The Efficacy and Safety of HER2-targeted Antibody-Drug Conjugates in Gastric and Gastro-oesophageal Junction Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: The HER2-targeted antibody-drug conjugate (ADC) is a novel approach for anti-HER2 treatment, and its efficacy in breast cancer patients has been demonstrated in clinical studies. However, the overall efficacy and safety of the various HER2-targeted ADCs in patients with gastric and gastroesophageal junction cancer has not been reported. Method: The PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov databases were systematically searched. We assessed the quality of the included studies and then/span>extracted the overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) to conduct the meta-analysis. Furthermore, we performed subgroup and sensitivity analyses to explore the sources of heterogeneity. The MINORS and RoB2 were used to assess the quality of the included studies, and STATA 17.0 software was used for data analysis. Results: Six single-arm studies and 2 randomized controlled trials (RCTs) with a total of 871 patients were included. The pooled ORR and DCR were 29% (95% CI: 20%-38%) and 71% (95% CI: 56%-86%), respectively. The pooled mOS and mPFS were 9.68 months (95% CI: 7.78-11.58 months) and 5.60 months (95% CI: 4.59-6.61 months), respectively. The incidence rates of all-grade adverse events (AEs) and grade[?]3 AEs were 98.8% and 58.8%, respectively (95% CI: 43.0%-74.5%). Conclusion: HER2-targeted ADCs showed great survival benefits in GC/GEJC patients as second- and later-line treatments. However, the relatively high incidence of grade[?]3 AEs needs to be considered.

Introduction

Stomach cancer, which includes gastric cancer (GC) and gastro-oesophageal junction cancer (GEJC), is the fifth most common malignancy and the fourth leading cause of cancer death globally, responsible for over 1 million new cases and 769000 new deaths in 2020[1, 2].Despite the decline in incidence rate worldwide during the past few decades, gastric cancer remains a significant contributor to the global cancer burden with a persistently high case fatality rate[3, 4]. Although many treatment options have been developed, survival in GC patients remains poor because most patients present with advanced disease at diagnosis. Intratumoral and intertumoral heterogeneity also leads to poor prognosis[5].

The selection of a treatment regimen for GC patients is associated with the disease stage and biomarker expression status[6]. HER2 (also known as ERBB2) is a member of the human epidermal growth factor receptor family and is an important proto-oncogene. Amplification of the HER2 gene and overexpression of the HER2 protein have been implicated in the tumorigenesis and poor prognosis of many types of cancer[7-11]. Approximately 20% of GC/GEJC patients harbor HER2 amplification or overexpression[12, 13]. Trastuzumab is the first monoclonal antibody targeting HER2. According the phase III ToGA trial, using trastuzumab plus chemotherapy could prolong the overall survival of HER2-positive GC/GEJC patients compared to use chemotherapy alone (13.8 vs. 11.1 months, HR=0.74; 95% CI 0.60-0.91; p =0[?]0046)[14]. Based on the results, the combination of trastuzumab and platinum-fluoropyrimidine doublet has been established

as the standard regimen for the first-line treatment of patients with HER2-positive GC/GEJC. Although the emergence of trastuzumab represented a breakthrough in anti-HER2 treatment, the second-line treatment options for patients progressing after trastuzumab-based treatment remain limited. Several studies that applied trastuzumab beyond progression showed inconsistent results. According to the current NCCN guidelines, it is not recommended to continue trastuzumab in second-line therapy[15-19]. Moreover, combined treatment regimens also failed to show superior survival benefits in the second-line setting[20-22]. There is an unmet need for effective anti-HER2 second-line treatment regimens.

Antibody-drug conjugates (ADCs) are a new kind of anticancer drug in which monoclonal antibodies (mAbs) and cytotoxic payloads are connected via a chemically synthetic linker. The mechanism of action of ADCs is that the antibody component recognizes and binds the specific antigen, upon which the ADC-antigen complex is internalized into the tumor cells, and the linker is cleaved in the lysosome, releasing the toxic drugs and allowing them to exert their effects. Compared to traditional medications for cancer therapy, the unique structure of ADCs enables these drugs to offer both the specific cell-targeting ability of mAbs and the cell-killing effect of chemotherapeutic drugs, which is anticipated to significantly improve overall survival and reduce side effects.

Human epidermal growth factor receptor 2 (HER2) is the most common target used in ADCs in studies[23, 24]. To date, over 60 HER2-targeted ADCs have been tested in clinical trials[25]. Trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), the two HER2-targeted ADCs, were granted approval for the treatment of HER2-positive breast cancer with different indications in 2013 and 2019, respectively[26]. Recent studies have shown that GC/GEJC patients can also benefit from HER2-targeted ADCs and T-DXd has been recommended as the second-line therapy in gastric cancer patients who received prior trastuzumab-based therapy by NCCN on the basis of the phase II DESTINY-Gastric01 trial with an ORR of 43% and the mOS was 12.5 months (9.6-14.3 months)[19]. However, the results of the GATSBY trial showed that the ORR of the patients treated with T-DM1 was only 21% and mOS was 7.9 months (6.7-9.5 months). Compared to taxane, T-DM1 did not show overall survival superiority in the treatment of advanced HER2-positive GC/GEJC patients[27].

Given the discrepancies shown in the different drugs in GC/GEJC, thus, we performed a meta-analysis to figure out the efficacy and safety of HER2-targeted ADCs in GC/GEJC patients and the characteristics of benefit population, moreover, to provide reference for the studies of ADCs and the utilization in GC/GEJC patients in the future.

Materials and Methods

Search Strategy

This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the protocol has been registered in PROPERO (CRD42023454582). We systematically searched the PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov databases from their inception dates to August 21, 2023. The main search terms used for retrieval were “gastric” OR “stomach” AND “cancer” AND “HER2-targeted antibody-drug conjugate”. In addition, the references cited in the included studies were checked to identify additional potentially relevant studies. The complete search strategy is provided in the Supplementary file.

Inclusion Criteria

Articles were included if they met the following criteria: (1) prospective phase I-III randomized/nonrandomized or single-arm intervention studies conducted in patients diagnosed with GC or GEJC via pathology or cytology regardless of HER2 status; (2) studies including at least one arm treated with HER2-targeted ADC as a single agent; and (3) studies reporting at least one of the following outcomes: progression-free survival (PFS); overall survival (OS); objective response rate (ORR); disease control rate (DCR) and incidence of adverse events (AEs).

Exclusion Criteria

Articles were excluded if they met any of the following criteria: (1) Trials with GC/GEJ patients enrolled in single phase I dose-escalation trials; (2) sample sizes of less than 10 patients; (3) reviews, meta-analyses, case reports, conference abstracts, letters, notes, trial registry records, duplicated studies, guidelines, irrelevant articles and nonhuman studies; (4) trials for which data were not available; or (5) trials of medication no longer in development.

Data Extraction

Two investigators (YZQ and CZH) independently conducted the study selection in accordance with the inclusion and exclusion criteria above and extracted data from the included trials. The extracted information included first author's name, year of publication, country, National Clinical Trials (NCT) registry number, phase, treatment regimen, sample size, basic patient characteristics (i.e., age, primary tumor type, HER2 expression status), efficacy outcomes (PFS, OS, ORR, DCR) and incidences of ang grade or grade[?]3 AEs. Disputes during the process were resolved by discussion with a third investigator (WS).

Quality assessment

Since 6 out of 8 included studies were nonrandomized trials without control groups, the Methodological Index for Nonrandomized Studies (MINORS) tool was used to assess the article quality. The 8 methodological items in MINORS are as follows: include a clearly stated aim, inclusion of consecutive patients, prospective collection of data, endpoints appropriate to the aim of the study, unbiased assessment of the study endpoint, follow-up period appropriate to the aim of the study, loss to follow up less than 5% and prospective calculation of the study size. Every item can be scored as 0 (not reported), 1 (reported but inadequately), or 2 (reported adequately)[28].

In addition, the quality of the 2 included randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias Tool (RoB2), which evaluates the following aspects: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. Each domain of RoB2 is rated as "low risk of bias", "some concerns", or "high risk of bias"[29].

Statistical analysis

The data analysis was performed using STATA 17.0 software. We merged the ratios of dichotomous data when data were presented as proportions (ORR, DCR, incidence of AEs), and merged the mean of continuous variables when data were presented as the mean with 95% CIs (OS, PFS). The heterogeneity among studies was calculated using Cochrane's Q and I^2 statistics. Significant heterogeneity was deemed to exist when $p<0.05$ or $I^2>50\%$ and a random-effects model was used for analysis, otherwise, a fixed-effects model was used.

In addition, we conducted sensitivity analysis to assess the stability and reliability of the pooled results, and the publication bias was also assessed for each outcome by Egger's regression test.

Results

Systematic review and characteristics of the included studies

To determine the efficacy of safety of HER2-ADCs in GC/GEJC patients, we first aimed to identify studies published on the topics of 'gastric cancer', 'gastro-oesophageal junction cancer', 'HER2' and 'antibody-drug conjugates' for our meta-analysis. Following our retrieval strategy, 325 records were initially identified in the selected databases. After removing 105 , based on the titles and abstracts, 185 articles were excluded due to irrelevant trials, reviews, meta-analyses or other types mentioned in the exclusion criteria, leaving 35 trials considered eligible. After full-text review and removal of duplicate datasets and studies without data available, 27 studies were further excluded due to the type of publication; 8 studies were finally included[27, 30-36]. The flowchart of the detailed retrieval process is shown in Figer 1. As the DESTINY-Gastric01 trial (NCT03329690) consisted of one primary cohort and two exploratory cohorts involving patients with different HER2-expression statuses, the *Shitara 2020* and *Yamaguchi 2023* papers were considered two separate studies in this meta-analysis.

A total of 871 patients were enrolled in the 8 studies, and the sample sizes ranged from 17 to 345. Among the included patients, 590 (67.7%) patients were identified HER2-positive (IHC 3+ or IHC 2+/ ISH-positive) and 54 (6.2%) patients were identified HER2-low (IHC 2+/ISH-negative or IHC 1+). Additionally, of the HER2-positive patients, 528 (89.5%) had previously trastuzumab therapy. Among all anti-HER2 ADCs applied in the eligible trials, except T-DXd, which was used as an intervention regimen in 4 studies, the other medications including T-DM1, ARX788, SYD985 and RC48 were used in only one study each. The complete characteristics of all included studies are presented in Table 1.

Table 1. Characteristics of the included studies

NCT registry number	Author, name	country	phase	Treatment regimen	Sample size	age	Primary tumor type (GC/GEJC)	HER2 expression status	ORR	DCR	mOS (months)	mPFS (months)	Any grad AEs
NCT02564900	Shitara 2019	USA, Japan	I	T-DXd	44	68.0 (62.5-72.0)	36/8	positive	19 (43%)	35 (80%)	12.8 (1.4–25.4)	5.6 (3.0-8.3)	44 (100
NCT03329690	Shitara 2020	Japan, South Korea	II	T-DXd/PC	125	65 (34-82)	108/17	positive	51 (43%)	102 (82%)	12.5 (9.6–14.3)	5.6 (4.3-6.9)	125 (100
NCT04014075	Catenacci 2023	USA, Europe	II	T-DXd	79	60.7 (52.0–68.3)	27/52	positive	33 (42%)	64 (81%)	12.1 (9.4-15.4)	5.6 (4.2-8.3)	79 (100
NCT02277717	Banerji 2019	Belgium, the Netherlands, Spain, the UK.	I	SYD985	17	61 (52-68)	17/0	positive	1 (6%)	-	-	3.2 (1.6-5.3)	-
NCT03556345	Peng 2021	China	II	RC48	125	58 (24-70)	97/28	positive	31 (25%)	53 (42%)	7.9 (6.7-9.9)	4.1 (3.7-4.9)	218 (97.3
NCT01641939	Hurwitz 2017	28 countries	II/III	T-DM1	228	62.0 (19-79)	151/77	positive	42 (21%)	-	7.9 (6.7-9.5)	2.7 (1.6-2.7)	218 (97.3
CTR20192539	Zhang 2022	China	I	ARX788	30	57 (26–72)	22/8	positive	11 (38%)	16 (55%)	10.7 (4.8–NR)	4.1 (1.4-6.4)	28 (93.3
NCT03329690	Yamaguchi 2023 Cohort 1	Japan, South Korea	II	T-DXd	20	64.0 (29-74)	16/4	low	5 (26%)	17 (89%)	7.8 (4.7-NR)	4.4 (2.7-7.1)	20 (100
NCT03329690	Yamaguchi 2023 Cohort 2	Japan, South Korea	II	T-DXd	24	58.5 (30-72)	22/2	low	2 (10%)	15 (71%)	8.5 (4.3-10.9)	2.8 (1.5-4.3)	24 (100

ORR: overall response rate; DCR: disease control rate; mOS: median overall survival; mPFS: median progression-free survival; AE: adverse events; NR: Not reached

Assessment of quality

The results of the quality assessment showed, the MINORS quality scores of 6 nonrandomized studies generated by MINORS ranged from 10 to 14. The item 'Unbiased assessment of the study endpoint' of all 6 single-arm studies were scored 0 because of the absence of description about blind evaluation of the endpoints (Table 2). The quality of two RCTs (*Shitara 2020 and Peter 2017*) was assessed by RoB2 and the two studies were rated as low risk (Figure 2). In brief, no study was excluded due to a high risk of bias.

Table 2. Quality assessment of included single-arm studies

Study ID	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints app
Shitara 2019	2	2	2	2
Cutsem 2023	2	2	2	2
Banerji 2019	2	2	2	2
Peng 2021	2	2	2	2
Zhang2022	2	2	2	0
Yamaguchi 2023	2	2	2	2

Efficacy

Given heterogeneity was observed in each efficacy analysis, the random-effects model was employed to calculate the pooled outcomes. The ORR of all 8 studies ranged from 6% to 43%. The pooled ORR was 29% (95% CI: 20%-38%) and there was considerable heterogeneity in the results (I^2=84.5%, p =0.000) (Figure 3A). Six studies reported DCR, which ranged from 42% to 86%. The pooled DCR was 71% (95% CI: 56%-86%) and significant heterogeneity was identified in the DCR analysis (I^2=93.1%, p =0.000) (Figure 3B).

Although OS data were reported in seven studies, the results of*Zhang 2022* and cohort 1 in *Yamaguchi 2023* were not included in the analysis because they did not reach the upper confidence interval. The mOS of the other 6 studies ranged from 7.90 to 12.80 months, the pooled result was 9.68 months (95% CI: 7.78-11.58 months), and the heterogeneity in the mOS analysis was moderate (I^2=71.1%, p=0.004) (Figure 3C). PFS data were available in all 8 studies and the results of the two cohorts in *Yamaguchi 2023* were analyzed and presented separately. The mPFS of the studies ranged from 2.70 to 5.60 months and the pooled result was 4.06 months (95% CI: 3.22-4.90 months). The mPFS analysis indicated moderate heterogeneity (I^2=73.3%, p =0.000) (Figure 3D). To sum up, HER2-targeted ADCs could induce tumor response and bring survival benefits for GC/GEJC patients.

Safety

Seven studies reported AEs data, and almost all patients enrolled in these studies had at least one AE (98.8%). The most common treatment-emergent AEs (TEAEs) included nausea, decreased appetite, anemia, decreased neutrophil count, asthenia and vomiting, with incidences of 54.7% (95% CI: 37.0%-72.4%), 48.7% (95% CI: 33.2%-64.1%), 39.6% (95% CI: 28.6%-50.7%), 34.3% (95% CI:16.5%-52.2%), 28.5% (95% CI: 7.0%-50.1%) and 28.1% (95% CI: 20.6%-35.6%), respectively. The pooled incidence of grade 3 or higher TEAEs was 58.8% (95% CI: 43.0%-74.5%). Anemia was the most common grade [?]3 TEAE, with an incidence of 21.3% (95% CI: 12.1%-30.5%). Other common grade [?]3 TEAEs included decreased neutrophil count, decreased white blood cell count, decreased platelet count, decreased appetite and decreased lymphocyte count, the incidences of 20.4% (95% CI: 7.9%-33.0%), 12.5% (95% CI: 6.8%-18.2%), 7.5% (95% CI: 3.0%-11.9%), 6.3% (95% CI: 2.5%-10.1%) and 6.1% (95% CI: 2.3%-10.0%), respectively. A detailed description of TEAEs is presented in Table 3.

Table 3. TEAEs of the included studies

TEAE	Any grade % (95% CI)	I2 (%)	Grade [?]3 % (95% CI)	I2 (%)
nausea	54.7 (37.0-72.4)	95.5	1.4 (0.5-2.3)	49.2
decreased appetite	48.7 (33.2-64.1)	94.0	6.3 (2.5-10.1)	85.4
anemia	39.6 (28.6-50.7)	88.7	21.3 (12.1-30.5)	89.7
decreased neutrophil count	34.3 (16.5-52.2)	96.6	20.4 (7.9-33.0)	95.6
asthenia	28.5 (7.0-50.1)	96.4	2.2 (0.8-3.5)	0
vomiting	28.1 (20.6-35.6)	76.8	2.3 (0.6-4.0)	0
decreased white blood cell count	26.8 (9.3-44.4)	97.6	12.5 (6.8-18.2)	69.5
decreased platelet count	27.3 (20.8-33.7)	69.8	7.5 (3.0-11.9)	83.0
decreased lymphocyte count	11.2 (3.7-18.6)	83.5	6.1 (2.3-10.0)	60.8

TEAE: treatment-emergent adverse event

Subgroup analysis

Considering the high heterogeneity shown in the pooled results, subgroup analysis was performed to identify the sources of the heterogeneity. We chose several common factors that related to effectiveness including age, ECOG performance status (PS), primary site of tumor, region, and HER2 expression status as classification variables. However, only ORR data were used for subgroup analysis due to the limited data.

The results showed (Figure 4 A-D) that none of the differences in age, ECOG PS, primary tumor type or region was a source of heterogeneity, and there was no significant difference between the subgroups (p=0.941; p=0.748; p=0.625, p=0.734, respectively). The HER2 status subgroup analysis showed (Figure 4E) that the ORR of HER2-positive and HER2-low patients were significant different (39% vs 19%, p=0.037). The heterogeneity of ORRs in both the HER2-postive group (I^2=35.5%, p =0.171) and HER2-low group (I^2=0.0%, p =0.843) was reduced significantly compared to the pooled results (I^2=53.0%,p =0.037), indicating that HER2 expression status was one of the factors leading to heterogeneity.

Given T-DXd was the only drug which has been used as intervention regimen in more than one study in this meta-analysis, we further calculated the efficacy of T-DXd in patients with HER-2 overexpression. As the results showed (Figure 4 F-I), the pooled ORR and DCR were respectively 43% (95% CI: 36%-49%) and 83% (95% CI: 79%-88%). The pooled mOS and mPFS were respectively 12.36 months (95% CI: 10.53-14.19 months) and 5.60 months (95% CI: 4.59-6.61 months). And no heterogeneity was observed among these results.

Sensitivity analysis and publication bias

To further explore the sources of heterogeneity, a sensitivity analysis was conducted by excluding each study. The results are presented in Figure 5. No study had a significant effect on the pooled results, which suggested that although heterogeneity exists, the summary outcomes of the meta-analysis are stable.

Egger's regression test was employed to detect publication bias. As shown in Figure 6, the ORR, DCR, mPFS, mOS and incidence of grade 3 or higher AEs were p=0.427 (95% CI: -4.25 to 8.79), p=0.571 (95% CI: -18.22 to 11.61), p=0.193 (95% CI: -1.03 to 4.25), p=0.264 (95% CI: -0.23 to 6.43) and p=0.258 (95% CI: -20.34 to 6.85), respectively. No publication bias was identified for any of the outcomes. In brief, the results of this meta-analysis were reliable.

Discussion

ADCs are a novel class of promising antitumor drugs which have made great breakthrough in recent years. As a representative of second-generation ADCs, trastuzumab emtansine (T-DM1), which is composed of trastuzumab and a derivative of maytansine, was the first ADC approved for solid tumor treatment. According to the EMILIA trial, T-DM1 showed superior efficacy and safety compared to lapatinib plus capecitabine in posterior-line treatment of patients with advanced HER2-positive breast cancer (BC) [37]. Thereafter, studies of other ADCs targeting HER2 showed encouraging survival benefits as well. T-DXd was granted accelerated approval for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who received two or more prior anti-HER2-based regimens in the metastatic setting in 2019 based on the phase II DESTINY-Breast 01 trial[38, 39]. T-DXd also demonstrated promising antitumor activity in patients with heavily pretreated HER2-expressing or *HER2* -mutant solid tumors and HER2-low advanced BC[40-42]. The phase III DESTINY-Breast 03 study compared the efficacy and safety of T-DXd with T-DM1 in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, and the results showed that T-DXd significantly improved PFS and overall response with a 12-month PFS rate of 75.8% vs. 34.1% (HR 0.28; 95% CI, 0.22 to 0.37; P<0.001) and an ORR of 79.7% vs. 34.2%, respectively[43]. In a preclinical study, ARX788 showed strong antitumor activity in HER2-positive and HER2-low expression breast and gastric cancer patient-derived xenografts as well as in a T-DM1-resistant model[44]. Trastuzumab duocarmazine (SYD985) presented remarkable activity in epithelial ovarian cancer cell lines with strong and moderate to low HER2/neu expression[45]. These novel anti-HER2 agents bring hope to the subpopulation. On the basis of the promising survival outcomes, anti-HER2 ADCs have also been investigated in many clinical trials of patients with GC and GEJC. However, the clinical efficacy varies with different HER2-targeted ADCs.

In this meta-analysis, we included 6 single-arm trials and 2 RCTs with a total of 871 patients and thoroughly evaluated the efficacy and safety of HER2-targeted ADCs in the treatment of patients with GC and GEJC. T-DXd was used in four of the studies, and one study involved patients with HER2-low expression only. Despite the HER2 expression status, the pooled efficacy results showed that the ORR and DCR were 29% and 71%, respectively. The pooled mOS and mPFS were 9.68 months and 4.06 months, respectively. According to our subgroup analysis, the patients positive for HER2 expression benefitted more from anti-HER2 ADCs, with an ORR of 39%. The ORR of HER2-low patients is 19%, and the result of ADC treatment is moderately better than that of the standard second-line treatment (ramucirumab in combination with paclitaxel)[46]. Given that only two studies provided data on the HER2-low patient subgroup and that survival time data were unavailable, the efficacy of anti-HER2 ADCs in HER2-low GC and GEJC needs to be validated in more studies in the future. However, there is no doubt that the results of this meta-analysis confirmed HER2-targeted ADCs were potential therapy options for previously treated GC/GEJC patients regardless of HER2 expression status.

Among all currently developed anti-HER2 ADCs, T-DXd was the most representative. It has been approved as second- or later-line treatment for patients with HER2-overexpressing GC or GEJC. We calculated the pooled results of the 3 studies that conducted T-DXd on HER2-positive GC and GEJC patients[32-34]. The pooled ORR and DCR were 43% and 83%, respectively. The pooled mOS and mPFS were 12.36 month and 5.60 months, respectively. These results were better than that of overall anti-HER2 ADCs and no heterogeneity was observed in the results.

Notably, in contrast to the case in breast cancer, T-DM1 is not as effective as expected in HER2-positive GC and GEJC. One possible reason is that HER2 loss after trastuzumab and the higher intratumoral heterogeneity in gastric cancer than in breast cancer affect the activity of T-DM1 due to the lack of a bystander effect which can kill both antigen-positive cells and adjacent antigen-negative tumor cells in the heterogeneous tumors[47]. Another potential explanation is that the payload of T-DM1 (emtansine) might be less active in gastric cancer[12, 27]. The worst ORR result was provided by the *Banerji 2019* study which employed SYD985; only one of 16 patients achieved an objective response, significantly lower than the ORRs of the cohorts of enrolled patients with breast cancer, urothelial cancer and endometrial cancer. However, the sample size of this study is too small to draw a conclusion, and the clinical activity of SYD985 in HER2-positive GC/GEJC patients needs to be validated in more studies on a larger scale in the future.

In terms of safety, almost all patients experienced at least one AE during the treatment. The pooled incidence of all-grade AEs was 98.8%. Gastrointestinal and hematologic toxicity were the most common, with the five most common AEs including nausea, decreased appetite, anemia, decreased neutrophil count and asthenia. The pooled incidence of grade [?]3 TEAEs was 58.8%, and it is worth paying attention to the serious hematologic toxicity such as anemia, decreased neutrophil count, decreased white blood cell count and decreased platelet count. The considerable incidence of high-grade AEs might be related to off-target effects and the toxic payload. In this meta-analysis, the incidence of ang grade TEAEs related to T-DXd was 100%. Additionally, despite the unusual ocular toxicity exhibited in ARX788, it seemed like the most safety ADC with a grade[?]3 TEAE incidence of 13.3%.

Overall, based on their clinical efficacy and acceptable safety, HER2-targeted ADCs have emerged as a promising class of anti-HER2 therapeutics and could serve as a new option for second- or later-line treatment in GC and GEJC patients. At present, a variety of anti-HER2 ADCs are under clinical investigation. Beyond breast and gastric cancer, the efficacy of these medications has also been explored in other solid tumors, such as urothelial carcinoma, colorectal cancer and non-small cell lung cancer. With the constant development of production technology, next-generation ADCs with optimized structural designs may simultaneously further improve activity and decrease toxicity in normal tissues in the future.

There are some limitations in the study. First, because the investigation of HER2-ADCs in GC and GEJC has just started in the last few years, the number of eligible trials and the sample size are not too large. Except for T-DXd, the other 5 types of drugs were used in just one study each. Second, due to the limited data, thorough subgroup analyses could not be conducted and the sources of high heterogeneity across the results remain unclear. Finally, the fact that most of the included studies were sing-arm trials may lead to an overestimation of efficacy. In the future, large-scale RCTs are needed to further evaluate and compare the efficacy of HER2-targeted ADCs with other anti-HER2 treatment regimens.

Conclusion

This meta-analysis demonstrated the efficacy of HER2-targeted ADCs in GC and GEJC patients as second- and later-line treatments. Patients with HER2 overexpression benefitted more from these novel drugs than patients with low HER2 expression. Regarding safety, the high incidence of grade3 and above AEs is worthy of attention. However, given the currently limited clinical data, further validation is needed in larger-scale RCTs in the future.

Author Contributions

Fanghua Song : Conceptualization (lead); supervision (lead); writing-review&editing (lead). **Ziqi Ye** : Formal analysis (equal); methodology (lead); writing-original draft (lead).**Zhenhao Cheng** : Data curation (lead); investigation (lead).**Sen Wu** : Investigation (equal); software (lead). **Feiyan Zhou** : Data curation (supporting); formal analysis (supporting).

Conflict of Interest Statement

None of the authors has reported any conflicts of interest related to the study.

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