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ORIGINAL ARTICLE

A phase II study of capecitabine and cisplatin (XP) as first-line chemotherapy in patients with advanced esophageal squamous cell carcinoma

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Abstract
Purpose The combination of 5-fluorouracil (5-FU) and cisplatin (FP) remains the mostly used regimen for metastatic esophageal squamous carcinoma. This phase II study assessed the efficacy and safety of capecitabine/cisplatin (XP) as a first-line chemotherapy in a homogenous cohort of patients with metastatic or recurrent esophageal squamous cell carcinoma.
Materials and methods Patients received 60 mg/m^2 of cisplatin intravenously (IV) on day 1 and capecitabine 1,250 mg/m^2/dose orally twice a day on days 1–14. Treatment cycles were repeated every 3 weeks until the documented disease progression, unacceptable toxicity, or patient's refusal. Immunohistochemical studies against thymidylate synthase (TS) and thymidine phosphorylase (TP) were performed to seek predictive markers for treatment response.
Results Between December 2003 and March 2006, 45 patients entered the study. All patients had histologically proven squamous cell carcinoma of the esophagus. The overall response rate (ORR) was 57.8% (95% CI, 43.3–72.2) with 0 CR and 26 PRs. The median duration of response in responders was 4.6 months (1.0–15.6 months). With a median follow-up duration of 25.7 months (10.8–42.6 months), the median time to progression was 4.7 months (95% CI, 2.5–7.0) and the median survival time was 11.2 months (95% CI, 8.5–13.9). Common grade 3 or 4 non-hematological adverse events were anorexia (18/191, 9.4%), fatigue (9/191, 4.7%), constipation (6/191, 3.1%), hand-foot syndrome (6/191, 3.1%) and diarrhea (4/191, 2.1%). The most common grade 3 or 4 hematological adverse events were neutropenia (33/191, 17.3%), followed by leucopenia (11/191, 5.8%), anemia (2/191, 1.0%) and thrombocytopenia (1/191, 0.5%). There was no treatment-related death. Neither TS nor TP showed predictive value for treatment response.
Conclusion The XP regimen demonstrated a promising antitumor activity in metastatic esophageal squamous cell carcinoma, which may potentially replace the FP regimen.

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Introduction

The incidence of esophageal cancer has increased in recent years, reflecting a shift in histologic type and primary tumor location in the USA [1, 2]. Although, adenocarcinoma of the esophagus is more prevalent than squamous cell carcinoma in the Western countries, squamous cell carcinoma is still the most prominent histologic type in other countries. There is no difference in long-term outcome between the two histologic types, however [3]. Esophageal cancer is a highly aggressive disease with a 5-year survival rate of 10–15% [4]. At presentation,

approximately 50% of patients show distant metastasis and the half of the remaining patients who initially present with locoregional disease will develop distant metastases [5]. Metastatic esophageal carcinoma is an incurable disease with median survival duration of 6 to 8 months. Cytotoxic chemotherapy has been used to control tumor growth, improve quality of life and prolong survival although a survival advantage for chemotherapy over best supportive care alone in patients with metastatic cancer of the esophagus has not been proven in randomized trials. Nevertheless, a standard and effective chemotherapeutic regimen for first-line chemotherapy has not yet been vigorously defined in metastatic, recurrent esophageal carcinoma. Moreover, many previous clinical trials included heterogeneous patient populations of gastric adenocarcioma, esophageal adenocarcinoma, gastroesophageal junctional tumor, or esophageal squamous cell carcinoma owing to relative rarity of the disease.

Although there is no standard chemotherapy regimen for metastatic esophageal cancer, various kinds of chemotherapy regimens have been investigated in an attempt to prolong survival and improve quality of life. The most commonly used regimen as a first-line chemotherapy is the combination of cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (5-FU) (1,000 mg/m^2/day continuous infusion for 96 to 120 h) in metastatic esophageal cancer [6]. The randomized phase II study comparing cisplatin/5-FU (FP) to cisplatin alone in advanced squamous cell esophageal cancer showed that the combination arm was superior in terms of response rate of 35% as compared with cisplatin alone arm (response rate = 19%), and overall survival (33 vs 28 weeks, respectively) [7]. However, the toxicity was prominent with high treatment-related deaths (16%). In addition, continuous infusion of 5-FU requires an indwelling venous access, which provides a source for venous thrombosis and sepsis and makes therapy burdensome to the patient. More recently, newer agents such as taxanes (paclitaxel, docetaxel), vinorelbine, irinotecan, capecitabine and oxaliplatin have been investigated as single agents or in combination in pre-operative or advanced settings. Several phase II trials have assessed combinations of taxanes (paclitaxel and docetaxel) or cisplatin and capecitabine, with response rates of 40–56%. Capecitabine (Xeloda®) is an oral fluoropyrimidine that is preferentially metabolized in tumor tissues via an enzymatic pathway to fluorouracil [8]. The North Central Cancer Treatment Group (NCCTG) phase II study of capecitabine and oxaliplatin as first-line therapy in patients with adenocarcinoma of the esophagus and gastroesophageal junction, and gastric cardia demonstrated a tumor response rate of 35%, median survival of 6.4 months (95% CI, 4.6–10.0 months), and median time to progression of 4.0 months (95% CI, 3.1–4.6 months) [9]. However, the toxicity profile was high with four treatment-related deaths. Several phase II trials tested the safety and efficacy of capecitabine (1,250 mg/m^2 twice daily for 2 weeks) with cisplatin 60 mg/m^2 on day 1 in 3-week cycles for chemonaïve gastric cancer patients and reported response rates ranging from 28 to 55% with tolerable toxicity profile [10–12]. Furthermore, in a recent pivotal phase III trial comparing the efficacy of capecitabine/cisplatin (XP) versus FP in advanced gastric cancer, XP was non-inferior, in terms of progression-free survival (5.6 vs 5.0 months, XP vs FP, respectively), overall survival (10.5 vs 9.3 months) and overall response rate (41 vs 29%) [13].

On the basis of these promising results, we conducted a phase II study in order to assess the efficacy and safety of XP as a first-line chemotherapy in a homogenous cohort of patients with metastatic or recurrent esophageal squamous cell carcinoma. The primary objective was to evaluate the anti-tumor activity in terms of response rate, and secondary objectives were progression-free survival, overall survival and safety of the regimen. Additionally, we performed thymidylate synthase (TS) and thymidine phosphorylase (TP) immunohistochemistry in an attempt to seek predictive markers for treatment response.

Materials and methods

This was an open-label, single-center, phase II study of palliative chemotherapy with XP in previously untreated advanced esophageal squamous cell carcinoma.

Patient eligibility

Eligible patients were required to have histologically confirmed squamous cell carcinoma of the esophagus, at least one bidimensionally measurable lesion, age between 18 and 75, an Eastern Cooperative Oncology Group performance status of two or less, a life expectancy of at least 3 months, adequate hematologic parameters (hemoglobin ≥ 9.0 g/dl, absolute neutrophil count (ANC) ≥ 1,500/μl, platelet count ≥ 100,000/μl), renal function (creatinine clearance by Cockroft formula ≥ 50 ml/min), and liver function (aspartate aminotransferase, alanine aminotransferance ≤ 3× the upper limits of normal (ULN), total bilirubin <2× ULN). Patients who received 5-FU containing adjuvant chemotherapy > 12 months from the date of study entry were eligible for the study. Esophageal adenocarcinoma or gastroesophageal junction tumors were excluded from the study. Before the study was initiated, the protocol was approved by the Institutional Review Board, and all patients provided written informed consent prior to any study-specific procedures.

Exclusion criteria were as follows; history of clinically significant cardiac disease as defined by symptomatic ventricular arrhythmias, congestive heart failure, or previous myocardial infarction within 12 months of study entry; presence of parenchymal brain metastasis or leptomeningeal metastasis, active infection and psychiatric illness that would preclude obtaining informed consent; history of another malignancy within 5 years of study entry, apart from basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix.

Treatment

Patients received 60 mg/m^2 of cisplatin intravenously (IV) on day 1 and capecitabine 1,250 mg/m^2/dose orally twice a day on days 1–14. Treatment cycles were repeated every 3 weeks until the documented disease progression, unacceptable toxicity, or patient's refusal. All patients received hyper-hydration (pre- and post-cisplatin hydration) and mannitol before cisplatin infusion for nephrotoxicity prevention and 5-HT3 inhibitors for emesis prophylaxis. Toxicity was assessed according to the National Cancer Institute common toxicity criteria (NCI-CTC) scale version 2.0. The severity of any toxicity not defined in the NCI-CTC was graded as 1 = mild, 2 = moderate, 3 = severe, or 4 = very severe. The capecitabine dose was adjusted for hematological adverse events as follows. If ANC was greater than 1,000/μl and platelet greater than 75,000/μl, chemotherapy was administered without dose reductions. If ANC was less than 1,000/μl or platelet less than 75,000/μl, chemotherapy was delayed for 1 week until recovery. If ANC was greater than 1,000/μl and platelet count greater than ≥75,000/μl following delay from the planned date of chemotherapy, doses of capecitabine was reduced by 25%. If patients required a delay of longer than 3 weeks for recovery, patients went off the study protocol. For non-hematological toxicity, capecitabine dose was adjusted as previously described. The capecitabine dose was adjusted for non-hematologic adverse events as described elsewhere. [12] Dose adjustment criteria for cisplatin were based on serum creatinine levels just prior to each cycle. If serum creatinine was <1.5 mg/dl, full-dose cisplatin was given; if serum creatinine was 1.5–2.5 mg/dl, 50% cisplatin was administered; if serum creatinine was >2.5 mg/dl, the patient was excluded from the study.

Immunohistochemistry

Immunohistochemical study was performed using the streptavidin–biotin complex method and TechMateTM 1000 automated staining system (DakoChemmate, Glostrup, Denmark). Primary antibodies used and working dilutions employed were as follows; TS mouse mAb (Clone TS106/4H4B1, 1:50 dilution in Tris/EDTA buffer (pH 9.0), Zymed, San Francisco, USA) and TP mouse mAb (PGF.44C, 1:100 dilution, NeoMarkers, Fremont, USA). Deparaffinized sections were treated with 3% hydrogen peroxide in methanol for 10 min to inhibit endogenous peroxidase. Sections were immersed in 0.01 M citrate buffer (pH 6.0) and heated in a pressure cooker for 30 min. Sections were then incubated with primary antibody for 50 min at room temperature. Each section was treated sequentially with biotinylated secondary antibody (anti-mouse immunoglobulin) and streptavidin–peroxidase complex (DakoChemmate). 3,3′-diaminobenzidine tetrahydrochloride was used as a chromogen, and then Mayer's hematoxylin counterstain was applied. Negative controls (isotype-matched irrelevant antibody) were run simultaneously.

The slides were assessed without knowledge of the clinical outcome. The intensity and extent of the immunohistochemical (IHC) staining was graded as the following. Intensity was graded on a semiquantitative scale from 0 to 3, where 0 = no staining, 1 = weak staining, 2 = strong staining, and 3 = very strong staining. The area of the most intense staining was graded on a scale from 0 to 4, where 0 = no staining, 1 = staining of 0–10% of tumor cells, 2 = staining of 10–25% of tumor cells, 3 = staining of 25–50% of tumor cells, and 4 = staining of more than 50% of tumor cells. A TS score was calculated by multiplying the intensity and extent grades. TS scores less than 6 were considered low, and scores greater than 6 were defined as high in this study. [14] The same criteria were applied for TP staining results.

Pre-treatment and follow-up evaluations

The primary objective of the study was response rate, and secondary objectives were toxicity, overall survival and time to progression. Pre-treatment evaluation included history and physical examination, complete blood cell count with differentials, chemistry, chest X-ray, computed tomography (CT) scan of thorax and any other diagnostic procedures as clinically indicated. During treatment, a history taking, physical examination including toxicity assessment, complete blood cell count and chemistry were performed every 3 weeks before each cycle. Appropriate imaging studies including thoracic CT scan were performed every 2 cycles (6 weeks) to evaluate treatment response, or sooner if needed for documentation of disease progression. Responses were to be confirmed by subsequent CT scans 4 to 6 weeks after the initial response documentation. Patients

were assessed every 2 months for disease progression following the completion of the chemotherapy. The clinical tumor response was assessed according to WHO criteria: complete response (CR, total disappearance of invasive cancer), partial response (PR, a reduction of ≥50% of the product of the two largest perpendicular dimensions), stable disease (SD, a reduction of <50% or an increase of ≤25%), and progressive disease (PD, an increase of >25%).

Statistical analysis

According to a Simon's two-stage phase II optimal design, [15] a sample size of 45 was required to accept the hypothesis that the true response rate is greater than 40% with 90% power, and to reject the hypothesis that the response rate is less than 20% with 5% significance. At the first stage, if there were fewer than 5 responses out of the initial 19 patients, an early termination of the study was required.

Descriptive statistics were reported as proportions and medians. Kaplan–Meier estimates were used in the analysis of time-to-event variable, and the 95% confidence interval (CI) for the median time to event was computed. The dose intensity (DI) was calculated as the ratio of the total dose in milligrams per square meter of the patient, divided by the total treatment duration expressed in days. The relative DI was calculated as the ratio of the DI actually delivered to the DI planned by the protocol. For comparison between the TS and TP subgroups, chi square test was used.

Results

Patient characteristics

Between December 2003 and March 2006, 45 patients entered the study. Patient baseline characteristics are listed in Table 1. All patients had histologically proven squamous cell carcinoma of the esophagus, and no patient had gastroesophageal junction carcinomas. Twenty-four (53.3%) patients had undergone esophagectomy, and more than 80% of the patients received prior post-operative 5-FU-based chemotherapy with or without radiotherapy. The median age was 62 with a range of 47 to 72. Forty-nine percent of the patients had mid-esophageal cancer, and 44% of the patients had distal esophageal cancer. A great majority of patients (82.2%) had metastatic disease at the time of treatment with the most common site of metastasis being lymph node (77.8%) followed by lung (26.7%), and liver (20.0%).

Table 1 Patient characteristics

	No. of patients (%)
Total number of patients	45 (100.0)
Median age (range)	62 (47–72)
Gender	
Male	44 (97.8)
ECOG PS	
0–1	41 (91.1)
2	4 (8.9)
Anatomic site	
Upper	3 (6.7)
Mid	22 (48.9)
Distal	20 (44.4)
Initial disease status	
Metastatic	19 (42.2)
Relapsed	26 (57.8)
Previous adjuvant 5-FU-based chemotherapy	15 (57.7)
Previous adjuvant radiotherapy alone	4 (15.4)
Previous adjuvant radiotherapy + 5-FU-based chemotherapy	7 (26.9)
Metastatic sites	
Lymph node	35 (77.8)
Lung	12 (26.7)
Liver	9 (20.0)
Bone	2 (4.4)
Pleura	3 (6.7)
Anastomosis site	2 (4.4)
Abdominal wall	3 (6.7)
Others	3 (6.7)
Tumor grade	
Well differentiated	3 (6.7)
Moderately differentiated	29 (64.4)
Poorly differentiated	8 (17.8)
Unknown	5 (11.1)

Treatment response and survival

Of the 45 patients, 38 patients were evaluable for tumor response; however, tumor response was analyzed based on intent-to-treat analysis. Seven patients were not assessable due to the following reasons: loss at follow-up (4 patients), tracheoesophageal fistula (1 patient), upper gastrointestinal bleeding (1 patient) and refusal to further treatment (1 patient). The overall response rate (ORR) was 57.8% (95% CI, 43.3–72.2) with 0 CR and 26 PRs (Table 2). Considering the fact that there was no difference in response rate according to disease status (metastatic vs recurrent, Table 2), prior exposure to 5-FU-containing regimen > 12 months did not influence the anti-tumor

Table 2 Treatment response

	Initial metastatic (n = 19)	Recurrent (n = 26)	Overall (n = 45)
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	12 (63.2%)	14 (53.8%)	26 (57.8%)
SD	1 (5.3%)	5 (19.2%)	6 (13.3%)
PD	5 (26.3%)	1 (3.8%)	6 (13.3%)
Not evaluable	1 (5.3%)	6 (23.1%)	7 (15.6%)

activity. The median duration of response in responders was 4.6 months (1.0–15.6 months). With a median follow-up duration of 25.7 months (10.8–42.6 months), the median time to progression was 4.7 months (95% CI, 2.5–7.0) (Fig. 1) and the median survival time was 11.2 months (95% CI, 8.5–13.9) (Fig. 2). At the time of analysis, 38 patients (84.4%) were dead.

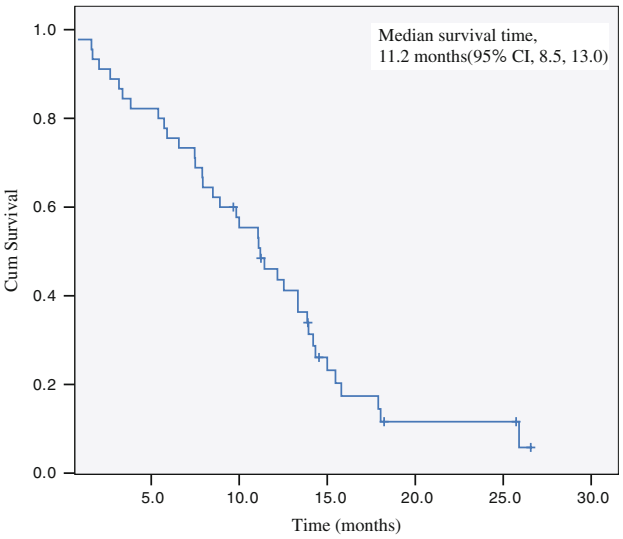

Fig. 2 Overall survival

Drug delivery and safety

A total of 191 cycles (median 4, range 1–10) were administered. Treatment was delayed in 22.5% of cycles. A capecitabine dose was reduced in 49.7% of all cycles. The relative dose intensity was 76.5% for capecitabine and 87.7% for cisplatin. Of the 45 patients, 27 patients (60.0%) received 75 ~ 100% of the planned dose of capecitabine, and 15 patients (33.3%) received between 50 and 74% of the planned dose. The most common cause of capecitabine dose reductions was neutropenia (39/191, 20.4%), followed by hand-foot syndrome (21/191, 11.0%), fatigue (22/191, 11.5%), thrombocytopenia (8/191, 4.2%), stomatitis (4/191, 2.1%), diarrhea (2/191, 1.0%), and infection (1/191, 0.5%). For treatment delay, neutropenia was also the most common adverse event (25/191, 13.1%) followed by thrombocytopenia (6/191, 3.1%), infection (5/191, 2.6%), diarrhea (3/191, 1.6%), hand–foot syndrome (2/191, 1.0%), and stomatitis (2/191, 1.0%). Common grade 3 or 4 non-hematological adverse events were anorexia (18/191, 9.4%), fatigue (9/191, 4.7%), constipation (6/191, 3.1%), hand-foot syndrome (6/191, 3.1%) and diarrhea (4/191, 2.1%). The most common grade 3 or 4 hematological adverse events were neutropenia (33/191, 17.3%), followed by leucopenia (11/191, 5.8%), anemia (2/191, 1.0%) and thrombocytopenia (1/191, 0.5%). Two patients experienced neutropenic fever, which was controlled by intravenous antibiotics. There was no treatment-related death. All 45 patients were evaluated for toxicity profile (Table 3).

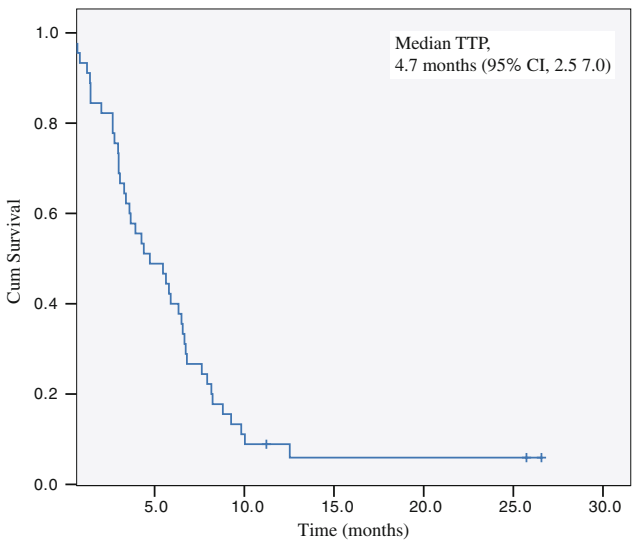

Fig. 1 Time-to-progression

Correlation between TS, TP and treatment response

A total of 34 (76%) patients had tumor samples available for immunohistochemical studies of TS and TP. The association between TP, TS and response to capecitabine plus cisplatin, as measured by IHC, is listed in Table 4. Neither of the extent nor the TS score predicted response with statistical significance (TS < 50% vs TS ≥ 50%, RR 66.6% vs 72.7%, P-value = 0.85; TS score ≤ 6 vs TS score > 6, RR 65.3 vs 83.3%, P-value = 0.45). The extent or the TP score did not significantly correlate with treatment response to capecitabine/cisplatin regimen either (TP < 50% vs TP ≥ 50%, RR 66.7 vs 72.7%, P-value = 0.62; TP score ≤ 6 vs TP score > 6, RR 64.7 vs 75.0%, P-value = 0.56).

Table 3 Toxicity profile

CTC grade	No. of cycles (%) (n = 191)			
	1	2	3	4
Hematologic toxicities				
Anemia	152 (79.6)	19 (9.9)	1 (0.5)	1 (0.5)
Leukopenia	38 (19.9)	23 (12.0)	8 (4.2)	3 (1.6)
Neutropenia	29 (15.2)	30 (15.7)	29 (15.2)	4 (2.1)
Ffebrile neutropenia	–	–	1 (0.5)	1 (0.5)
Thrombocytopenia	58 (30.4)	8 (4.2)	1 (0.5)	–
Non-hematologic toxicities				
Anorexia	70 (36.6)	49 (25.7)	16 (8.4)	2 (1.0)
Fatigue	90 (47.1)	37 (19.4)	8 (4.2)	1 (0.5)
Diarrhea	24 (12.6)	9 (4.7)	4 (2.1)	1 (0.5)
Stomatitis	47 (24.6)	22 (11.5)	2 (1.0)	1 (0.5)
Constipation	18 (9.4)	41 (21.5)	6 (3.1)	–
Hand-foot syndrome	53 (27.5)	17 (8.9)	6 (3.1)	–
Infection	13 (6.8)	9 (4.7)	3 (1.6)	–
Thrombosis	–	–	1 (0.5)	–
Alopecia	38 (19.9)	8 (4.2)	–	–
Vomiting	11 (5.8)	15 (7.9)	–	–

Table 4 Correlation between TP, TS and treatment response

IHC results	Total	PR		SD		PD		P value
	No.	No.	%	No.	%	No.	%	
TS < 50%	18	12	66.6	3	16.7	3	16.7	0.85
TS ≥ 50%	11	8	72.7	1	9.1	2	18.2	
TS score ≤ 6	23	15	65.3	3	13.0	5	21.7	0.45
TS score > 6	6	5	83.3	1	16.7	0	0	
TP < 50%	18	12	66.7	2	11.1	4	22.2	0.62
TP ≥ 50%	11	8	72.7	2	18.2	1	9.1	
TP score ≤ 6	17	11	64.7	2	11.8	4	23.5	0.56
TP score > 6	12	9	75.0	2	16.7	1	8.3	

Discussion

This phase II study showed that the combination of capecitabine 1,250 mg/m^2/dose twice daily and cisplatin 60 mg/m^2 (XP) was very active as first-line treatment in patients with esophageal squamous cell carcinoma. Given the fact that a great majority of patients had metastatic disease at the time of treatment, the ORR was relatively high with 57.8% (95% CI, 43.3–72.2). After a median follow-up duration of 25.7 (10.8–42.6 months), the median survival time was 11.2 months (95% CI, 8.5–13.9). This study suggests that the regimen is safe with encouraging antitumor activity.

There are several lines of evidence that continuous 5-FU infusion can be safely replaced by capecitabine without endangering the efficacy. Firstly, a milestone phase III study in 316 gastric cancer patients showed that XP was non-inferior to FP in terms of progression-free survival (5.6 vs 5.0 months) and overall survival (10.5 vs 9.3 months) [13]. Moreover, the ORR was significantly superior in XP arm (41%) than in FP arm (29%, P = 0.03) with comparable safety profile [13]. Secondly, in a pivotal REAL2 phase III trial randomizing 964 esophagogastric cancer patients in a 2 × 2 design to receive one of four treatments [epirubicin/cisplatin/capecitabine (ECX), epirubicin/oxaliplatin/capecitabine (EOX), epirubicin/cisplatin/5-FU (ECF) or epirubicin/oxaliplatin/5-FU (EOF)] demonstrated that the capecitabine-based (ECX + EOX, n = 480) regimens were non-inferior to the 5-FU-based (ECF + EOF, n = 484) regimens in regard to median overall survival (10.9 vs 9.6 months) and 1-year survival rate (44.6 vs 39.4%) [16]. Therefore, the role of capecitabine-based regimen, especially the most widely studied XP combination, should be actively investigated in various solid tumors.

There has been a lack of phase III trials testing for efficacious first-line chemotherapeutic regimen, especially those incorporating novel agents, in metastatic or recurrent esophageal cancer despite about half of the patients are being diagnosed with metastatic disease. A recent phase II study on oxaliplatin/capecitabine (oxaliplatin 130 mg/m^2 on day 1, capecitabine 1,000 mg/m^2 twice daily, XELOX) in 43 patients with metastatic esophageal, gastroesophageal junction or gastric cardia demonstrated that the tumor response rate was 35% with median survival of 6.4 months [9]. Nevertheless, four treatment-related deaths after 50% enrollment subsequently prompted the investigators to reduce dose of capecitabine from 1,000 mg/m^2 twice daily to 850 mg/mg^2 twice daily. Another capecitabine-based phase II trial with capecitabine (1,000 mg/m^2 twice daily) plus docetaxel (75 mg/m^2 on day 1) in metastatic esophageal cancer reported a response rate of 46% and median survival time of 15.8 months [17]. The incidence of severe (grade 3/4) neutropenia, hand-foot syndrome and diarrhea was markedly higher (42, 29, 13%, respectively) than those observed in our study (17.3, 3.1, 2.1%, respectively). The toxicity profile was similar to that reported in a phase III trial of XP (capecitabine 1,000 mg/m^2 twice daily, cisplatin 80 mg/m^2 on day 1) vs FP in advanced gastric cancer patients [13]. For instance, the most common severely adverse events in patients receiving XP (n = 139) compared with our cohort were neutropenia (16 vs 17%), diarrhea (5 vs 2%), anemia (5 vs 1%) and stomatitis (2 vs 1%). Notably, the frequency of all grade hand-foot syndrome was higher (22/45, 49%) in this study as compared with 22% of all patients in phase III trial of XP vs FP,

which may be due to higher dose of capecitabine (1,250 vs 1,000 mg/m^2) used.

The relative dose intensity was relatively low (76.5%) for capecitabine in this study. Only 60% of the patients received 75 to 100% of the planned capecitabine dose and one-third of the patients received only 50 to 74% of the planned dose. Dose reductions were due to neutropenia, hand-foot syndrome, fatigue and thrombocytopenia in most cases. Despite this study was conducted in esophageal cancer patients in whom dysphagia may be prevalent, no patients actually suffered from dysphagia during chemotherapy that led to termination of the study drug. In support of this observation, the North Central Cancer Treatment Group (NCCTG) focused on dysphagia in metastatic esophageal cancer patients undergoing chemotherapy and concluded that dysphagia did not predict poor response to chemotherapy and most patients receiving chemotherapy remained capable of swallowing liquid (not severe dysphagia) [18]. Thus, dysphagia should not preclude from administering oral chemotherapeutic drugs in esophageal cancer patients.

The impact of previous adjuvant 5-FU-based chemotherapy on the anti-tumor activity of subsequent XP is yet to be determined. Less than 50% of the patients received 5-FU-based chemotherapy with or without radiotherapy in our trial. Additionally, we excluded those patients, who had been treated with post-operative 5-FU-based chemotherapy within 12 months of the study entry. Therefore, a prior exposure to 5-FU at least more than 12 months did not seem to adversely influence the activity of XP based on our data.

To identify predictive markers for treatment response to XP in this cohort, we collected tumor specimens from 34 patients and stained for TS and TP. The final step of the capecitabine metabolism involves the conversion of 5′-deoxy-5-fluorouridine to 5-FU by TP, which is highly expressed in tumor tissues. TS is a target enzyme for 5-FU. A recent study reported that TP expression by IHC significantly predicted the tumor response and overall survival following capecitabine plus irinotecan chemotherapy in metastatic colorectal cancer patients [19]. Additionally, high TP expression levels were associated with favorable tumor response in non-small cell lung cancer [20]. On contrary, we did not observe any predictive value of TP or TS for treatment outcome in this study (Table 4). The role of TP or TS as a predictive factor for treatment response of XP is difficult to conclude from our study due to the inadequate sample size.

Based on our data, the XP regimen was a promising combination therapy in metastatic or recurrent esophageal cancer patients with tolerable toxicity profile. A phase III trial comparing XP to XP plus novel targeted agents should be considered in esophageal cancer.

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