzumab, the treatment landscape for HER2-PSC has significantly improved. Clinical trials have demonstrated that adding trastuzumab to standard chemotherapy can enhance survival and progression-free survival in individuals with HER2-PSC. Moreover, other HER2-targeted therapies such as lapatinib and pertuzumab are being studied in clinical trials. Overall, early and accurate HER2 testing, along with the appropriate use of targeted therapies, can lead to improved outcomes for patients with HER2-PSC.

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