

Clinical efficacy of irinotecan plus raltitrexed chemotherapy in refractory esophageal squamous cell cancer

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Our retrospective study assessed the efficacy and safety of irinotecan plus raltitrexed in esophageal squamous cell cancer (ESCC) patients who were previously treated with multiple systemic therapies. Between January 2016 and December 2018, records of 38 ESCC patients who underwent irinotecan plus raltitrexed chemotherapy after at least one line of chemotherapy were reviewed. Efficacy assessment was performed every two cycles according to the RECIST version 1.1. A total of 95 cycles of chemotherapy were administered, and the median course was 3 (range 2–6). There was no treatment-related death. Nine patients had partial response, 21 had stable disease and eight had progressive disease. The overall objective response rate was 23.68% (9/38) and the disease control rate was 78.94% (30/38). After a median follow-up of 18.5 months, the median progression-free survival and overall survival were 105 and 221 days, respectively. There were five patients (13.15%) with grade 3/4 leukopenia, three patients (7.89%) with grade 3/4 neutropenia and one

patient (2.63%) with grade 3/4 diarrhea. The combination of irinotecan plus raltitrexed was effective for pretreated ESCC patients. Further studies are needed to determine the optimal dose of the two drugs. *Anti-Cancer Drugs* 31:403–410 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Esophageal cancer (EC) ranks seventh in terms of incidence and sixth in leading cause of cancer death globally [1]. In Asia, esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of all EC cases. China has the largest number of both newly diagnosed EC cases and EC cancer-related deaths. Despite the evolution of multidisciplinary treatments, the prognosis of EC has not improved much with a five-year survival rate only about 19% [2].

At present, platinum-based chemotherapy, 5-fluorouracil (5-FU) and taxanes are the most widely used as first-line chemotherapeutic agents for advanced EC, with response rates (RRs) ranging from 34 to 72.7% [3–5]. However, many patients who responded initially to chemotherapy or chemoradiotherapy ultimately develop progressive disease (PD). Currently, there are no standard second-line chemotherapeutic options for these patients. Second-line chemotherapy used in clinical practice includes docetaxel, paclitaxel, irinotecan and fluorouracil

plus irinotecan or pembrolizumab. RRs remain low, ranging from 21.2 to 29.6% [6–8]. Therefore, there is a need of development for more active drug combinations to treat refractory or relapsed advanced EC.

Irinotecan (CPT-11) is a topoisomerase I inhibitor, which has been proven to significantly improve survival and quality of life in 5-FU refractory colorectal cancer [9]. In addition, CPT-11 was considered as a second-line option in the treatment of advanced gastric cancer refractory to platinum plus fluoropyrimidine [10]. In EC, CPT-11 was also active as a single drug in the treatment of cisplatin-refractory cases [11]. In a retrospective study by Wang *et al.* [6], the efficacy and safety of irinotecan combined with a fluorouracil-based regimen as second- or third-line chemotherapy in the treatment of recurrent/metastatic ESCC who were refractory to prior paclitaxel plus platinum chemotherapy was evaluated. The RR was 29.6%, while the median progression-free survival (PFS) and overall survival (OS) were 4.8 and 10.5 months, respectively. This indicates that this combination was effective as a second- or third-line treatment for ESCC [6].

However, the use of 5-FU has several disadvantages, such as the requirement for a venous catheter system and

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infusion pump, risk for cardiac toxicity (overall incidence: 0.55–19%) [12,13], and frequent hospital visits. Moreover, it was reported that 5-FU could result in severe toxicity (such as stomatitis and severe pancytopenia) for patients who are deficient in dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU.

Raltitrexed, a thymidylate synthase (TS) inhibitor, has been considered as a potential substitute for 5-FU. In patients with advanced colorectal cancer, a meta-analysis conducted by Liu *et al.* [14] showed that raltitrexed-based chemotherapeutic regimen led to equivalent RRs and OS when compared to traditional 5-FU-based regimen. Furthermore, raltitrexed combined with either CPT-11 or oxaliplatin is also active against 5-FU-refractory advanced colorectal cancer, with overall objective response rates (ORRs) ranging from 15.4 to 33.3% and is well-tolerated [15–17]. In addition, raltitrexed alone or in combination with other chemotherapeutic drugs was shown to be a safe option for cancer patients who had experienced prior cardiac toxicity when treated with 5-FU. A systematic review has shown that no cardiotoxicity associated with raltitrexed was reported and no patients who were switched to raltitrexed because of cardiac symptoms from 5-FU experienced further cardiac toxicity [13].

In this light, the combination of irinotecan and raltitrexed might be an effective and safe treatment as a second- or later-line for ESCC. But there is currently no study on the efficacy of this combination in the treatment of recurrent/metastatic ESCC. The goal of this retrospective study was to evaluate the clinical efficacy and safety of irinotecan plus raltitrexed as second- or later-line chemotherapy in ESCC patients who had been previously treated with multiple systemic therapies, which included standard first-line chemotherapy with or without intensity modulated radiation therapy.

Materials and methods

Patient population

Between January 2016 and December 2018, a total of 38 consecutive patients who were histologically diagnosed as ESCC and had progressed after at least one-line treatment were treated by irinotecan plus raltitrexed as a second- or later-line chemotherapy from our institution of clinical medical college, Yangzhou University. The medical records of total 38 patients were reviewed for this study. During pretreatment evaluation, detailed medical history was collected. Laboratory studies included bone marrow function, hepatic function and kidney function. For disease evaluation and responses assessment, chest computerized tomography (CT), ultrasound examination and/or X-ray barium swallow were performed. All patients gave written informed consent before administering the chemotherapy.

The eligibility criteria included the following: (1) age between 20 and 75 years, (2) Eastern Cooperative

Oncology Group (ECOG) performance status 0-2, (3) at least one measurable lesion, (4) no prior exposure to irinotecan or raltitrexed chemotherapy, (5) adequate bone marrow function (leukocyte $\geq 3.5 \times 10^9/L$, neutrocyte $\geq 1.5 \times 10^9/L$, hemoglobin $\geq 10g/dl$ and platelets $\geq 80 \times 10^9/L$), (6) adequate hepatic function [total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), transaminase levels $\leq 2.0 \times$ ULN in the absence of liver metastases or $\leq 4.0 \times$ ULN in the presence of liver metastases] and (7) normal renal function (serum creatinine \leq ULN). Exclusion criteria were as follows: (1) with uncontrolled brain metastasis, (2) prior malignant tumor and (3) concomitant severe uncontrolled diseases (such as active infections, diabetes mellitus and heart diseases).

Treatment schedule

Patients were treated with irinotecan in a 90-min infusion on day 1, and raltitrexed in a 30-min infusion on day 2. The treatment was repeated every 3 weeks up to a maximum of six cycles or until either unacceptable side-effects or PD occurred.

Treatment evaluation

Tumor responses and toxicity were evaluated for every two cycles of chemotherapy according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1) criteria and National Cancer Institute Common Toxicity Criteria (NCI-CTC) respectively. Diameter changes of the target lesion were measured on CT imaging. Complete response (CR) was considered as the disappearance of all evaluable disease, and partial response (PR) meant that the target lesions were reduced by 30% or more. We regarded PD as the target lesions increased at least 20% or there were one or more new lesions, and stable disease (SD) as the target lesions reduced by less than 30% and increased by less than 20%. The ORR was defined as the percentage of cases with either CR or PR. The disease control rate (DCR) was defined as the percentage of cases, which achieved CR, PR or SD. Furthermore, we calculated PFS from the begin of the regimen to the first documented disease progression or death, and we defined the time between the initiation of the regimen and the date of dead or the last follow-up assessment as OS. All patients were followed up until death or loss to follow-up.

Statistical analysis

Results were analyzed using the SPSS software package (SPSS 25.0). The Kaplan–Meier method was performed to estimate PFS and OS. Fisher's exact test was used in comparing the RRs of different subgroups.

Ethical statement

This study was approved by the ethics committee of clinical medical college, Yangzhou University. The study

was performed in accordance with the Declaration of Helsinki.

Results

Patients' characteristics

The 38 patients' characteristics were summarized in Table 1. There were 34 males and four females. The median age was 63 years old, and ECOG performance status was 0–2. The primary tumors were all located in the thoracic esophagus. Twenty-seven patients had metastatic disease, among which 22 patients had single organ metastasis and five patients had multiorgan metastasis. The main metastatic sites were lung (23 patients) and liver (five patients). Eleven patients had local recurrences. Prior treatments included surgery plus chemoradiotherapy (12/38, 31.58%), surgery plus adjuvant chemotherapy (3/38, 7.89%), chemoradiotherapy (18/38, 47.37%) and chemotherapy alone (5/38, 13.16%). Twenty-two (57.89%) cases were receiving irinotecan plus raltitrexed chemotherapy as second-line treatment and 16 (42.11%) cases as third- or latter-line treatment.

Treatment summary

A total of 95 cycles of irinotecan plus raltitrexed were administered, and the median number of treatment cycle was 3 (range 2–6). The median doses of irinotecan and raltitrexed were 178 mg/m² (118–217) and 0.7 mg/m² (2.17–3.07), respectively. Because of the hematological toxicity, 15 cycles (15.79%) of chemotherapy were delayed, and

two cycles (2.11%) of chemotherapy required 25% dose reduction.

Response and survival

Details for treatment response are listed in Table 2 and the percentage changes of lesion size in each patient are shown in Fig. 1. In all 38 patients, there was no CR, nine (23.68%) patients had PR, 21(55.26%) patients had SD, and eight (21.06%) patients had PD. After a median follow-up of 18.5 months (2–32 months), two (5.26%) patients were lost to follow-up and no early treatment-related death was observed. The median PFS was 105 days (25–357, Fig. 2), and 3, 6 and 9 months PFS rate were 52.94%, 29.41% and 14.71%, respectively. The median OS was 221 days (32–632, Fig. 2), and 3, 6, 9, 12 and 18 months OS rate were 85.29%, 61.76%, 38.24%, 14.71% and 5.88%, respectively.

In the 20 patients who received prior chemotherapy without 5-FU, seven (35.00%) patients achieved PR, nine (45.00%) patients had SD and four (20.00%) patients had PD. The median PFS and OS were 154 days (53–357, Fig. 3a) and 290 days (67–632, Fig. 3b), respectively. In the remaining 18 patients who previously received chemotherapy containing 5-FU, two (11.11%) patients achieved PR, 12 (66.67%) patients had SD, and four (22.22%) patients had PD. The median PFS and OS were 66 days (25–343, Fig. 3a) and 150 days (32–431, Fig. 3b), respectively. The ORR in patients who previously received chemotherapy without 5-FU was numerically higher than the one in patients who previously received chemotherapy containing 5-FU, but was not statistically significant ($P = 0.088$, Table 3). The PFS and OS were also similar between the two groups (PFS: $P = 0.278$; OS: $P = 0.300$, Fig. 3a and b). In the 30 patients who previously received chemoradiotherapy, six (20.00%) patients achieved PR, 17 (56.67%) patients had SD, and seven (23.33%) patients had PD, while among eight patients who previously received chemotherapy only, three (37.50%) patients achieved PR, four (50.00%) patients had SD and one (12.50%) patient had PD. The ORR between the two groups showed no statistical difference ($P = 0.275$, Table 3). Furthermore, the PFS and OS had no significant difference between the two groups (PFS: $P = 0.259$; OS: $P = 0.222$, Fig. 3c and d). In the 22 patients who received the study drug combination as a second-line treatment, seven (31.82%) patients achieved

Table 1 Patient characteristics of the 38 treated esophageal squamous cell cancer patients: median age 63 years (range 47–73 years)

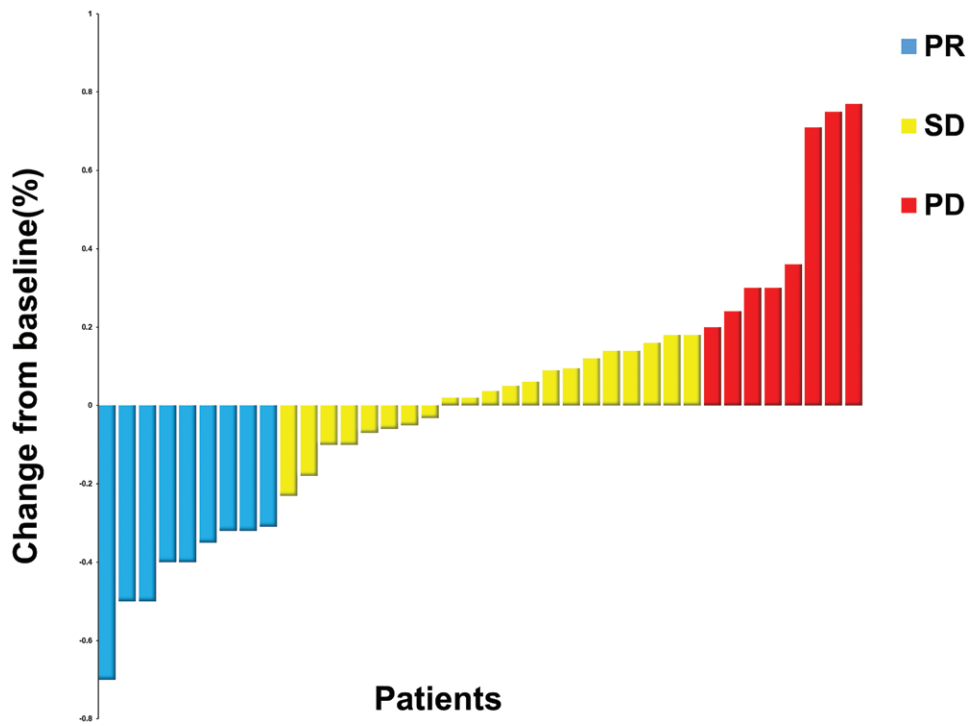
Characteristic	No. of patients	Percent
Sex		
Male	34	89.47
Female	4	10.53
Performance status		
0	4	10.53
1	32	84.21
2	2	5.26
Site of the primary cancer		
Upper esophagus	3	7.89
Middle esophagus	29	76.32
Lower esophagus	6	15.79
Grading of the primary cancer		
Poor-differentiated	25	65.79
Moderate-differentiated	9	23.68
Well-differentiated	4	10.53
Prior treatment		
Surgery + chemoradiotherapy	12	31.58
Surgery + chemotherapy	3	7.89
Chemoradiotherapy	18	47.37
Chemotherapy only	5	13.16
Disease extent		
Local recurrence	11	28.95
Metastatic	27	71.05
Site of metastatic disease		
Lung	23	67.65
Liver	5	14.71
Bone	3	8.82
Other	3	8.82
No. of metastatic sites		
Single	22	81.48
Multiple (2)	4	14.81
Multiple (>2)	1	3.71

Table 2 Treatment response according to the Response Evaluation Criteria in Solid Tumors criteria (version 1.1)

Treatment efficacy	No. of patients (%)
Entered	38 (100.00)
CR	0 (0.00)
PR	9 (23.68)
SD	21 (55.26)
PD	8 (21.06)

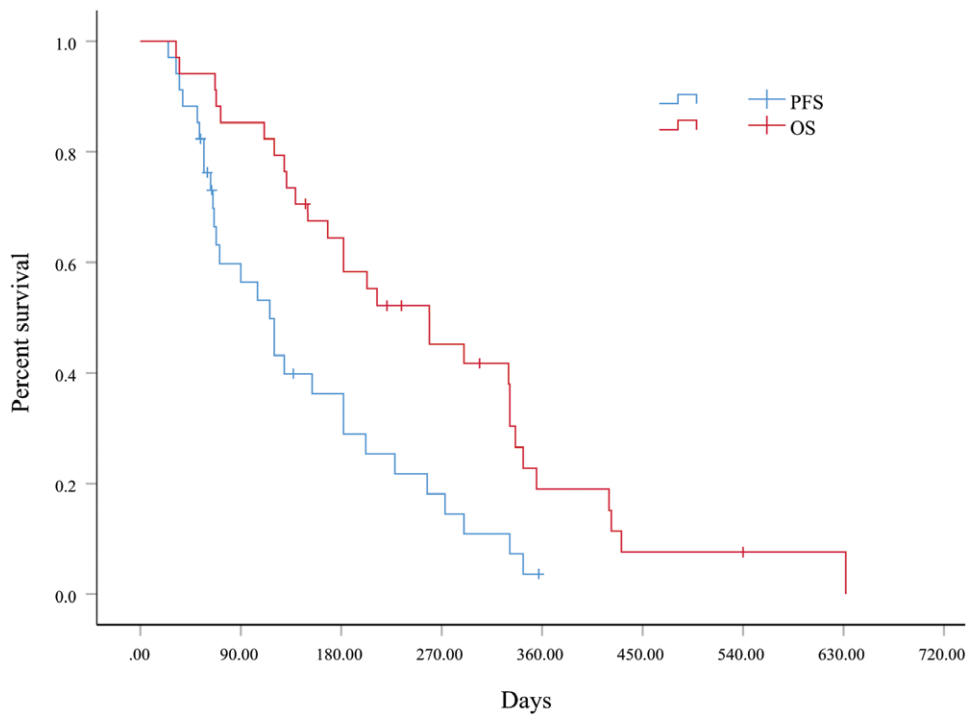
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Fig. 1



Percentage change from baseline in tumor size. Each bar represents one case (n = 38) and bars represent best response in dimension of target lesions.

Fig. 2



Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) in all patients. The median PFS and OS were 105 and 221 days, respectively.

Table 3 Subgroups analyses of treatment response between different groups

Subgroups	Total	PR (%)	SD (%)	PD (%)	ORR (%)	DCR (n %)	<i>P</i> value
With prior 5-Fu exposure	18	2 (11.11)	12 (66.67)	4 (22.22)	2 (11.11%)	14 (77.78)	0.08
Without prior 5-Fu exposure	20	7 (35.00)	9 (45.00)	4 (20.00)	7 (35.00)	16 (80.00)	
Prior chemoradiotherapy	30	6 (20.00)	17 (56.67)	7 (23.33)	6 (20.00)	23 (76.67)	0.27
Prior chemotherapy only	8	3 (37.50)	4 (50.00)	1 (12.50)	3 (37.50)	7 (87.50)	
Second-line	22	7 (31.82)	9 (40.91)	6 (27.27)	7 (31.82)	16 (72.73)	0.16
Third-line or later	16	2 (12.50)	12 (75.00)	2 (12.50)	2 (12.50)	14 (87.50)	

DCR, disease control rate; 5-FU, 5-fluorouracil; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4 Hematological and nonhematological toxicity according to National Cancer Institute Common Toxicity Criteria

Toxicity	Grade 1–2		Grade 3		Grade 4	
	n	%	n	%	n	%
Leucopenia	11	28.95	2	5.26	3	7.89
Neutropenia	4	10.53	0	0.00	3	7.89
Thrombocytopenia	3	7.89	1	2.63	0	0.00
Anemia	10	26.32	2	5.26	0	0.00
Cholinergic syndrome	2	5.26	0	0.00	0	0.00
Nausea–vomiting	15	39.47	0	0.00	0	0.00
Diarrhea	4	10.53	1	2.63	0	0.00
Allergic reaction	0	0.00	1	2.63	0	0.00
Fever	3	7.89	1	2.63	0	0.00
Transaminitis	3	7.89	0	0.00	0	0.00
Renal toxicity	1	2.63	0	0.00	0	0.00

PR, nine (40.91%) patients had SD, and six (27.27%) patients had PD, while among 16 patients who received the study drug combination as third- or later-line treatment, two (12.50%) patients achieved PR, 12 (75.00%) patients had SD, and two (12.50%) patients had PD. The ORR between these two groups also showed no statistical difference ($P = 0.160$, Table 3). And the PFS and OS still had no significant difference between the two groups (PFS: $P = 0.470$; OS: $P = 0.663$, Fig. 3e and f). Details for subgroup analyses were shown in Table 3.

Toxicity

Treatment-related toxicities are shown in Table 4. Grade 1-2 leukopenia, anemia and nausea–vomiting were the most common toxicities. For grade 3-4 hematological toxicity, five patients had grade 3/4 leukopenia (one had fever), three patients had grade 3/4 neutropenia, and one patient had grade 3/4 thrombocytopenia. For nonhematological toxicities, one (2.63%) patient had grade 3/4 diarrhea, and one (2.63%) patient had grade 3/4 allergic reaction. Two patients had grade 1/2 cholinergic syndrome. There was no treatment-related death in this study.

Discussion

We conducted this retrospective study to evaluate clinical efficacy and safety of irinotecan plus raltitrexed as salvage therapy in a group of 38 ESCC patients who had progressed after the failure of multiple systemic therapies. Our data showed an encouraging ORR of 23.68% and DCR of 78.94%, as well as less than 15% incidence of grade 3/4 toxicities. Median PFS was 105 days and

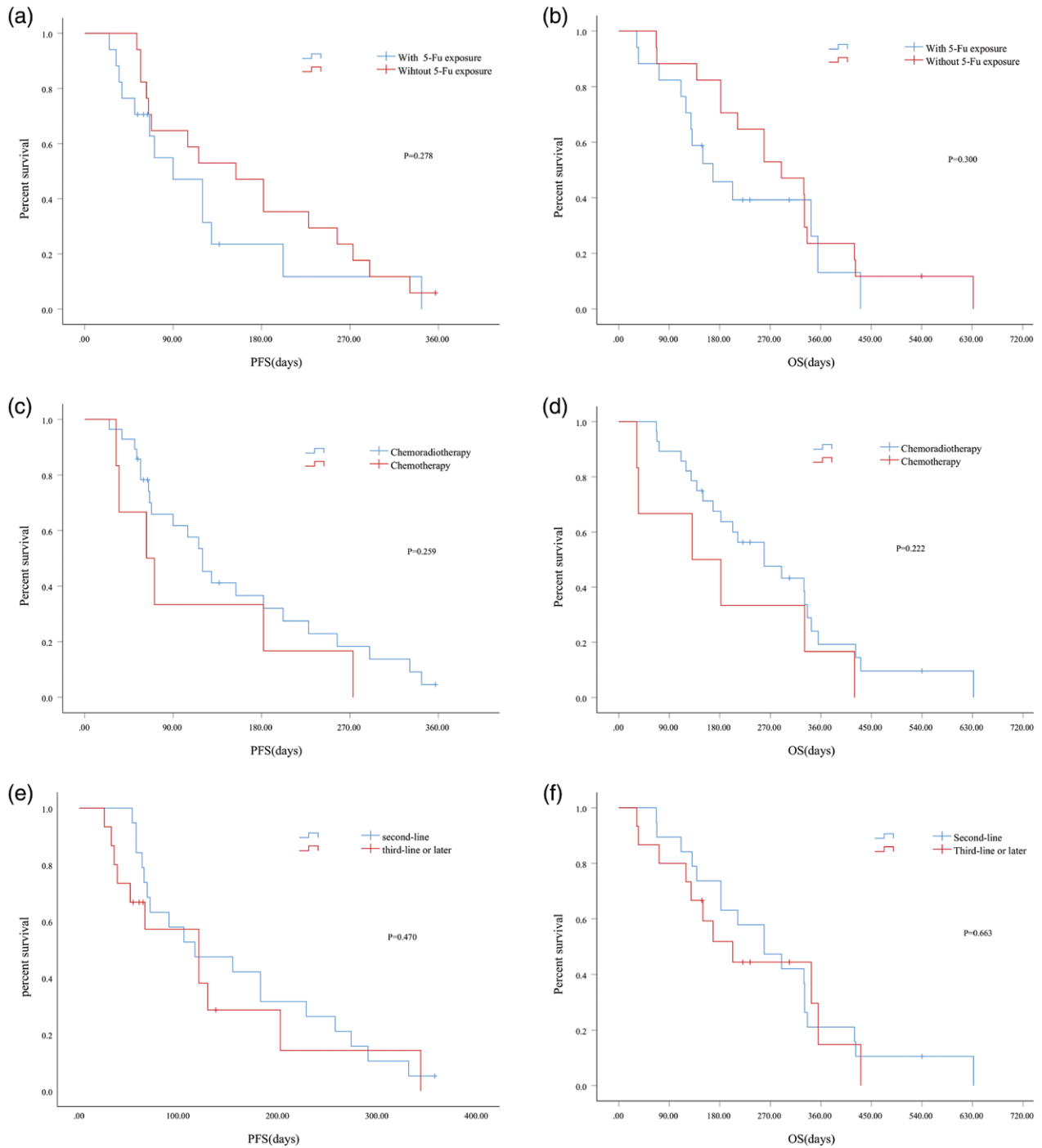
the median OS was 221 days. These results indicate that this combination might be an option for refractory ESCC patients.

In preclinical study, it had been demonstrated a significant schedule-dependent synergism between irinotecan and raltitrexed in vitro. Aschele *et al.* [18] found that greatest synergism was observed when SN-38 (an active metabolite of irinotecan) was administered 24h before raltitrexed by comparing ED₅₀ (the dose required for 50% inhibition of cell growth) in different intervals (1, 4 and 24h), while smaller enhancement or nearly additive interactions was found when the two drugs were switched or used simultaneously. Thereafter, several clinical studies employed 24h or 1h earlier schedule to treat different cancer [9,16,19]. In the present study, we administered irinotecan and raltitrexed in a suggested 24h earlier schedule to observe its clinical efficacy and safety in the treatment of ESCC.

Currently, no standard second- or third-line chemotherapy has been well established in the treatment of ESCC. Although there are a few reports on raltitrexed combination chemotherapy in patients with advanced gastro-esophageal adenocarcinoma [20,21] the clinical experience of raltitrexed in patients with ESCC is still unavailable. Recently, Ding *et al.* reported that raltitrexed could decrease cell viability and proliferation, cause apoptosis and enhance the radiosensitivity of ESCC cells [22]. In patients with advanced colorectal cancer, raltitrexed has produced comparable efficacy as first-line treatment when compared to 5-FU-based regimen [9] and still showed activity when combined with irinotecan as second-line chemotherapy [16]. Since 5-FU plus irinotecan was an effective combination as a second-line chemotherapy in ESCC [6], and raltitrexed was considered as a potential substitute for 5-FU, we investigated the clinical efficacy and safety of irinotecan plus raltitrexed and its potential utility as second- or later-line therapy in ESCC patients.

Our data showed that the ORR was 23.68% and the DCR was 78.94%, which were slightly higher than results in colorectal cancer and pancreas cancer (ORR: 16–16.7%, DCR: 56.7–58%) [16,19]. The survival results (median PFS and median OS) were similar to recently reported results from a prospective randomized, multicenter, open-labeled phase3 ESWN 01 trial [23]. Together with

Fig. 3



Subgroups analyses of survival between different groups. (a) Kaplan–Meier estimates of progression-free survival (PFS) in patients who previously received chemotherapy containing 5-fluorouracil (5-FU) or not. (b) Kaplan–Meier estimates of overall survival (OS) in patients who previously received chemotherapy containing 5-FU or not. (c) Kaplan–Meier estimates of PFS in patients who previously received chemotherapy or chemoradiotherapy. (d) Kaplan–Meier estimates of OS in patients who previously received chemotherapy or chemoradiotherapy. (e) Kaplan–Meier estimates of PFS in patients who previously received different lines of treatment. (f) Kaplan–Meier estimates of OS in patients who previously received different lines of treatment.

the previous reports, our results showed that irinotecan plus raltitrexed could be a possible alternative regimen for previously treated ESCC patients.

Unlike our present study, only patients with no prior exposure to irinotecan or 5-FU were enrolled in the retrospective study conducted by Wang *et al.* [6] and the

prospective ESWN 01 trial [23]. The reason might be partly because of similar action and thus similar resistance mechanisms associated with 5-FU and raltitrexed. In our present study, we found that patients without prior 5-FU exposure are sensitive to irinotecan plus raltitrexed chemotherapy with an ORR of 35.00%, which was numerically higher than the ORR in patients with prior 5-FU exposure. However, 5-FU inhibits TS through its metabolite 5-fluoro-deoxyuridine monophosphate (FdUMP), while raltitrexed directly and specifically inhibits TS without requiring any modulating agent [24]. Therefore, incomplete cross-resistance between 5-FU and raltitrexed has been confirmed in both preclinical research [25] and clinical studies [16]. In 5-FU refractory advanced colorectal cancer, irinotecan plus raltitrexed had a moderate improvement in RR when compared indirectly with data from trial of second-line CPT-11 monotherapy [16,26]. Our present study had shown that patients with prior 5-FU exposure are still sensitive to irinotecan plus raltitrexed chemotherapy with an ORR of 11.11%. This matter of cross-resistance between 5-FU and raltitrexed in irinotecan treatment is an interesting question to further study. In general, irinotecan plus raltitrexed was effective in heavily treated (previous two-line or more chemotherapy or chemoradiotherapy) patients. However, the results provided are from a limited number of cases. To provide more evidence, a large-scale study is needed in the future.

In this study, we had lower toxicity compared with other reports [9,16,19,27]. Hematological and gastrointestinal toxicities were the main toxicities. Grade 3/4 leukopenia occurred in five (13.15%) patients. According to previous reports, most studies used 300–350 mg/m² irinotecan in the treatment of colorectal cancer [28,29]. A lower dose of irinotecan (200 mg/m²) combined with raltitrexed was administered to treat patients with advanced pancreatic adenocarcinoma from a randomized multicenter phase II study [19]. However, there was no study to determine the maximum-tolerated dose (MTD) of this combination in EC. In a multicenter phase II study, 130 mg/m² irinotecan combined with cisplatin were used to treat metastatic, unresectable EC [30]. A slightly higher dose of 160 mg/m² irinotecan combined with S-1 were used to treat Chinese EC patients from a prospective randomized, multicenter, open-labeled phase 3 trial [23]. In our study, the median dose of irinotecan was 178 mg/m² (118–217 mg/m²). Compared with the ESWN 01 trial, both survival results and incidences of grade 3–4 leukopenia/neutropenia in the present study were similar. This indicates that irinotecan plus raltitrexed is a safe choice in previously treated recurrent/metastatic ESCC. In the future, a prospective clinical study of irinotecan plus raltitrexed in patients with refractory esophageal squamous cell cancer is needed to determine the MTD and clinical efficacy of this combination.

In conclusion, the combination of irinotecan and raltitrexed was effective as second- or later-line chemotherapy with controllable toxicity for ESCC patients after the failure of multiple systemic therapies. Due to the limitations in the study design and sample size, a prospective randomized clinical trial detecting the merits of irinotecan combined with raltitrexed should be conducted in the future.

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Conflicts of interest

There are no conflicts of interest.

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