In era of immunotherapy: the value of trastuzumab beyond progression in patients with trastuzumab-resistant HER2-positive advanced or metastatic gastric cancer

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Abstract

Background: For patients with human epidermal growth factor receptor-2 (HER2)-positive advanced or metastatic gastric cancer who have progressed on first-line trastuzumab therapy, the clinical value of the continuous use of trastuzumab beyond progression (TBP) is controversial.

Objectives: The present study was conducted to evaluate the efficacy and explore new treatment strategies of TBP for patients with trastuzumab-resistant HER2-positive advanced or metastatic gastric cancer in the era of cancer immunotherapy.

Design: Retrospective analysis.

Methods: Patients with HER2-positive advanced or metastatic gastric cancer who have failed first-line treatment based on trastuzumab-targeted therapy from June 2019 to December 2020 were retrospectively analyzed. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. Survival curves of patients were estimated by the Kaplan–Meier method and compared using the log-rank test.

Results: In all, 30 patients received TBP with chemotherapy, immunotherapy, or anti-angiogenic therapy, and the other 26 patients received treatment of physician's choice without trastuzumab. The median PFS in the TBP and non-TBP population was 6.0 [95% confidence interval (CI) = 3.8–8.2] and 3.5 (95% CI = 2.2–4.8) months, respectively ($p = 0.038$), and the median OS was 12.3 (95% CI = 10.4–14.2) and 9.0 (95% CI = 6.6–11.4) months ($p = 0.008$). The patients who received TBP treatment had more favorable PFS and OS than the non-TBP population. In the TBP group, patients who received trastuzumab plus chemotherapy and immunotherapy had higher ORR (40.0% *versus* 16.7%), DCR (90.0% *versus* 50.0%), and showed a significant improvement in PFS (7.0 *versus* 1.9 m) compared to TBP with chemotherapy alone. Subgroup analysis suggested that patients with male, HER2 positive with immunohistochemistry score 3+ and PFS of first-line treatment less than 6 months had a greater benefit from TBP. The incidence of Grade 3–4 adverse events in the TBP and non-TBP groups was 43.3% and 38.5%.

Conclusion: The continuous use of TBP improves PFS and OS in patients with trastuzumab-resistant HER2-positive advanced or metastatic gastric cancer with well-tolerated toxicity. In the era of immunotherapy, TBP combined with chemotherapy and immunotherapy may further enhance the clinical benefit and provide a new treatment strategy.

Trial registration: This study is a retrospective study, which does not require clinical registration.

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Plain language summary

The value of TBP in trastuzumab-resistant HER2-positive advanced or metastatic gastric cancer

Patients with human epidermal growth factor receptor-2 (HER2) positive advanced or metastatic gastric cancer who have failed from first-line treatment based on trastuzumab targeted therapy from June 2019 to December 2020 were retrospectively analyzed. 30 patients received TBP with chemotherapy, immunotherapy or anti-angiogenic therapy, and the other 26 patients received treatment of physician's choice without trastuzumab. The median PFS in the TBP and non-TBP population was 6.0(95% CI = 3.8-8.2) and 3.5 (95% CI = 2.2-4.8) months, respectively (P = 0.038), and the median OS was 12.3 (95% CI = 10.4-14.2) and 9.0 (95% CI = 6.6-11.4) months (P = 0.008). In TBP group, patients who received trastuzumab plus chemotherapy and immunotherapy had higher ORR, DCR and showed a significant improvement in PFS compared to TBP with chemotherapy-alone (p = 0.024). Subgroup analysis suggested that patients with male, HER2-positive with IHC score 3+ and PFS of first-line treatment less than 6 months had a greater benefit from TBP. The continuous use of TBP does not increase the incidence of adverse events (AEs). The continuous use of TBP improve PFS and OS in patients with trastuzumab-resistant HER2-positive advanced or metastatic gastric cancer with well tolerated toxicity. In the era of immunotherapy, TBP combined with chemotherapy and immunotherapy further enhanced the clinical benefit and provide new treatment strategy.

Keywords: ErbB-2, molecular targeted therapy, stomach neoplasms, trastuzumab, treatment outcome

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Introduction

According to the latest global cancer burden data in 2020, gastric cancer is currently the fifth most common cancer type and the fourth leading cause of death in the world.[1] The incidence of gastric cancer is related to some demographic factors such as geographic region, patient's race, gender, and socioeconomic status.[2] China is the country with the largest number of gastric cancer incidences and deaths in the world. Meanwhile, the proportion of early gastric cancer patients in China is only about 20%, and 80% of gastric cancer patients are in the advanced stage when they are first diagnosed, which seriously affects the prognosis of patients.[3]

With the deepening understanding of the biological behavior of gastric cancer, advanced or metastatic gastric cancer has entered the era of comprehensive treatment mode including chemotherapy, targeted therapy, and immunotherapy.[4,5] The positive rate of HER2 in Chinese patients is 12–13%, and immunohistochemistry (IHC) 3+ or IHC 2+ and fluorescence *in situ* hybridization (FISH) positive was defined as human epidermal growth factor receptor-2 (HER2) positive. However, due to the highly heterogeneous gastric cancer, there is a significant difference in the positive rate of HER2, which is below 10% in East Europe.[6] The results of the ToGA study showed that trastuzumab combined with 5-Fluorouracil (5-FU)/capecitabine and cisplatin improved the efficacy and survival benefit in patients with newly diagnosed HER2-positive advanced or metastatic gastric cancer compared with chemotherapy alone.[7] A number of phase II studies have evaluated trastuzumab in combination with other chemotherapeutics, showing good efficacy and safety.[8] Trastuzumab combined with chemotherapy has become the first-line treatment recommendation for HER2-positive advanced or metastatic gastric cancer.[9]

For patients with HER2-positive advanced or metastatic gastric cancer who have progressed on first-line trastuzumab therapy, there is currently no

standard second-line anti-HER2 regimen, and the results of phase II studies and retrospective studies in recent years have shown that the clinical value of the continuous use of trastuzumab beyond progression (TBP) is controversial.[10,11] Meanwhile, recent studies have shown that immune checkpoint inhibitors exhibit superior efficacy in both first-line and above therapy of advanced or metastatic gastric cancer compared to traditional treatments. In the era of immunotherapy, the value of TBP is still unclear. Our present study was conducted to evaluate the efficacy and safety of TBP for patients with trastuzumab-resistant HER2-positive advanced or metastatic gastric cancer in the era of cancer immunotherapy.

Methods

Patients population

This was a retrospective study. From June 2019 to December 2020, patients with HER2-positive advanced or metastatic gastric cancer who have failed from prior first-line trastuzumab in combination with chemotherapy treatment were collected in this study. In this study, the patients were consecutively selected. We have de-identified all patient details.

Pathological evaluation

The pathological diagnosis and HER2 detection of the enrolled patients in this study were all completed by the gastric cancer pathology sub-professional team. The HER2 status was determined by the guidelines and detection process for HER2 testing in gastric cancer.[6] The conventional slides were used for IHC assessment and the membrane expression of HER2 was independently evaluated by two experienced pathologists, including score 0 (negative), score 1 (negative), score 2 (equivocal), and score 3 (positive). For patients with IHC 2+, HER2 was further assessed by FISH. Cases with a HER2/CEP17 ratio under 1.8 were considered negative and those with a ratio $\geqslant$2.2 were classified as positive. HER2 positive was defined as an IHC score of 3+ or an IHC score of 2 and FISH positive.

Study treatment

In this study, the patients received first-line trastuzumab in combination with chemotherapy treatment, including oxaliplatin + S-1, oxaliplatin + capecitabine, oxaliplatin + S-1 + docetaxel, and S-1 + docetaxel. After disease progression, the patients received second-line treatment with or without trastuzumab. For the continuous use of the TBP group, trastuzumab was given continuously concurrent with chemotherapy, chemotherapy plus immunotherapy, chemotherapy plus anti-angiogenic therapy until disease progression, unacceptable toxicity, or death. In the discontinuation use of the TBP group, treatment of the physician's choice was given, including chemotherapy, chemotherapy plus immunotherapy, and chemotherapy plus anti-angiogenic therapy. The patients received irinotecan or paclitaxel chemotherapy. Irinotecan was administered intravenously at a dose of 125 mg/m^2 on d1 and d8 every 3 weeks. The paclitaxel was given intravenously, the dosage was 80 mg/m^2 on d1, d8, and d15 every 4 weeks. For immunotherapy, a programmed cell death protein 1 (PD-1) inhibitor was administered intravenously at the recommended dose, including sintilimab, camrelizumab, or tislelizumab. For anti-angiogenic therapy, apatinib was administered orally daily at the dosage of 250 mg.

Efficacy and safety assessments

After treatment, all patients underwent imaging examination every two cycles to evaluate the clinical efficacy. The efficacy evaluation criteria are RECIST version 1.1 response evaluation criteria in solid tumors, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was CR + PR, and the disease control rate (DCR) was CR + PR and SD. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[12] Differences between groups were determined by Pearson's χ^2 test or Fisher's exact test. Survival curves of patients were estimated by the Kaplan–Meier method and compared using the log-rank test. The follow-up deadline is 31 December 2021. Progression-free survival (PFS) was defined as starting second-line with or without trastuzumab treatment to disease progression or death. Overall survival (OS) was defined as the period from the time of second-line treatment with or without

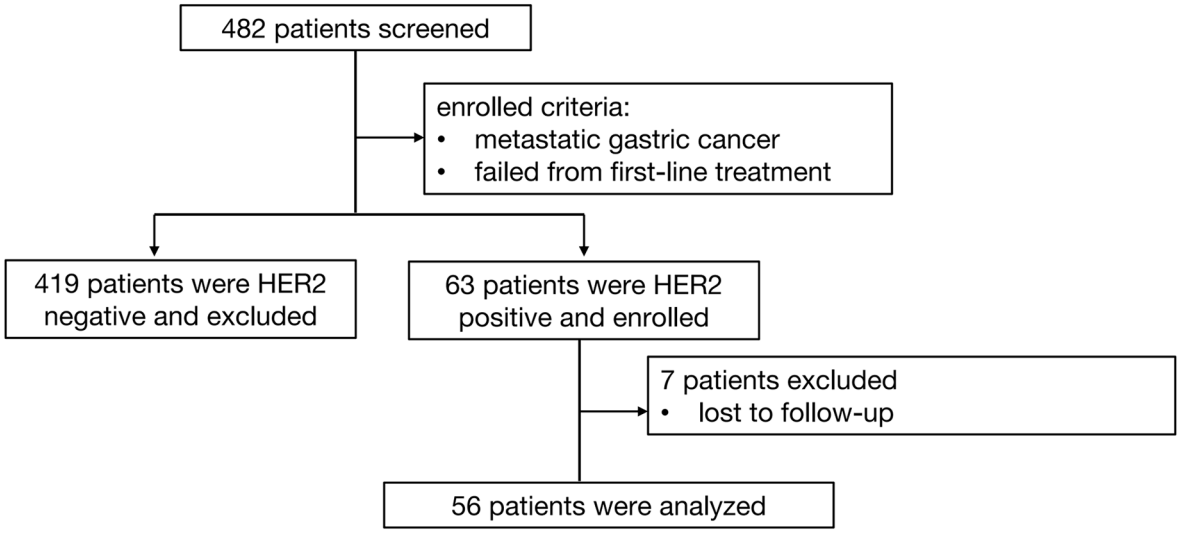

Figure 1. The flowchart of this study.

trastuzumab to patient death or last follow-up. Subgroup analysis of predictive factors for PFS was carried out by Cox proportional hazards model. All the statistical descriptive analyses were performed with SPSS 22.0 software (SPSS Inc., IL, USA) software. $p < 0.05$ was considered significant.

Results

Patient and treatment characteristics

A total of 56 patients with HER2-positive advanced or metastatic gastric cancer who have failed from prior first-line trastuzumab in combination with chemotherapy treatment were included in the present study (Figure 1). Patient and treatment characteristics are summarized in Table 1. The median age was 61 years (range, 25–79), with 19 female patients and 37 male patients. In all, 38 patients had advanced gastric cancer, and the other 18 patients had gastroesophageal junction (GEJ) adenocarcinoma. The common metastatic sites included lymph nodes (82.1%), liver (42.9%), peritoneum (10.7%), and lung (26.8%). Proportions of patients with HER2 IHC score 3+ and IHC score 2+/FISH-positive were 62.5% and 37.5%, respectively. All the patients received first-line trastuzumab in combination with chemotherapy treatment, and the median PFS was 5.1 months (95% CI = 3.8–6.4). The duration of trastuzumab in combination with chemotherapy treatment in 26 patients was more than 6 months, and the other 30 patients were less than 6 months.

In second-line treatment, 30 patients received continuous use of TBP and the other 26 patients received treatment of physician's choice without trastuzumab. In the TBP group, concurrent treatment includes chemotherapy ($n = 12$, 40.0%), chemotherapy plus immunotherapy ($n = 10$, 33.3%), and chemotherapy plus anti-angiogenic therapy ($n = 8$, 26.7%). In the non-TBP group, treatment manner includes chemotherapy ($n = 12$, 46.2%), chemotherapy plus immunotherapy ($n = 8$, 30.8%), and chemotherapy plus anti-angiogenic therapy ($n = 6$, 23.1%). Except for trastuzumab, there were no statistically significant differences in treatment regimens between the two groups ($p = 0.89$).

Efficacy

In the general population, CR was not observed, 11 patients achieved PR, 26 patients had SD, and 19 patients had PD. The overall ORR and DCR were 19.6% (11/56) and 66.1% (37/56), respectively (Table 2). In the TBP population, CR was not observed, 7 patients achieved PR, 14 patients had SD, and 9 patients had PD. The overall ORR and DCR were 23.3% (7/30) and 70.0% (21/30), respectively. In the non-TBP population, CR was not observed, 4 patients achieved PR, 12 patients had SD, and 10 patients had PD. The overall ORR and DCR were 15.4% (4/26) and 61.5%

Table 1. Patient and treatment characteristics.

Characteristic	Total ($n=56$), n (%)	TBP ($n=30$), n (%)	Non-TBP ($n=26$), n (%)	p
Age				–
Median	61	59	65	
Range	25–79	40–79	25–77	
Sex				0.505
Female	19 (33.9)	9 (30.0)	10 (38.5)	
Male	37 (66.1)	21 (70.0)	16 (61.5)	
ECOG				0.547
0–1	45 (80.4)	25 (83.3)	20 (76.9)	
2	11 (19.6)	5 (16.7)	6 (23.1)	
Primary tumor site				0.436
Gastric	38 (67.9)	19 (63.3)	19 (73.1)	
GEJ	18 (32.1)	11 (36.7)	7 (26.9)	
Metastatic site				0.873
Lymph node	46 (82.1)	26 (86.7)	20 (76.9)	
Liver	24 (42.9)	12 (40.0)	12 (46.2)	
Peritoneum	6 (10.7)	3 (10.0)	3 (11.5)	
Lung	15 (26.8)	8 (26.7)	7 (26.9)	
Others	17 (30.4)	7 (23.3)	10 (38.5)	
Number of metastatic sites				0.757
1–2	42 (75.0)	22 (73.3)	20 (76.9)	
⩾3	14 (25.0)	8 (26.7)	6 (23.1)	
Prior surgery				0.873
Yes	20 (35.7)	11 (36.7)	9 (34.6)	
No	36 (64.3)	19 (63.3)	17 (65.4)	
HER2 status				0.678
IHC 3+	35 (62.5)	18 (60.0)	17 (65.4)	
IHC 2+, FISH positive	21 (37.5)	12 (40.0)	9 (34.6)	
PFS of first-line therapy				0.300
<6 months	30 (53.6)	18 (60.0)	12 (46.2)	
⩾6 months	26 (46.4)	12 (40.0)	14 (53.9)	
Second-line regimens (used with or without trastuzumab)				0.894
Chemotherapy	24 (42.9)	12 (40.0)	12 (46.2)	
Chemotherapy + immunotherapy	18 (32.1)	10 (33.3)	8 (30.8)	
Chemotherapy plus anti-angiogenic therapy	14 (25.0)	8 (26.7)	6 (23.1)	

ECOG, Eastern Cooperative Oncology Group performance status; FISH, fluorescence *in situ* hybridization; GEJ, gastroesophageal junction tumors; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; PFS, progression-free survival; TBP, trastuzumab beyond progression.

Table 2. Efficacy of second-line treatment in patients with HER2-positive advanced or metastatic gastric cancer.

Parameter	Best response				ORR	DCR	Median PFS (95% CI)	*p*	Median OS (95% CI)	*p*
	CR	PR	SD	PD						
Total	0	11	26	19	19.6% (11/56)	66.1% (37/56)	4.0 (2.3–5.7)		9.5 (7.4–11.6)	
Treatment programs								**0.038**		**0.008**
TBP	0	7	14	9	23.3% (7/30)	70.0% (21/30)	6.0 (3.8–8.2)		12.3 (10.4–14.2)	
Non-TBP	0	4	12	10	15.4% (4/26)	61.5% (16/26)	3.5 (2.2–4.8)		9.0 (6.6–11.4)	
Combination type in the TBP group								0.073		0.689
Chemotherapy	0	2	4	6	16.7% (2/12)	50.0% (6/12)	1.9 (0.7–3.1)		11.5 (7.6–15.4)	
Chemotherapy + immunotherapy	0	4	5	1	40.0% (4/10)	90.0% (9/10)	7.0 (3.7–10.3)	**0.024***	9.0 (2.0–16.0)	0.787*
Chemotherapy + anti-angiogenic therapy	0	1	5	2	12.5% (1/8)	75.0% (6/8)	6.0 (1.4–10.6)	0.243*	13.0 (11.5–14.5)	0.381*
Combination type in non-TBP								0.135		0.851
Chemotherapy	0	2	5	5	16.7% (2/12)	58.3% (7/12)	2.3 (1.0–3.6)		7.0 (3.6–10.4)	
Chemotherapy + immunotherapy	0	2	3	3	25.0% (2/8)	62.5% (5/8)	3.2 (1.1–5.3)	0.209*	7.0 (1.5–12.5)	0.531*
Chemotherapy + anti-angiogenic therapy	0	0	4	2	0% (0/6)	66.7% (4/6)	4.0 (0–9.8)	0.077*	9.0 (3.6–14.4)	0.695*

**Versus* chemotherapy.
Bold values: $P < 0.05$.
CI, confidence interval; CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor-2; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TBP, continuous use of trastuzumab beyond progression.

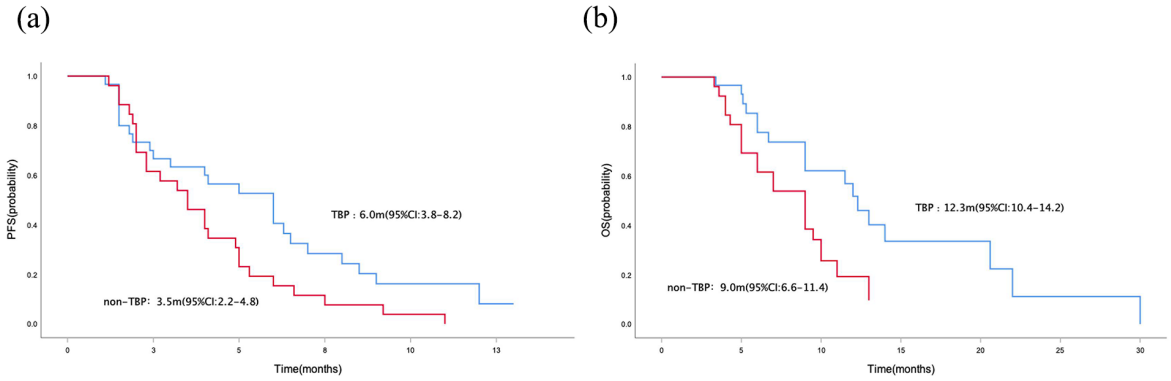

Figure 2. Kaplan–Meier curve of (a) PFS and (b) OS in the TBP and non-TBP therapy population.
OS, overall survival; PFS, progression-free survival.

(16/26), respectively. The patients in the TBP group had higher ORR and DCR than the non-TBP population, but there was no statistical difference between the two groups.

The median PFS was 6.0 (95% CI = 3.8–8.2) and 3.5 (95% CI = 2.2–4.8) months in the TBP and non-TBP population, respectively [$p = 0.038$; Figure 2(a)]. The median OS was 12.3 (95% CI = 10.4–14.2) and 9.0 (95% CI = 6.6–11.4) months in the TBP and non-TBP population, respectively [$p = 0.008$; Figure 2(b)]. The patients who received TBP treatment had more favorable PFS and OS than the non-TBP population. The present study also performed exploratory research to evaluate the efficacy of different concurrent treatment programs in the TBP and non-TBP populations, respectively, including chemotherapy, chemotherapy plus immunotherapy, and chemotherapy plus anti-angiogenic therapy. In the TBP group, patients who received trastuzumab plus chemotherapy and immunotherapy had higher ORR and DCR, and PFS was longer with chemotherapy and immunotherapy compared to chemotherapy alone [$p = 0.024$, Figure 3(a)]. OS was similar among the three subgroups [$p = 0.689$, Figure 3(b)]. In the non-TBP group, there was no significant difference in ORR, DCR, PFS, and OS between the chemotherapy plus immunotherapy group, chemotherapy plus anti-angiogenic therapy group, and the chemotherapy-alone group [Figure 3(c) and (d)].

Subgroup analysis

In the general population, a subgroup analysis of PFS was carried out to evaluate clinicopathologic factors, including sex, age, number of metastatic sites, HER2 status, and PFS of first-line treatment. In subgroup analyses, the notable heterogeneity of treatment effect was according to sex, HER2 status, and PFS of first-line treatment. The results suggested that patients with male [hazard ratio (HR), 0.38; 95% confidence interval (CI) = 0.19–0.80; $p = 0.010$], HER2 positive with IHC score 3+ (HR, 0.37; 95% CI = 0.18–0.80; $p = 0.011$), and PFS of first-line treatment less than 6 months (HR, 0.39; 95% CI = 0.16–0.94; $p = 0.036$) and had a greater benefit from TBP treatment than that with non-TBP therapy (Figure 4).

Safety

The incidence of Grade 3–4 AEs in the TBP and non-TBP groups was similar (Table 3). In the TBP group, the Grade 3–4 treatment-related AEs were decreased white blood count ($n = 5$, 16.7%), increased alanine aminotransferase/aspartate aminotransferase (ALT/AST) ($n = 2$, 6.7%), fatigue ($n = 2$, 6.7%), nausea or vomiting ($n = 2$, 6.7%), muscle pain/joint pain ($n = 1$, 3.3%), and oral mucositis ($n = 1$, 3.3%). In the non-TBP group, the Grade 3–4 treatment-related AEs were decreased white blood count ($n = 4$, 15.4%), anemia ($n = 1$, 3.9%), nausea or vomiting ($n = 3$, 11.5%), muscle pain/joint pain ($n = 1$, 3.8%), and secondary hypertension ($n = 1$, 3.8%). No severe cardiac AEs were observed in relation to trastuzumab treatment, including subclinical loss of mean left ventricular ejection fraction (defined as >10% relative loss) and congestive heart failure.

Discussion

For patients with advanced and metastatic gastric cancer, traditional treatments such as surgery,

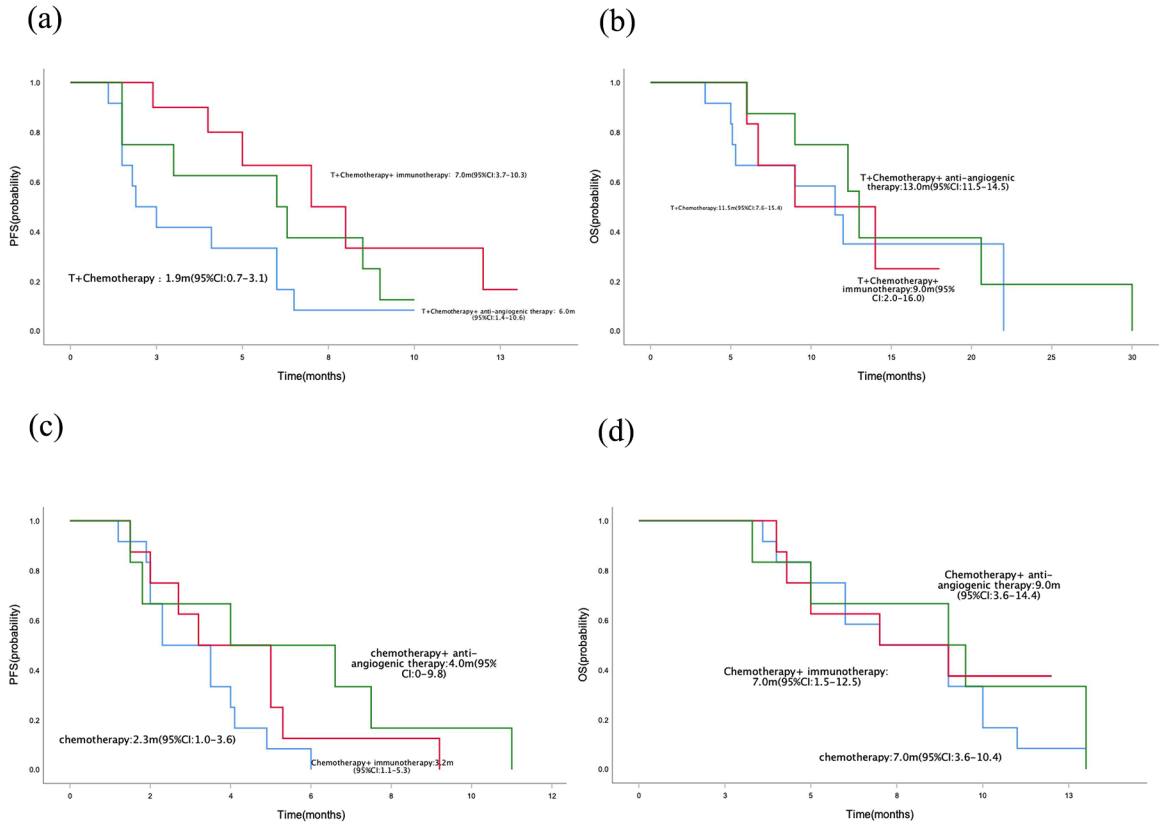

Figure 3. Kaplan–Meier curve of (a) PFS and (b) OS in TBP therapy population with different treatment programs. Kaplan–Meier curve of (c) PFS and (d) OS in non-TBP therapy populations with different treatment programs.
OS, overall survival; PFS, progression-free survival; TBP, trastuzumab beyond progression.

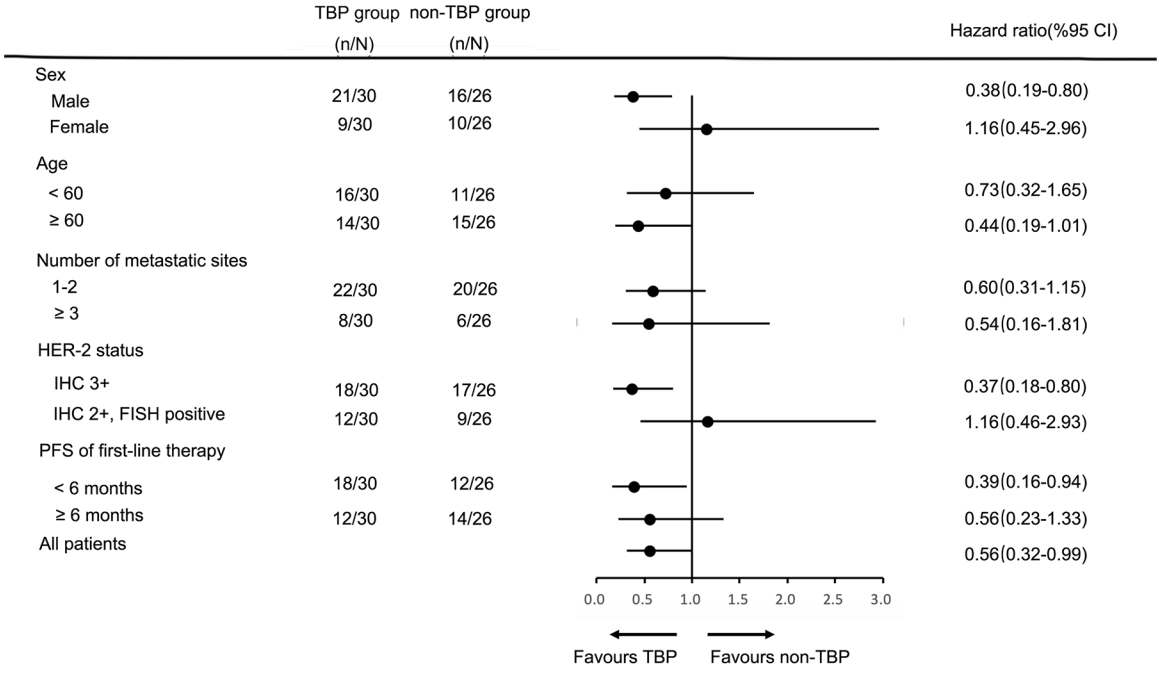

Figure 4. Subgroup analysis of PFS according to clinicopathologic factors, including sex, age, number of metastatic sites, HER2 status, and PFS of first-line treatment.
HER2, human epidermal growth factor receptor-2; PFS, progression-free survival.

Table 3. Treatment-related adverse events.

Adverse event	TBP (≥Grade 3)	Non-TBP (≥Grade 3)
Hematologic		
Decreased white blood count	5 (16.7)	4 (15.4)
Anemia	0	1 (3.8)
Decreased platelet	0	0
Increased ALT/AST	2 (6.7)	0
Hyperbilirubinemia	0	0
Non-hematologic		
Fatigue	2 (6.7)	0
Nausea or vomiting	2 (6.7)	3 (11.5)
Muscle pain/joint pain	1 (3.3)	1 (3.8)
Diarrhea	0	0
Secondary hypertension	0	1 (3.8)
Hand–foot syndrome	0	0
Proteinuria	0	0
Rash	0	0
Pneumonitis	0	0
Oral mucositis	1 (3.3)	0
Hypothyroidism	0	0
Cardiac		
Congestive heart failure	0	0
Subclinical loss of mean LVEF	0	0

LVEF, left ventricular ejection fraction; TBP, continuous use of trastuzumab beyond progression.

chemotherapy, and radiotherapy have limited efficacy. In recent years, with a deep understanding of the biological behavior of gastric cancer and the continuous research and development of innovative drugs such as targeted therapy and immunotherapy, comprehensive therapy has become the main treatment strategy for gastric cancer, and the overall treatment level of gastric cancer has been significantly improved. Among them, anti-HER2-targeted therapy is an important part of comprehensive treatment for gastric cancer.[13]

HER2 is considered to be an important therapeutic target for gastric cancer. It was reported that the global positive rate of HER2 in gastric cancer is 7.3–20.2%, and the positive rate of HER2 in Chinese patients is 12–13%.[14,15] Due to the highly heterogeneous aspect of gastric cancer, the correct detection and evaluation of HER2 protein expression and gene amplification status in gastric cancer is of great significance for the clinical diagnosis and treatment of gastric cancer. Different detection antibodies and specimens can have an impact on the HER2 detection results. To standardize the HER2 detection of gastric cancer, Chinese pathology experts have compiled the 'Guidelines for HER2 Detection of Gastric Cancer' based on the actual situation in China,

which provides detailed descriptions and regulations on various aspects of the HER2 status detection process for gastric cancer.

Based on the results of the phase III ToGA study, trastuzumab combined with first-line chemotherapy can significantly improve the OS of HER2-positive advanced or metastatic gastric cancer, and trastuzumab has become the only anti-HER2-targeted drug approved for first-line treatment of advanced gastric cancer. After the progression of first-line treatment based on trastuzumab, there is no effective anti-HER2 second-line treatment at present. Compared with chemotherapy, pertuzumab, lapatinib, and T-DM1 failed to bring survival benefits to patients.[16–18] New antibody–drug conjugate (ADC) drugs, such as T-DXd (DS-8201) and RC-48 have shown favorable antitumor efficacy.[19] However, due to the influence of drug accessibility and the economy, such drugs have not been widely used in clinics.

Many studies have shown that after the progression of trastuzumab therapy in HER2-positive breast cancer, the continuous use of TBP can improve the prognosis of patients, and the efficacy of TBP in breast cancer is affirmative and widely accepted.[20] GBG26/BIG03-05 study confirmed that among patients who progressed after previous trastuzumab therapy, continuous use of trastuzumab and capecitabine achieved longer PFS (8.2 *versus* 5.6 months, $p = 0.034$) compared with capecitabine alone. In the phase III EGF 104900 study, compared with lapatinib alone, trastuzumab combined with lapatinib showed OS advantage (14 *versus* 9.5 months, $p = 0.026$). However, although TBP has been also explored in HER2-positive advanced or metastatic gastric cancer, the results of phase II studies and retrospective studies in recent years are controversial. Akitaka Makiyama *et al.* reported that the TBP strategy failed to improve PFS in patients with HER2-positive advanced or metastatic gastric cancer, and another study demonstrated that TBP plus capecitabine showed a significant improvement in ORR and time to progression compared with capecitabine alone. In our present study, the patients who received TBP treatment had more favorable PFS and OS than the non-TBP population. In the TBP group, median PFS and OS were 6.0 (95% CI = 3.8–8.2) and 12.3 (95% CI = 10.4–14.2) months, respectively, which was significantly better than the non-TBP population. Our present retrospective analysis suggests that the TBP in patients with HER2-positive advanced or metastatic gastric cancer is feasible and safe.

Standardized and accurate detection of HER2 status is vitally important for molecular subtyping of gastric cancer and the selection of anti-HER2-targeted therapy. In this study, HER2 detection strictly followed the guidelines for HER2 testing in gastric cancer, including test specimens, standardized sample preparation, detection methods, and quality control. Especially for gastroscopy biopsy specimens, multi-point sampling was used to minimize the impact of tumor heterogeneity on the results.

In the clinical practice of anti-tumor treatment, the continuous use of TBP has become a special treatment strategy, which is significantly different from the traditional replacement of therapeutic drugs after disease progression.[21] Patients with relapse or disease progression after trastuzumab treatment used to be known as trastuzumab resistance, but previous studies have suggested that many so-called 'trastuzumab-resistant' patients can still benefit from re-treatment with trastuzumab. This may be related to the mechanism of trastuzumab. In addition to inhibiting HER2-mediated tumor cell proliferation, trastuzumab has other mechanisms, such as activating antibody-dependent cellular cytotoxicity, anti-angiogenesis mechanism, and so on. The exact mechanism through which TBP is effective in HER2-positive advanced or metastatic gastric cancer is still unclear.

Why are the conclusions of relevant clinical studies on TBP in HER2-positive advanced or metastatic gastric cancer inconsistent, we hypothesize that there are some differences in the design of these trials. In most previous studies, the concomitant treatment was chemotherapy, including trastuzumab plus paclitaxel *versus* paclitaxel, trastuzumab plus capecitabine *versus* capecitabine, trastuzumab plus docetaxel *versus* docetaxel, and other second-line therapy regimens.[22,23] In our present study, some patients also received chemotherapy alone with or without trastuzumab. The results showed that compared with chemotherapy, TBP combined with chemotherapy did not improve ORR (16.7% *versus* 16.7%) and DCR (50.0% *versus* 58.3%). And the meantime, there were no significant differences in PFS [1.9 (0.7–3.1) *versus* 2.3 (1.0–3.6) months] between the two

groups, which suggests that TBP with chemotherapy alone may not be the preferred treatment strategy. In the other patients who received chemotherapy combined with immunotherapy or anti-angiogenic therapy, TBP combined with chemotherapy and immunotherapy obtained the best ORR and DCR, and the median PFS reached 7.0 (3.7–10.3) months, which was significantly longer than TBP combined with chemotherapy or chemotherapy alone.

Previous cohort studies demonstrated that PD-L1 expression positively correlated with HER2 overexpression and simultaneously, anti-HER2-targeted therapy and immunotherapy may have synergistic antitumor effects in gastric cancer.[24,25] Preclinical study showed that trastuzumab can upregulate PD-L1 expression by mediating immune effector cells and may function as a potential mechanism of trastuzumab resistance.[26] In an animal model, the combination of anti-HER2-targeted therapy and immunotherapy can significantly improve antitumor activity compared with any one of them alone, through improving immune response and the proportion of CD8+ T lymphocytes and Interferon-gamma (IFN-γ).[27] Our study also confirmed that anti-HER2-targeted therapy and immunotherapy is an effective treatment strategy for gastric cancer and meanwhile, combined with chemotherapy and immunotherapy may be preferred TBP therapy manner. Comparing the survival data of immune monotherapy in advanced or metastatic gastric cancer, immunotherapy combined with TBP achieved better clinical efficacy.[28]

Identification of patients who would benefit from TBP treatment is vitally important. The results of subgroup analysis suggested that patients with HER2 positive with IHC score 3+ and PFS of first-line treatment less than 6 months had a greater benefit from TBP treatment than that with non-TBP therapy. The definition of HER2-positive which was defined as IHC score 3+ or IHC score 2 and FISH positive originally came from breast cancer.[29] The definition of HER2 positive in gastric cancer was referenced to that in breast cancer. Novel ADC drugs expand the benefit population of targeted therapy in HER2-positive advanced or metastatic gastric cancer patients and are effective for both HER2 IHC2+ and IHC3+.[23,30] However, the expression of HER2 in gastric cancer has high heterogeneity,[31] whether IHC score 3+ or IHC score 2 and FISH-positive affects the effect of TBP treatment still needs to be further explored. The result that PFS of first-line treatment less than 6 months and had a greater benefit from TBP treatment is interesting which may be different from our traditional perception. Our hypothesis is that, for patients who are insensitive to previous first-line treatment, early detection and modification of treatment strategy may improve survival benefit. Numerous previous studies have confirmed that trastuzumab has good drug safety and tolerance,[32,33] our present study also demonstrated that the continuous use of TBP does not increase the incidence of AEs, including cardiotoxicity.

Our study has several strengths and limitations because it is a retrospective study with not sufficiently large patient cases. Future validation and prospective clinical trials would be needed to confirm the value of continuous use of TBP in HER2-positive advanced or metastatic gastric cancer. However, to our knowledge, this is the first study that confirmed that the continuous use of TBP brings PFS and OS benefits to patients with HER2-positive advanced or metastatic gastric cancer based on a novel treatment strategy.

Conclusion

In conclusion, these data support that the continuous use of TBP improves PFS and OS in patients with trastuzumab-resistant HER2-positive advanced or metastatic gastric cancer with well-tolerated toxicity. In the era of immunotherapy, new therapeutic programs, such as TBP combined with chemotherapy and immunotherapy obtained the best ORR and DCR, and the median PFS, which may further enhance the clinical benefit and provide a new treatment strategy.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of the Affiliated Cancer Hospital of Zhengzhou University (KY-0192). Written informed consent was obtained from all patients for the use of the medical records for research purposes.

Consent for publication

Not applicable.

Author contributions

Hui Wang: Methodology; Software; Visualization; Writing – original draft; Writing – review & editing.

Caiyun Nie: Funding acquisition; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing.

Weifeng Xu: Data curation; Investigation.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The raw data of this article will be made available by contacting the corresponding author upon reasonable request.

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Supplemental material

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