Original Article

Immune checkpoint inhibitors plus paclitaxel-based chemotherapy *vs.* oxaliplatin-based therapy as first-line treatment for patients with HER2-negative unresectable or metastatic gastric/gastroesophageal junction cancer: results of a multicenter retrospective study

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Background: For unresectable or metastatic gastric/gastroesophageal junction cancer (G/GEJC), immune checkpoint inhibitors (ICIs) plus platinum-based doublet chemotherapy [FOLFOX (leucovorin, fluorouracil, and oxaliplatin) and XELOX (capecitabine and oxaliplatin)] are currently recommended as the standard first-line treatment. Research indicates that ICIs combined with paclitaxel have a synergistic effect, but the evidence is insufficient. This multicenter, retrospective study aimed to compare the efficacy and tolerability of ICIs [mainly anti-programmed cell death-1 (anti-PD-1) antibodies] plus a paclitaxel-based chemotherapy regimen (ICIs plus PTX) *vs.* an oxaliplatin-based regimen (ICIs plus OXA) as the first-line therapy for advanced G/GEJC.

Methods: This research involved 123 patients with advanced G/GEJC at three institutions in China from August 2019 to June 2022. The ICIs plus PTX group included 58 patients, whereas the ICIs plus OXA group included 65 patients. We compared the efficacy and safety of two treatment regimens.

Results: Fifty-eight patients (47.2%) received ICIs plus PTX, and 65 patients (52.8%) received ICIs plus OXA. The median progression-free survival (PFS) [8.07 *vs.* 7.23 months; hazard ratio (HR) =0.845; 95% confidence interval (CI): 0.568–1.257; P=0.40] and overall survival (OS) (14.83 *vs.* 15.10 months; HR =0.852; 95% CI: 0.536–1.355; P=0.50) were not significantly different between the ICIs plus PTX group and the ICIs plus OXA group. The objective response rate (ORR) (50.0% *vs.* 53.8%, P=0.67) and disease control rate (DCR) (98.3% *vs.* 93.8%, P=0.21) were also similar between the PTX and OXA groups, and both treatments exhibited manageable side effects. Subgroup analysis based on patient characteristics suggested that PFS HRs favored the ICIs plus PTX subgroup in patients aged <65 years or without liver metastasis.

Conclusions: In summary, ICIs plus PTX are as effective as ICIs plus OXA for treating advanced G/GEJC with manageable toxicity. The advantages of ICIs plus PTX in terms of adverse events (AEs) may support it as an alternative to ICIs plus OXA.

Keywords: Immune checkpoint inhibitors (ICIs); advanced gastric cancer (advanced GC); paclitaxel; oxaliplatin; chemotherapy

Submitted Jun 27, 2024. Accepted for publication Nov 26, 2024. Published online Jan 23, 2025.
doi: 10.21037/tcr-24-1089
View this article at: https://dx.doi.org/10.21037/tcr-24-1089

Introduction

Background

Globally, gastric cancer (GC) is the fifth most common cancer (1), with more than 700,000 deaths worldwide each year. Among gastric/gastroesophageal junction cancer (G/GEJC) patients in China, more than 60% are diagnosed at progressive stages, and their survival period is quite short (2,3). The lack of effective treatments for stage IV G/GEJC has seriously restricted further improvements in the overall survival (OS) of G/GEJC.

For human epidermal growth factor receptor 2 (HER2)-negative advanced G/GEJC, immune checkpoint inhibitors (ICIs) plus chemotherapy have replaced traditional chemotherapy and are now the standard first-line treatment regimen, in which chemotherapy is standard oxaliplatin plus fluoropyrimidine regimens. The CheckMate-649 study demonstrated that nivolumab combined with chemotherapy prolonged the median OS of patients with a programmed cell death-ligand 1 (PD-L1) combined positive score (CPS) ≥5 from 11.1 to 14.4 months [hazard ratio (HR) =0.71; 95% confidence interval (CI): 0.59–0.86; P<0.0001]. Similarly, nivolumab combined with chemotherapy also prolonged the median progression-free survival (PFS) of patients with a PD-L1 CPS ≥5 from 6.0 to 7.7 months (HR =0.68; 95% CI: 0.56–0.81; P<0.0001). In addition, this research revealed that the greater the CPS is, the greater the survival benefit for patients treated with nivolumab combined with chemotherapy (4). Recently, sintilimab combined with XELOX (capecitabine and oxaliplatin) showed a significant improvement in OS in the whole population and the PD-L1 CPS ≥5 population in ORIENT-16, a study conducted in China (5). Currently, based on the findings of multiple clinical trials, such as CheckMate-649, international guidelines recommend platinum-based doublet chemotherapy along with ICIs [nivolumab and other programmed cell death-1 (PD-1)/PD-L1 antibody drugs] as the preferred initial treatment for advanced G/GEJC (6).

Highlight box

Key findings

- In first-line therapy of advanced gastric/gastroesophageal junction cancer (G/GEJC), immune checkpoint inhibitors (ICIs) plus paclitaxel-based chemotherapy demonstrated similar overall survival and response rates compared to ICIs plus oxaliplatin-based chemotherapy, with manageable adverse events.

What is known and what is new?

- Research indicates that ICIs plus paclitaxel have a synergistic effect, but the evidence is insufficient.
- ICIs plus paclitaxel-based chemotherapy are as effective as ICIs plus oxaliplatin-based chemotherapy for treating advanced G/GEJC with manageable toxicity.

What is the implication, and what should change now?

- ICIs plus paclitaxel-based chemotherapy may be an alternative to ICIs plus oxaliplatin-based chemotherapy. And patients younger than 65 years and patients who did not have liver metastasis are likely to benefit from ICIs plus paclitaxel-based chemotherapy.

Rationale and knowledge gap

As a conventional chemotherapeutic agent for advanced G/GEJC, paclitaxel has demonstrated promising efficacy both as a monotherapy and when combined with fluoropyrimidines with manageable toxicity (7,8). The effectiveness and toxicity of combining paclitaxel with fluoropyrimidines for G/GEJC in the Chinese population have been proven in previous phase III trials (9,10). Moreover, one study revealed that paclitaxel significantly enhances immunostimulatory activity (11). Studies have indicated that paclitaxel can enhance the antigen presentation ability, promote effector cells [cytotoxic T cells and natural killer (NK) cells], and inhibit the development

of immunosuppressive cells including cancer-associated fibroblasts and regulatory T cells (12-14). However, the interaction between paclitaxel and ICIs is currently not fully understood.

Objective

For advanced G/GEJC, the efficacy and toxicity of ICIs plus paclitaxel-based chemotherapy as first-line therapies have not yet been explored. To determine a new first-line treatment for advanced G/GEJC, we compared the efficacy and tolerability of ICIs plus a paclitaxel-based chemotherapy regimen (ICIs plus PTX) *vs.* an oxaliplatin-based regimen (ICIs plus OXA) in this multicenter, retrospective study. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1089/rc).

Methods

Patients

In this multicenter, retrospective study, data from 123 advanced G/GEJC patients who underwent first-line treatment at three institutions (Zhejiang Cancer Hospital, Taizhou Cancer Hospital, and Zhejiang Medical & Health Group Hangzhou Hospital) in China from August 2019 to June 2022 were included (*Figure 1*). Our research compared the effectiveness and tolerability of the ICIs plus PTX group *vs.* the ICIs plus OXA group. Before the treatment started, the patients signed written informed consent for antitumor treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Zhejiang Cancer Hospital (No. IRB-2022-443), Taizhou Cancer Hospital (No. 2023-031), and Zhejiang Medical & Health Group Hangzhou Hospital (No. 2023015). Individual consent for this retrospective analysis was waived.

All included eligible participants presented with initially unresectable, metastatic, or recurrent G/GEJC. Other key inclusion criteria included patients older than 18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and at least two cycles of first-line combination treatment. If the disease recurs after postoperative adjuvant therapy, the time from the last chemotherapy should be more than 6 months. In addition, only HER2-negative patients were included; HER2 was evaluated by immunohistochemistry from primary or metastatic tumor tissue, and those assessed with a score of 2+ underwent fluorescent in situ hybridization (FISH). If the HER2 score was 0, 1+, or 2+/FISH test was negative, the patient was considered to be HER2-negative, and positive patients were excluded.

Treatment methods

Patients in the ICIs plus PTX group received chemotherapy regimens included PS/AS (paclitaxel 75 mg/m^2 or nab-paclitaxel 125 mg/m^2 intravenously on days 1 & 8 combined with oral administration of S-1 and 40 mg/m^2 twice a day (bid) for 2 weeks; treatments were performed every 3 weeks), PX/AX (paclitaxel 75 mg/m^2 or nab-paclitaxel 125 mg/m^2 intravenously on days 1 & 8 combined with oral administration of capecitabine and 1,000 mg/m^2 bid for 2 weeks; treatments were performed every 3 weeks) and paclitaxel/nab-paclitaxel alone. Patients in the ICIs plus OXA group received chemotherapy regimens included SOX (S-1 and oxaliplatin, 130 mg/m^2 once combined with oral administration of S-1, 40 mg/m^2 bid for 2 weeks, treatments are performed every 3 weeks) and XELOX (oxaliplatin, 130 mg/m^2 once combined with oral administration of capecitabine, 1,000 mg/m^2 bid for 2 weeks, treatments are performed every 3 weeks). Patients in the two groups were treated with ICIs (360 mg for nivolumab, 240 mg for toripalimab, and 200 mg for other ICIs) on the first day of intravenous chemotherapy every 3 weeks. Combined treatments were performed for a maximum of 8 cycles. Depending on the patient's tolerance, the chemotherapy dose may be adjusted. After 8 cycles of combination therapy, patients were given the option to receive anti-PD-1 antibody with or without fluoropyrimidine unless their disease progressed or the side effects were intolerable.

Assessment

Imaging examinations were performed every two or three cycles during treatment and follow-up, and imaging changes were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. OS was calculated as the interval between the administration of ICIs combined with chemotherapy and death from any cause. PFS was computed from the date of initiation of ICIs combined with chemotherapy to the date of disease progression or death due to any cause before progression. The objective

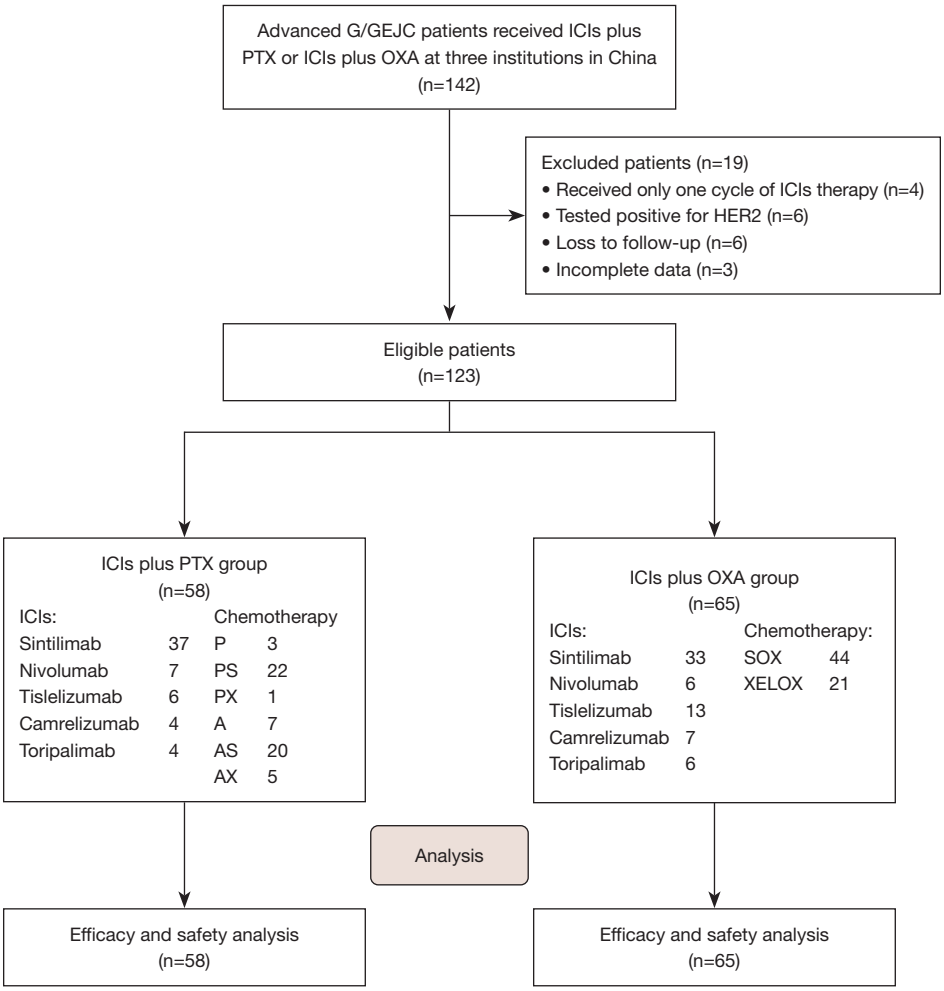

Figure 1 The flowchart of the study. G/GEJC, gastric/gastroesophageal junction cancer; ICI, immune checkpoint inhibitor; PTX, paclitaxel-based chemotherapy; OXA, platinum-based chemotherapy; HER2, human epidermal growth factor receptor 2; P, paclitaxel alone; PS, paclitaxel plus S-1; PX, paclitaxel plus capecitabine; A, nab-paclitaxel alone; AS, nab-paclitaxel plus S-1; AX, nab-paclitaxel plus capecitabine; SOX, S-1 and oxaliplatin; XELOX, capecitabine and oxaliplatin.

response rate (ORR) refers to the percentage of patients whose tumors achieved complete response (CR) or partial response (PR) after combined therapy. All treatment-related adverse events (AEs) were counted and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

The baseline characteristics, ORR, and disease control rate (DCR) were expressed as percentages, and the Chi-squared test (χ^2 test) was used to compare differences. The Kaplan-Meier method was used to construct survival curves for survival analysis. The significant differences in OS and PFS between the two groups were determined using the log-rank test. To determine HRs, Cox's proportional hazard model was utilized. Subgroup analysis for PFS was carried out to determine the associations between treatment efficacy and patient sex, age, ECOG PS, primary tumor location, signet ring cell carcinoma status, Lauren classification, histology, peritoneum metastasis status, lymph node metastasis status, liver metastasis status, *Helicobacter pylori* infection status and PD-L1 status. All data analyses were carried out with SPSS software, version 22.0.

Results

Patient characteristics

Among the 142 patients with advanced G/GEJC initially included, four patients were given only one cycle of combination therapy, six patients were lost to follow-up after a period of treatment, six patients tested positive for HER2, and four patients had incomplete treatment records. Ultimately, this research included 123 patients in total (*Figure 1*).

The ICIs plus PTX group included 58 patients, whereas the ICIs plus OXA group included sixty-five patients. There was no difference concerning age, sex, ECOG-PS, tumor location, Lauren classification, histology, main metastatic sites or *Helicobacter pylori* infection between the two groups (*Table 1*). The ICIs plus PTX group included more patients who had received prior treatment, including curative gastrectomy (34.5% *vs.* 16.9%) and adjuvant chemotherapy (13.8% *vs.* 7.7%). With regard to PD-L1 expression, 22 (37.9%) patients were positive, 10 (17.2%) patients tested negative, and 26 (44.8%) patients had an unknown status in the ICIs plus PTX group. Thirty-seven (56.9%) patients tested positive, 13 (20.0%) patients tested negative, and 15 (23.1%) patients had an unknown status in the ICIs plus OXA group. Since mismatch repair (MMR) deficiency/microsatellite instability (MSI) and Epstein-Barr encoding region (EBER) status were not routinely tested in China before 2021, a large proportion of patients had an unknown status. The MMR status in the ICIs plus PTX group was as follows: proficient MMR (pMMR), 31 (53.4%); deficient MMR (dMMR), 2 (3.4%); and unknown, 25 (43.1%). In the ICIs plus OXA group, the MMR status was as follows: pMMR, 42 (64.6%); dMMR, 1 (1.5%); and unknown, 22 (33.8%). With regard to EBER status, 3 (5.2%) patients tested positive, 17 (29.3%) patients tested negative, and 38 (65.5%) patients had an uncertain status in the ICIs plus PTX group. One (1.5%) patient had a positive EBER status, 29 (44.6%) patients had a negative status, and 35 (53.8%) patients had an uncertain status in the ICIs plus OXA group.

Therapeutic regimen

The median treatment cycles for intravenous chemotherapy plus immunotherapy was seven and six. For anti-PD-1 antibodies, sintilimab (37 patients, 63.8%), nivolumab (7 patients, 12.1%), tislelizumab (6 patients, 10.3%), toripalimab (4 patients, 6.9%), and camrelizumab (4 patients, 6.9%) were used in the ICIs plus PTX group. Sintilimab (33 patients, 50.8%), nivolumab (6 patients, 9.2%), tislelizumab (13 patients, 20.0%), camrelizumab (7 patients, 10.8%), and toripalimab (6 patients, 9.2%) were used in the ICIs plus OXA group. Paclitaxel-based chemotherapy regimens included paclitaxel alone (3 patients, 5.2%), PS (22 patients, 37.9%), PX (1 patient, 1.7%), nab-paclitaxel alone (7 patients, 12.1%), AS (20 patients, 34.5%), and AX (5 patients, 8.6%). Moreover, in the ICIs plus OXA group, the platinum-based chemotherapy regimens used were SOX (44 patients, 67.7%) and XELOX (21 patients, 32.3%). In addition, in the ICIs plus PTX group, eight patients received adjuvant chemotherapy after curative gastrectomy, seven patients received the SOX regimen, and one received the XELOX regimen. Five patients in the ICIs plus OXA group received adjuvant chemotherapy, including a DS regimen (n=2), S-1 monotherapy (n=2), and a SOX regimen (n=1). For subsequent therapy, 29 (50.0%) of 58 patients in the ICIs plus PTX group had received follow-up antitumor therapy by March 2023, including 17 (29.3%) patients who continued ICI therapies and 14 (24.1%) patients who had used oxaliplatin-containing chemotherapy. In the ICIs plus OXA group, 31 (47.7%) of 65 patients received subsequent anticancer therapy following progression, including 16 (24.6%) patients who continued ICI therapy and 23 (35.4%) patients who used paclitaxel-containing chemotherapy.

Efficacy

Twenty-nine of the 58 patients (50.0%; 95% CI: 36.7–63.3%) in the ICIs plus PTX group and 35 of the 65 patients (53.8%; 95% CI: 41.4–66.3%) in the ICIs plus OXA group showed a disease response (P=0.67; *Table 2*). One patient from each group achieved CR. In addition, 28 patients (48.3%) in the ICIs plus PTX group achieved PR and stable disease (SD). Twenty-six patients (40.0%) and 34 patients (52.3%) in the ICIs plus OXA group achieved PR and SD, respectively. In summary, the DCR (98.3% *vs.* 93.8%, P=0.21; *Table 2*) was similar in the two groups.

The median PFS times were 8.07 (95% CI: 5.52–9.62) and 7.23 months (95% CI: 5.68–8.79) (HR =0.845; 95% CI: 0.568–1.257; P=0.40; *Figure 2*) in the ICIs plus PTX and ICIs plus OXA groups, respectively. The median OS was 14.83 (95% CI: 10.32–19.35) and 15.10 months (95% CI: 11.04–19.16) (HR =0.852; 95% CI: 0.536–1.355; P=0.50; *Figure 3*) in the two groups, respectively. In addition, subgroup analysis based on patient characteristics suggested

Table 1 Baseline demographics and disease characteristics of patients in the two groups

Characteristics	ICIs plus PTX (n=58)	ICIs plus OXA (n=65)	P value
Age (years)			0.86
<65	33 (56.9)	38 (58.5)	
≥65	25 (43.1)	27 (41.5)	
Sex			0.42
Male	38 (65.5)	38 (58.5)	
Female	20 (34.5)	27 (41.5)	
ECOG PS			0.31
0	36 (62.1)	38 (58.5)	
1	21 (36.2)	22 (33.8)	
2	1 (1.7)	5 (7.7)	
Primary tumor location			0.98
Gastric	49 (84.5)	55 (84.6)	
GEJ	9 (15.5)	10 (15.4)	
Signet ring cell carcinoma			0.99
Yes	16 (27.6)	18 (27.7)	
No	42 (72.4)	47 (72.3)	
Lauren classification			0.60
Intestinal type	20 (34.5)	21 (32.3)	
Diffuse type	15 (25.9)	14 (21.5)	
Mixed	5 (8.6)	3 (4.6)	
Unknown	18 (31.0)	27 (41.5)	
Histology			0.44
Well differentiated	0	0	
Moderately differentiated	11 (19.0)	9 (13.8)	
Poorly differentiated	47 (81.0)	56 (86.2)	
Metastatic site			
Peritoneum	31 (53.4)	29 (44.6)	0.33
Lymph node	26 (44.8)	35 (53.8)	0.32
Liver	14 (24.1)	17 (26.2)	0.80
Ovary	6 (10.3)	6 (9.2)	0.84
Others	14 (24.1)	16 (24.6)	0.95
Helicobacter pylori			0.45
Yes	9 (15.5)	15 (23.1)	
No	25 (43.1)	22 (33.8)	
Unknown	24 (41.4)	28 (43.1)	
PD-L1 status			0.03*
≥1	22 (37.9)	37 (56.9)	
<1	10 (17.2)	13 (20.0)	
Unknown	26 (44.8)	15 (23.1)	
MMR			0.41
pMMR	31 (53.4)	42 (64.6)	
dMMR	2 (3.4)	1 (1.5)	
Unknown	25 (43.1)	22 (33.8)	
EBER			0.15
Positive	3 (5.2)	1 (1.5)	
Negative	17 (29.3)	29 (44.6)	
Unknown	38 (65.5)	35 (53.8)	
ICIs regimens			0.45
Sintilimab	37 (63.8)	33 (50.8)	
Nivolumab	7 (12.1)	6 (9.2)	
Tislelizumab	6 (10.3)	13 (20.0)	
Camrelizumab	4 (6.9)	7 (10.8)	
Toripalimab	4 (6.9)	6 (9.2)	
Prior treatment			
Curative gastrectomy	20 (34.5)	11 (16.9)	0.03*
Adjuvant chemotherapy	8 (13.8)	5 (7.7)	0.27

Data are presented as n (%). *, represents P<0.05. ICI, immune checkpoint inhibitor; PTX, paclitaxel-based chemotherapy; OXA, oxaliplatin-based chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; PD-L1, programmed cell death-ligand 1; MMR, mismatch repair; pMMR, proficient MMR; dMMR, deficient MMR; EBER, Epstein-Barr encoding region.

that PFS HRs favored the ICIs plus PTX subgroup in patients aged <65 years or without liver metastasis. In contrast, ICIs combined with oxaliplatin-based chemotherapy were more likely to be beneficial for patients with liver metastases (*Figure 4*).

AEs

All treatment-related AEs are listed in *Table 3*. Myelosuppression and gastrointestinal reactions were the

Table 2 Tumor response according to RECIST version 1.1

Tumor response	ICIs plus PTX (n=58)	ICIs plus OXA (n=65)	P value*
CR	1 (1.7)	1 (1.5)	–
PR	28 (48.3)	34 (52.3)	–
SD	28 (48.3)	26 (40.0)	–
Progressive disease	1 (1.7)	4 (6.2)	–
Objective response (95% CI)	29 (50.0; 36.7–63.3%)	35 (53.8; 41.4–66.3%)	0.67
Disease control (95% CI)	57 (98.3; 94.8–101.7%)	61 (93.8; 87.8–99.8%)	0.21

Data are presented as n (%) or n (%; 95% CI). *, P value for χ^2 test. RECIST, Response Evaluation Criteria in Solid Tumors; ICI, immune checkpoint inhibitor; PTX, paclitaxel-based chemotherapy; OXA, oxaliplatin-based chemotherapy; CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval.

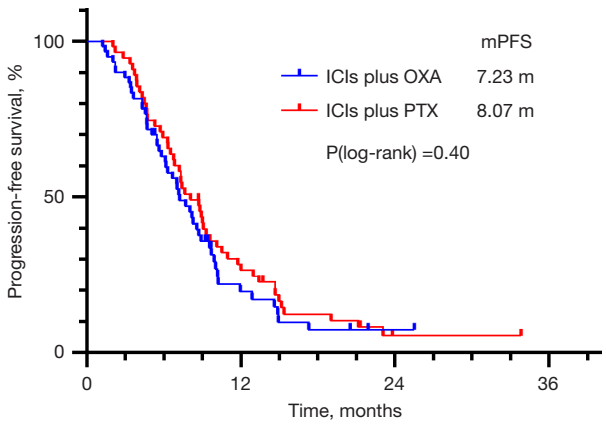

Figure 2 Kaplan-Meier estimated PFS in the ICIs plus PTX group was similar to that in the ICIs plus OXA group. Median PFS was 8.07 months (95% CI: 5.52–9.62) in the ICIs plus PTX group and 7.23 months (95% CI: 5.68–8.79) in the ICIs plus OXA group (HR =0.845; 95% CI: 0.568–1.257; P=0.40). mPFS, median progression-free survival; ICI, immune checkpoint inhibitor; OXA, oxaliplatin-based chemotherapy; m, months; PTX, paclitaxel-based chemotherapy; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio.

most frequent AEs, and most AEs were grade 1–2 and generally manageable. Two treatment-related deaths were recorded (one due to immune hepatitis and the other due to immune pneumonia and immune myocarditis) in the ICIs plus OXA group. The incidences of thrombocytopenia

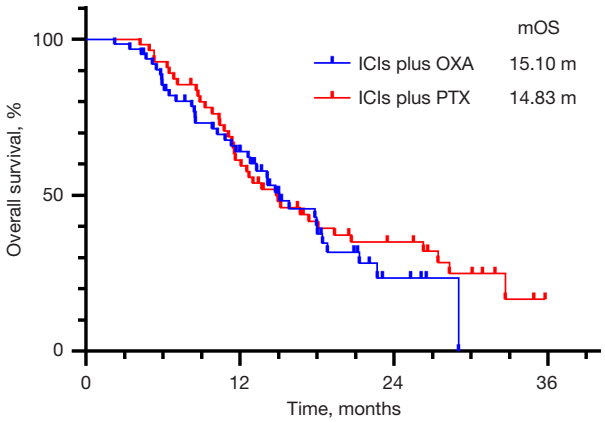

Figure 3 Kaplan-Meier estimated OS in the ICIs plus PTX group was similar to that in the ICIs plus OXA group. Median OS was 14.83 months (95% CI: 10.32–19.35) in the ICIs plus PTX group and 15.10 months (95% CI: 11.04–19.16) in the ICIs plus OXA group (HR =0.852; 95% CI: 0.536–1.355; P=0.50). mOS, median overall survival; ICI, immune checkpoint inhibitor; OXA, oxaliplatin-based chemotherapy; m, months; PTX, paclitaxel-based chemotherapy; OS, overall survival; CI, confidence interval; HR, hazard ratio.

(33.8% *vs.* 17.2%, P=0.04) and neurotoxicity (44.6% *vs.* 13.8%, P<0.001) in the ICIs plus OXA group were greater than those in the ICIs plus PTX group, which may be attributed to oxaliplatin. Conversely, alopecia (62.1% *vs.* 0.0%, P<0.001) occurred only in the ICIs plus PTX group.

Discussion

Key findings

Our results showed that with regard to PFS and OS, the effects of ICIs plus PTX were comparable to those of ICIs plus OXA. The median PFS was 8.07 (95% CI: 5.52–9.62) and 7.23 months (95% CI: 5.68–8.79) (HR =0.845; 95% CI: 0.568–1.257; P=0.40) in the two groups. The median OS was 14.83 (95% CI: 10.32–19.35) and 15.10 months (95% CI: 11.04–19.16) (HR =0.852; 95% CI: 0.536–1.355; P=0.50) in the two groups. The median PFS and OS were comparable to those of prior global phase III studies. In addition, subgroup analysis of PFS suggested patients younger than 65 years and patients who did not have liver metastasis were likely to benefit from ICIs plus PTX. For patients with liver metastasis, the PFS of patients treated with ICIs plus OXA was considerably longer than that of patients in the ICIs plus PTX group.

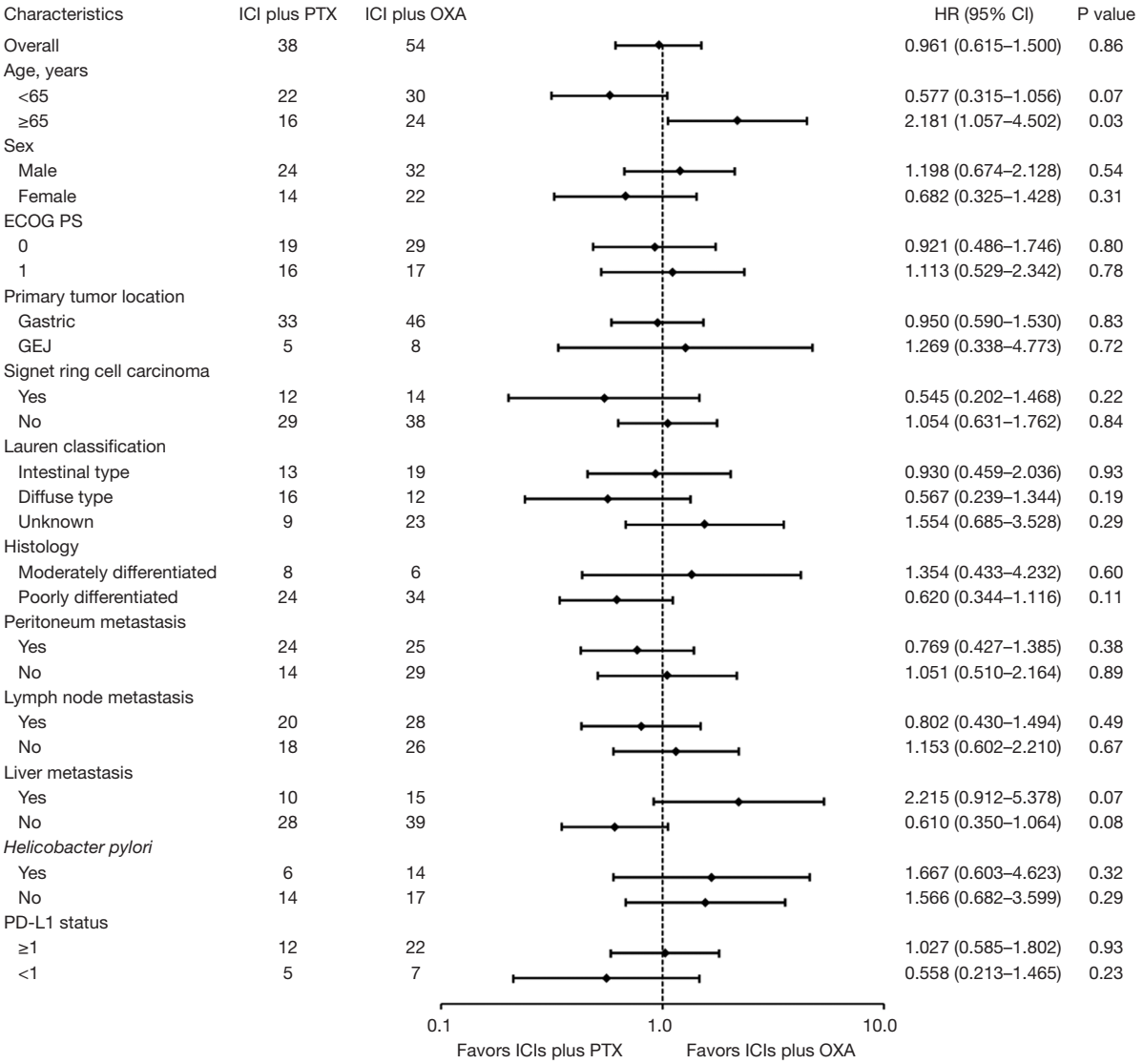

Figure 4 PFS in response to ICIs plus PTX or OXA is stratified by age, sex, ECOG PS, primary tumor location, signet ring cell carcinoma, Lauren classification, histology, metastasis site, *Helicobacter pylori*, and PD-L1 status. ICI, immune checkpoint inhibitor; PTX, paclitaxel-based chemotherapy; OXA, oxaliplatin-based chemotherapy; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Strengths and limitations

Our results indicate that combining ICI with paclitaxel-based chemotherapy presents a viable first-line treatment option for advanced G/GEJC. However, our study inevitably has several limitations. As this was a retrospective study, the patients were not strictly randomized, and the sample size was relatively small. The detection of biomarkers [such as microsatellite stable (MSS) and EBER] at baseline was insufficient in some patients for technical reasons; hence, the predictive value of these biomarkers for survival has not been fully evaluated.

Comparison with similar research

The guidelines in China recommend paclitaxel plus fluoropyrimidine as alternative first-line therapy (6). In

Table 3 Incidence of all-cause AEs and immune-related AEs

AEs	ICIs plus PTX (n=58)		ICIs plus OXA (n=65)		P value	
	Any	≥3 grade	Any	≥3 grade	Any	≥3 grade
Hematological						
Anemia	16 (27.6)	3 (5.2)	24 (36.9)	6 (9.2)	0.27	0.61
Neutropenia	35 (60.3)	14 (24.1)	31 (47.7)	12 (18.5)	0.16	0.44
Leucopenia	31 (53.4)	14 (24.1)	31 (47.7)	15 (23.1)	0.52	0.89
Thrombocytopenia	10 (17.2)	2 (3.4)	22 (33.8)	7 (10.8)	0.04*	0.23
Non-hematological						
Nausea/vomiting	34 (58.6)	4 (6.9)	31 (47.7)	3 (4.6)	0.23	0.88
Diarrhea	7 (12.1)	0	6 (9.2)	0	0.61	–
Fatigue	26 (44.8)	0	32 (49.2)	0	0.63	–
Neurotoxicity	8 (13.8)	1 (1.7)	29 (44.6)	4 (6.2)	<0.001*	0.33
Alopecia	36 (62.1)	0	0	0	<0.001*	–
Rash	14 (24.1)	3 (5.2)	10 (15.4)	2 (3.1)	0.22	0.90
Hepatic dysfunction	11 (19.0)	0	14 (21.5)	2 (3.1)	0.72	–
irAEs						
Hypothyroidism	5 (8.6)	0	8 (12.3)	0	0.45	–
Pneumonia	1 (1.7)	0	3 (4.6)	1 (1.5)	0.69	>0.99
Myocarditis	0	0	1 (1.5)	1 (1.5)	>0.99	>0.99
Hepatitis	2 (3.4)	0	4 (6.2)	1 (1.5)	0.78	>0.99

Data are presented as n (%). *, represents P<0.05. AEs, adverse events; ICI, immune checkpoint inhibitor; PTX, paclitaxel-based chemotherapy; OXA, oxaliplatin-based chemotherapy; irAEs, immune-related adverse events.

our study, second-line therapy in the ICIs plus PTX group was more often a regimen that included oxaliplatin. In the ICIs plus OXA group, many patients received second-line chemotherapy containing paclitaxel. Although we did not observe a survival advantage with ICIs plus PTX, previous studies have shown that paclitaxel-based chemotherapy has improved ORR and PFS as a first-line treatment compared with platinum-based chemotherapy (10,15). A phase III study revealed that first-line treatment with paclitaxel plus capecitabine can achieve a greater ORR than platinum-based chemotherapy (43.1% *vs.* 28.8%, P=0.012) (10). Therefore, using paclitaxel as initial treatment may reduce the size of the tumor to a greater extent, and even increase the chance of conversion. Based on the results of several global multicenter phase III clinical trials, ICIs combined with chemotherapy has currently become the standard first-line treatment for advanced esophageal squamous cell carcinoma. The main studies include CheckMate-648 (nivolumab) (16), KEYNOTE-590 (pembrolizumab) (17), Orient-15 (sintilimab) (18), and Jupiter-06 (toripalimab) (19). Among these, the chemotherapy regimens in the CheckMate-648 and KEYNOTE-590 studies are based on CF (cisplatin + fluorouracil), while in China, the TP (taxanes + platinum) regimen is more commonly used. The study results found that regardless of whether the chemotherapy regimen is CF or TP, the final efficacy is comparable.

Explanations of findings

The choice of chemotherapy drug is made not only on the basis of efficacy but also on safety, patient characteristics, and preference considerations. In our study, treatment-related toxicity was tolerable in both groups. For advanced GC, combined chemotherapy with oxaliplatin and fluoropyrimidine is currently the most commonly used

standard first-line systemic care (6,20). Oxaliplatin has been the preferred choice by doctors and patients given its efficacy, price, and ease of administration. Patients receiving oxaliplatin-based chemotherapy only required intravenous therapy every 21 days. However, resistance to platinum-based chemotherapy is common, and oxaliplatin has a high risk of toxic effects, such as sensory neuropathy and hematological effects, which limits its use (21). Neurotoxicity is a dose-limiting toxicity and the most serious adverse effect of oxaliplatin. The incidence of neurotoxicity is reported to be between 76% and 90%. There is no effective medication for neurotoxicity, and once severe neurotoxicity occurs, we have to reduce or even discontinue oxaliplatin, which will affect the outcome of therapy and patients' quality of life even long after the actual treatment is discontinued (22). In addition to neurotoxicity, thrombocytopenia is also a major adverse reaction induced by oxaliplatin, with an incidence rate of approximately 70% reported in the literature, of which 3% to 4% of patients will experience severe thrombocytopenia, leading to bleeding and even life-threatening events (23,24). Furthermore, with the widespread and high-dose application of oxaliplatin, the odds of allergic reactions during intravenous oxaliplatin infusion have gradually increased (21,24), and the median cycle was reported to be 4–9 cycles (25). The incidence of allergy during the use of oxaliplatin is approximately 0.55–15%, and the incidence of grade III–IV allergic reactions is 0.7–7.3% (26). Therefore, effective first-line platinum-free chemotherapy options are needed, especially when patients cannot tolerate platinum-based drugs due to renal insufficiency or the occurrence of serious adverse effects (such as thrombocytopenia or neurotoxicity).

In previous studies, paclitaxel showed commensurate efficacy and comparable toxicity to oxaliplatin-based chemotherapy and is considered an alternative for first-line treatment (7,9,10). Compared with oxaliplatin-based chemotherapy, paclitaxel-based chemotherapy is associated with lower rates of myelosuppression and gastrointestinal AEs (including nausea, vomiting, and diarrhea) (27). In addition, paclitaxel can be used as a mono-chemotherapy agent, which is more suitable for advanced G/GEJC patients with severe dysphagia symptoms who cannot take oral fluorouracil drugs. However, paclitaxel is more likely to cause alopecia and allergies. Nanoparticle albumin-bound paclitaxel uses nanotechnology to combine the drug with human albumin, which greatly improves the solubility of paclitaxel. In addition, due to its unique nano-dosage form, it can target tumors, thereby increasing the concentration of paclitaxel at the tumor site (28). Compared to ordinary paclitaxel, nab-paclitaxel has a much lower probability of allergic reactions (29). Furthermore, although paclitaxel can also cause neurotoxicity, the incidence is lower, and the symptoms are usually reversible between treatment cycles, whereas oxaliplatin-induced neuropathy is often durable (30). Therefore, paclitaxel can be selected as the first-line treatment when the patient has severe obstructive symptoms or when neurotoxicity has not recovered from adjuvant therapy containing oxaliplatin.

In the ICIs plus PTX group, 26 patients received paclitaxel, and 31 received nab-paclitaxel. Based on the findings from a prior phase III trial showing comparable efficacy between nab-paclitaxel and conventional paclitaxel, both formulations were included in our study (31). However, unlike nab-paclitaxel, pretreatment with glucocorticoids is required before patients receiving ordinary paclitaxel to prevent allergic reactions. Whether the use of glucocorticoids affects the efficacy of ICIs is still controversial. The KEYNOTE-407 study compared the efficacy of a pembrolizumab combining carboplatin and either conventional paclitaxel or nab-paclitaxel with that of chemotherapy alone for advanced squamous lung cancer (32). There was no disparity in OS observed across the different chemotherapy regimens. The addition of pembrolizumab to chemotherapy enhanced OS irrespective of whether paclitaxel or nab-paclitaxel was utilized. In addition, the findings of the KEYNOTE-355 trial demonstrated that in patients with advanced triple-negative breast cancer with a PD-L1 CPS ≥10, the combination of paclitaxel and pembrolizumab can significantly prolong OS, while nab-paclitaxel combined with pembrolizumab did not improve OS (33). Although the above studies have shown that the short-term use of supraphysiologic doses of glucocorticoids for pretreatment before chemotherapy does not significantly affect the efficacy of ICIs, data on the paclitaxel plus ICIs for GC treatment are limited. Comparative research data are worth exploring in the real world through clinical research.

Implications and actions needed

This study provides theoretical basis for first-line therapy of advanced GC with paclitaxel plus ICIs, potentially increasing treatment options for advanced GC. But due to some limitations of this study, it is necessary to conduct more prospective studies to verify our findings and to

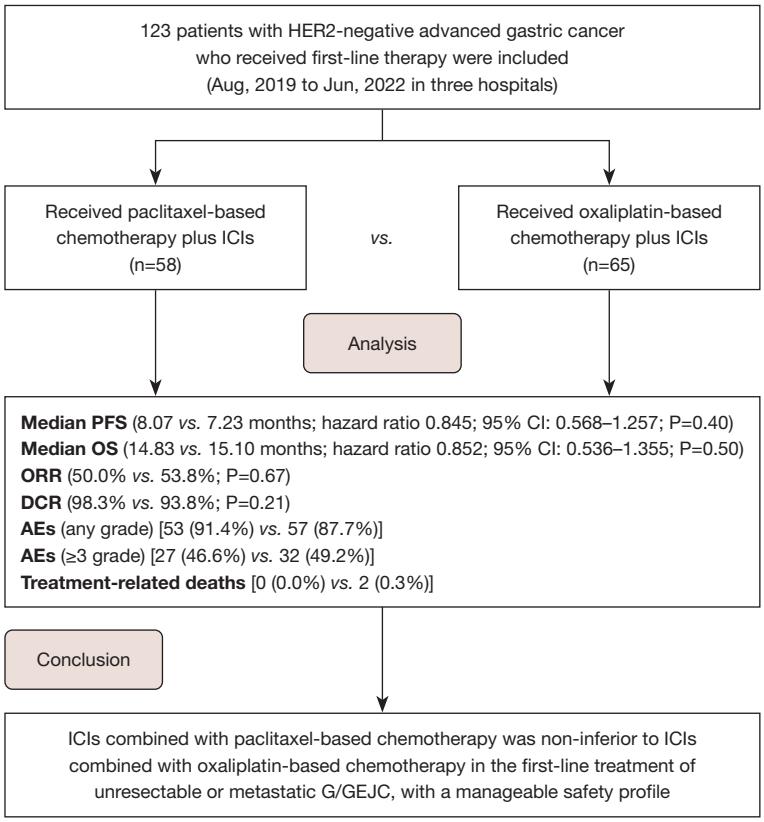

Figure 5 ICIs combined with paclitaxel-based chemotherapy demonstrates similar PFS, OS, ORR and DCR to ICIs combined with oxaliplatin-based chemotherapy, with a manageable safety profile. HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; PFS, progression-free survival; CI, confidence interval; OS, overall survival; ORR, objective response rate; DCR, disease control rate; G/GEJC, gastric/gastroesophageal junction cancer.

define the population that could benefit from different chemotherapy regimens.

Conclusions

In conclusion, in terms of advanced G/GEJC, ICIs plus paclitaxel-based chemotherapy are an encouraging alternative for first-line therapy and have shown equivalent efficacy and lower toxicity to ICIs plus oxaliplatin-based chemotherapy. Prospective clinical studies are needed to confirm our findings (*Figure 5*).

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1089/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1089/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1089/prf

Funding: This study was sponsored by the Zhejiang Province Chinese Medicine Science and Technology Project (No. 2024ZL297), the Natural Science Foundation of Zhejiang Province (No. LY22H160014), and the Medical

Science and Technology Project of Zhejiang Province (No. 2022KY112).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1089/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Zhejiang Cancer Hospital (No. IRB-2022-443), Taizhou Cancer Hospital (No. 2023-031), and Zhejiang Medical & Health Group Hangzhou Hospital (No. 2023015). Individual consent for this retrospective analysis was waived.

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Cite this article as: Fang Y, Zhao Y, Zhang X, Yu X, Liu S, Tao G, Yang Y, Zhong H, Shi Z. Immune checkpoint inhibitors plus paclitaxel-based chemotherapy *vs.* oxaliplatin-based therapy as first-line treatment for patients with HER2-negative unresectable or metastatic gastric/gastroesophageal junction cancer: results of a multicenter retrospective study. Transl Cancer Res 2025;14(1):327-339. doi: 10.21037/tcr-24-1089