ACTA ONCOLOGICA
2021, VOL. 60, NO. 7, 948–953
https://doi.org/10.1080/0284186X.2021.1928281

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

A randomized phase 2 trial of first-line docetaxel, carboplatin, capecitabine (CTX) and epirubicin, oxaliplatin, capecitabine (EOX) in advanced esophagogastric adenocarcinoma

Peter C. Petersen[a], Lone N. Petersen[a], Ivan Vogelius[a,b], Jon K. Bjerregaard[a] and Lene Baeksgaard[a]

[a]Department of Oncology, Rigshospitalet, Copenhagen, Denmark; [b]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Background: No preferred first-line chemotherapy regimen exists for advanced esophagogastric adenocarcinoma. Addition of docetaxel to cisplatin and 5-fluorouracil (DCF) has been shown to improve survival but is associated with increased toxicity. In this randomized, non-comparative phase 2 trial, we tested carboplatin, docetaxel, and capecitabine (CTX), a potentially useful modification of DCF (NCT02177552).

Patients and methods: Patients with advanced HER2-negative esophagogastric adenocarcinoma not previously treated in the first-line setting were randomized to intravenous docetaxel 60 mg/m^2 and carboplatin AUC5 plus oral capecitabine 1000 mg/m^2 bd days 1–14, q4w (CTX) or intravenous epirubicin 50 mg/m^2 and oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine 625 mg/m^2 bd days 1–21, q3w (epirubicin, oxaliplatin and capecitabine [EOX]). Treatment continued until progression, intolerance or for a maximum of nine cycles. The primary endpoint was 1-year survival for patients treated with CTX.

Results: Between June 2014 and January 2019, a total of 98 eligible patients were randomized. The 1-year survival rate was 34.7% (95% CI 21.8 – 47.9) with CTX and 36.7% (95% CI 23.6 – 50.0) with EOX. Progression-free survival and overall survival were 6.1 months (95% CI 5.5 – 7.1) and 9.8 months (95% CI 8.2 – 11.0) with CTX and 5.1 months (95% CI 4.3 – 7.0) and 10.2 months (95% CI 8.0 – 11.9) with EOX, respectively. Related grade 3 or 4 treatment-emergent adverse events (AEs) occurred in 86% of patients on CTX and 69% on EOX. Febrile neutropenia occurred in 31.4% of patients on CTX and 13.7% on EOX.

Conclusions: First-line CTX showed insufficient efficacy and caused a high rate of febrile neutropenia. CTX could not, therefore, be recommended for further study. This trial adds to current knowledge of docetaxel combined with platinum and 5-FU: that the combination is associated with increased toxicity and its use should be limited to fit patients in need of a response.

ARTICLE HISTORY
Received 4 December 2020
Accepted 5 May 2021

KEYWORDS
Gastric cancer; adenocarcinoma; antineoplastic agents; taxanes; carboplatin

Introduction

Chemotherapy is standard therapy for first-line systemic therapy for advanced esophagogastric adenocarcinoma. Combination chemotherapy is associated with a survival benefit [1], but no universally accepted preferred regimen exists. The backbone of most chemotherapy regimens consists of a platinum salt combined with a 5-fluorouracil (5-FU) compound. Often used combinations are either doublets or triplets with either epirubicin or taxanes. First-line chemotherapy options in international guidelines include combinations of epirubicin, oxaliplatin, and 5-FU (EOX); docetaxel, cisplatin, and 5-FU (DCF); cisplatin or oxaliplatin and 5-FU (CF, FOLFOX, CAPOX); and others (e.g., FOLFIRI) [2,3].

Addition of docetaxel to cisplatin and 5-FU (DCF) prolonged time-to-progression and overall survival compared to cisplatin and 5-FU (CF) in a randomized phase 3 trial but significantly increased the rate of febrile neutropenia [4]. Therefore, modifications of DCF (mDCF) have been developed that aim to be less toxic [5]. Regimens with mDCF use split doses on weekly or biweekly schedules or reduced doses on 3-weekly schedules. Regarding the platinum backbone, both cisplatin and oxaliplatin have been studied in phase 2 and 3 trials in combinations with 5-FU or capecitabine as doublets [6–8], and in combinations with epirubicin as triplets [9]. Previous trials with the third platinum carboplatin in the metastatic setting are mostly confined to small single-arm phase 2 trials [10]. Carboplatin as a single agent is thought to have little if any activity in this setting [11].

In our institution, a regimen of carboplatin, docetaxel and capecitabine (CTX) was the preferred option for first-line therapy of HER2-negative advanced esophagogastric adenocarcinoma until replaced by EOX following the REAL-2 trial [9]. The combination of CTX was originally established on clinical grounds rather than on evidence but a retrospective analysis had supported its use [12]. CTX differs from other modifications of DCF mainly because it is administered on a 4-weekly schedule with a 2-week pause in each cycle and by incorporating carboplatin. As CTX had been perceived to be efficacious and tolerable, it was decided to carry out an investigator-initiated randomized phase 2 trial with

CONTACT Peter C. Petersen peter.c.petersen@dadlnet.dk Department of Oncology, Rigshospitalet, Blegdamsvej 9, Copenhagen 2100, Denmark

experimental CTX and standard EOX in the first-line setting. The results of this trial are presented here.

Patients and methods

Study design

Study assessing the Effects of chemotherapy in advanced Esophagogastric aDenocarcinoma (SEED) was a randomized, non-comparative, open-label, single-center, phase 2 trial in patients who were treated with first-line CTX or EOX. Patients who met the eligibility criteria were randomized to CTX or EOX in a 1:1 ratio. The primary objective was to describe the 1-year survival rate for patients treated with CTX. The reason for randomization was to reduce the selection bias that would occur in a single-arm study with CTX. Eligible patients were allocated to treatment by a centralized randomization service (Sealed Envelope™) using random permuted blocks. The trial was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and ICH GCP. All patients provided informed consent before any study procedure was carried out. The trial is registered on ClinicalTrials.gov (NCT02177552).

Study population

Main inclusion criteria included age below 80 years; histologically confirmed, unresectable, HER2-negative, esophagogastric adenocarcinoma; Eastern Cooperative Oncology Group (ECOG) score of 0 or 1; life expectancy >12 weeks; and adequate organ function based on hematological, renal and hepatic blood counts, creatinine clearance ≥60 ml/min according to the Cockroft–Gault formula, and New York Heart Association (NYHA) classification score <2. Main exclusion criteria included less than 6 months from any previous perioperative chemotherapy, persistent ≥grade 2 toxicity from prior chemotherapy, or a cumulative dose of epirubicin exceeding 300 mg/m^2 at baseline.

After randomization, patients allocated to CTX had a chrome-EDTA clearance performed that was required to show a clearance of ≥60 ml/min, while patients allocated to EOX had a MUGA performed that was required to show an ejection fraction of ≥50%, otherwise, these patients would be withdrawn from study and replaced. Patients who withdrew consent before initiating assigned treatment, or who were unable to take capecitabine during their full first chemotherapy cycle, would also be withdrawn from study and replaced.

Treatment plan

In arm A (experimental arm), treatment consisted of intravenous docetaxel 60 mg/m^2 plus intravenous carboplatin AUC5 on day 1 plus oral capecitabine 1000 mg/m^2 bd days 1–14, repeated every 4 weeks (CTX). In arm B (standard arm), treatment consisted of intravenous epirubicin 50 mg/m^2 plus intravenous oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine 625 mg/m^2 bd days 1–21, repeated every 3 weeks (EOX). Treatment was to be initiated within seven calendar days of randomization, and was continued until progression, intolerance, withdrawal of consent, or for a maximum of nine cycles. Patients who had not progressed at treatment discontinuation were followed with CT chest and abdomen every 3 months. All patients were followed for survival until the end of the study.

Evaluation

Before random assignment, all patients had a complete medical history and physical examination including blood tests and ECG. During treatment, patients were evaluated by a physician for toxicity and clinical benefit prior to the administration of each chemotherapy cycle, and for efficacy with CT chest and abdomen every 12 weeks in arm A (CTX) and after every third cycle in arm B (EOX). Baseline scans had to be <4 weeks old at treatment initiation. In arm A, radiological disease status was reported according to RECIST criteria version 1.1. In both arms, an end of study treatment visit (ESTV) to collect safety data was carried out 30 days after treatment discontinuation. In arm A, quality of life was assessed using EORTC-QLQ-C30 and QLQ-OG25 at baseline, and prior to cycles 3, 5, 7, and 9, at ESTV and at follow-up visits.

Statistical considerations

The primary endpoint was one-year survival in arm A (CTX). Secondary efficacy endpoints were progression-free survival in arm A, 1-year survival in arm B (EOX), and overall survival in both arms. Secondary toxicity endpoints were grade 3 and 4 adverse events (AEs). Other secondary endpoints included further lines of therapy and quality of life.

One-year survival was defined as the percentage of patients who were alive 1 year after random assignment. Progression-free survival was measured from the day of random assignment until radiological or clinical progression, or death, whichever came first. Overall survival was defined from the day of random assignment until death due to any cause. AEs were graded according to Common Terminology Criteria for AEs version 4.0.

The study sought to accept or reject treatment in arm A without making direct comparisons to arm B. For the primary endpoint, 1-year survival was measured as crude proportions using Fleming's one-stage procedure for acceptance sampling [13]. As complete follow-up at 1 year was expected Fleming's design was applicable without modification for censoring. Arm B served as an internal control and did not influence sample size. It was considered that a 1-year survival rate of ≤40% in arm A would be unworthy of further study (rejection) while a rate of ≥55% would merit recommendation for a phase 3 study (acceptance). With a 20% risk of rejecting a true value of ≥55% (power 0.8) and a 10% risk of accepting a true value of ≤40% (alpha 0.1) 49 patients were required for arm A. For a 1:1 randomization a total of 98 patients were required.

Efficacy analyses were based on the per-protocol population defined by those that were randomized, initiated

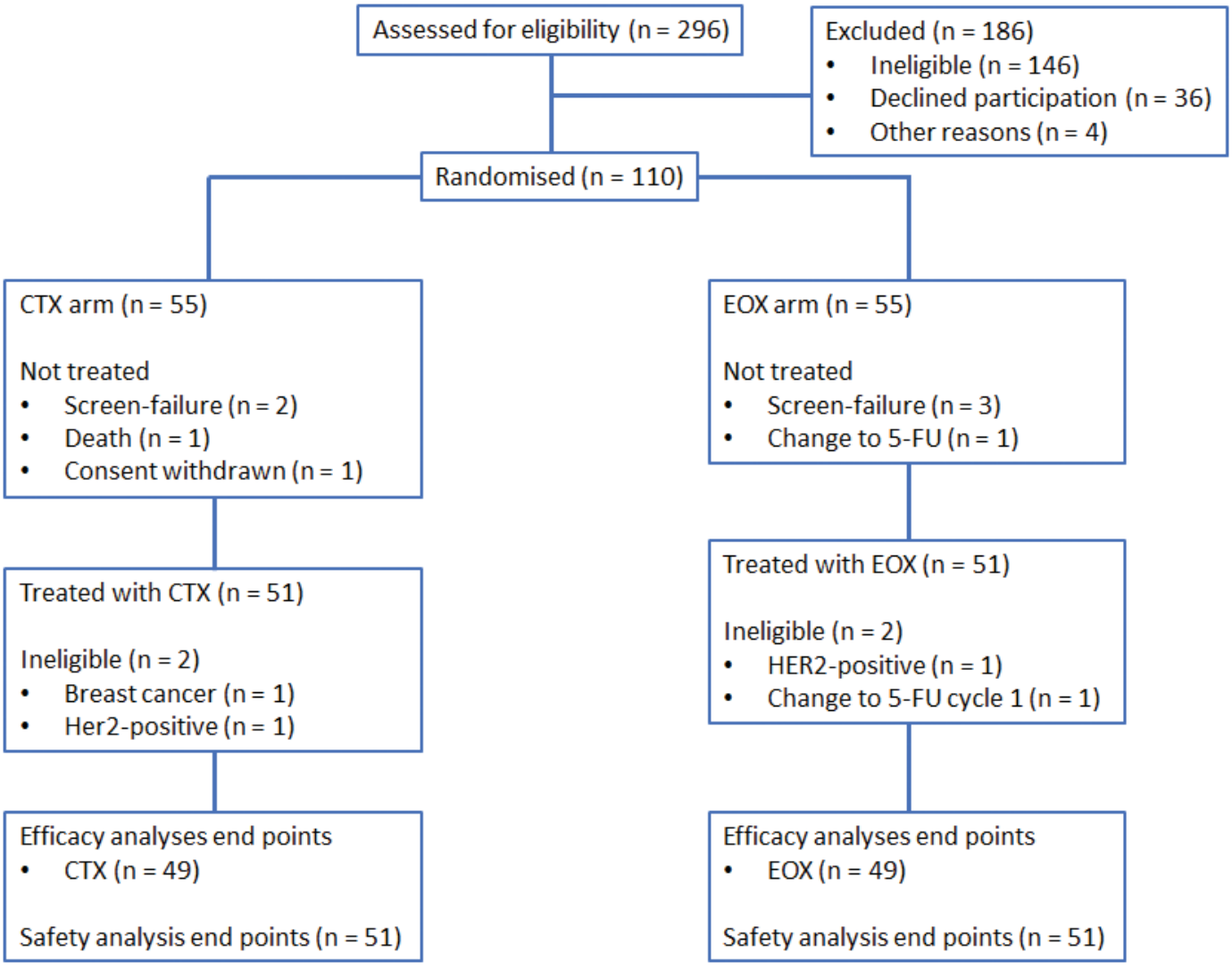

Figure 1. Consort diagram. CTX: carboplatin, docetaxel, and capecitabine; EOX: epirubicin; oxaliplatin, and capecitabine.

assigned treatment, and were not replaced according to the pre-specified criteria described above. Safety analyses were based on the safety-population defined by those that were randomized and initiated assigned treatment. Distributions of time-to-event variables were estimated using the Kaplan–Meier method. Quality-of-life (QoL) analysis included those subjects in arm A who had a baseline and at least one post-baseline assessment. The primary interest of the QoL-assessment – and the one reported here – was median time to definitive deterioration from baseline on the global health status QoL-scale (question number 30 in QLQ-C30). The date of progression was considered as the date of definitive deterioration if no deterioration had occurred at the last assessment.

Results

Patient and disease characteristics

Between June 2014 and January 2019, a total of 296 patients were assessed for eligibility of whom 110 were randomized and 98 were eligible per protocol (49 in each arm). Figure 1 shows the Consort diagram. Overall, the eligible group had a median age of 64 years (range 36−79), a male:female ratio of 4:1 and mostly de novo metastatic disease (89.8%). Table 1 shows the baseline characteristics for each arm. In arm A, there were less patients with performance status 0 (40.8% in arm A; 53.1% in arm B) and more patients with two or more metastatic sites (51.0% in arm A; 38.8% in arm B).

Treatment compliance

In total, 257 cycles of CTX and 246 cycles of EOX were administered, with a median of 6 cycles in each arm (range 1−9). The median time between randomization and first intravenous infusion was 6 days (range, 1−16) for CTX and 5 days (range, 1−16) for EOX. The median duration of therapy was 24 weeks with CTX (range, 4–46 weeks) and 19 weeks with EOX (range, 3–38 weeks). Dose reductions occurred in 32 patients (65.3%) with CTX and 31 patients (63.2%) with EOX. Cycle delays occurred in 16 patients (32.7%) for CTX and 28 patients (57.1%) for EOX. In the CTX-arm the

Table 1. Patient demographics and baseline characteristics (efficacy population).

Treatment (no. of patients)	CTX ($n = 49$)		EOX ($n = 49$)		All ($n = 98$)	
Characteristic	No.	%	No.	%	No.	%
Sex						
Male	37	75.5	42	85.7	79	80.6
Age, years						
Median	66		63		64	
Range	43-79		36-75		36-79	
<70	30	61.2	39	79.6	69	70.4
≥70	19	38.8	10	20.4	29	29.6
ECOG Performance Status						
0	20	40.8	26	53.1	46	46.9
1	29	59.2	23	46.9	52	53.1
Primary tumor site						
Esophageal	13	26.5	16	32.7	29	29.6
Gastroesophageal junction	21	42.9	23	46.9	44	44.9
Gastric	15	30.6	10	20.4	25	25.5
Histology						
Adenocarcinoma	46	93.9	49	100	95	97.0
MANEC	1	2.0	0	0	1	1.0
Carcinoma	2	4.1	0	0	2	2.0
Disease status						
Locally advanced/recurrent	3	6.1	7	14.3	10	10.2
Metastatic	46	93.9	42	85.7	88	89.8
No. of organs involved						
0 or 1	24	49.0	30	61.2	54	55.1
≥2	25	51.0	19	38.8	44	44.9
Prior therapy						
Surgery	2	4.1	6	12.2	8	8.2
Neoadjuvant chemoradiotherapy	1	2.0	3	6.1	4	4.1
Perioperative chemotherapy	0	0	3	6.1	3	3.1

CTX: carboplatin, docetaxel, and capecitabine; EOX: epirubicin, oxaliplatin, and capecitabine; MANEC: mixed adenoneuroendocrine carcinoma

docetaxel dose was most commonly reduced whereas the oxaliplatin dose was most commonly reduced in the EOX-arm. The most common AEs leading to dose reduction were febrile neutropenia in the CTX-arm and peripheral neuropathy in the EOX-arm. The most common AE leading to cycle delay was neutropenia for both CTX and EOX. The main reason for therapy discontinuation was progressive disease in both groups (51.0% for CTX, 59.2% for EOX). Treatment toxicity was the reason for therapy discontinuation in 12 (24.5%) and 9 (18.4%) patients in the CTX-arm and EOX-arm, respectively.

Efficacy

The 1-year survival rate was 34.7% (95% CI 21.8−47.9) for patients treated with CTX. This was below the threshold for rejection and CTX could, therefore, not be recommended for further study. The 1-year survival rate for patients treated with EOX was 36.7% (95% CI 23.6−50.0). Progression-free survival was 6.1 months (95% CI 5.5−7.1) in the CTX-arm and 5.1 months (95% CI 4.3−7.0) in the EOX-arm, Figure 2. Overall survival was 9.8 months (95% CI 8.2−11.0) in the CTX-arm and 10.2 months (95% CI 8.0−11.9) in the EOX-arm, Figure 3. Of note, 43% and 51% of patients received further systemic therapy in the CTX and EOX arms, respectively.

In an unplanned analysis of response rates (without confirmation of response) in the CTX-arm 20 patients (40.8%) had a partial response and 2 patients (4.1%) had a complete response for an overall response rate of 44.9% (95% CI 30.7−59.8).

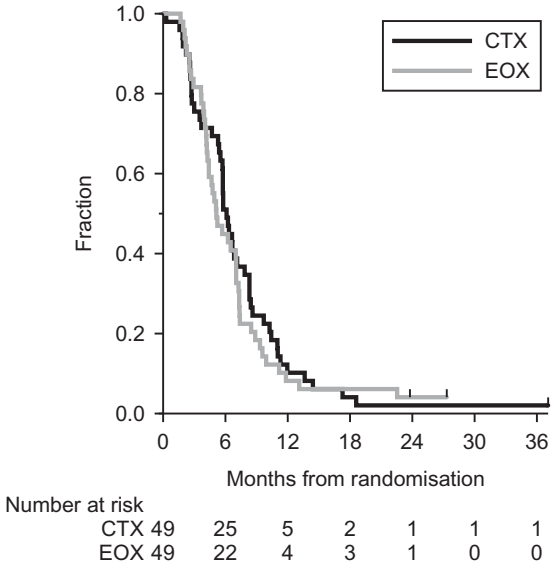

Figure 2. Progression-free survival outcomes. CI: confidence interval; CTX: carboplatin, docetaxel, and capecitabine; EOX: epirubicin, oxaliplatin, and capecitabine; PFS: progression-free survival.

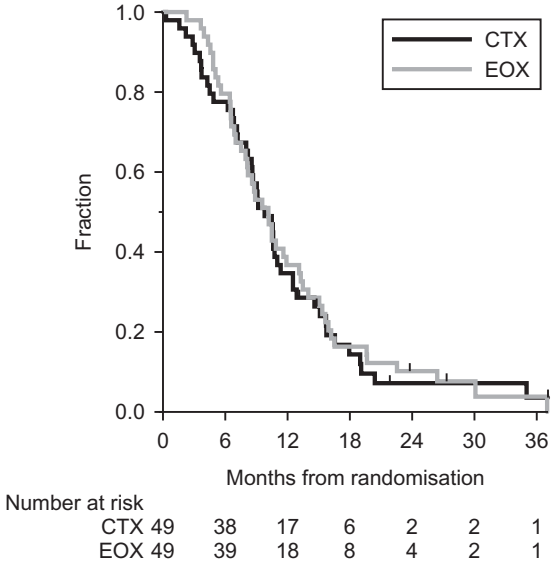

Figure 3. Overall survival outcomes. CI: confidence interval. CTX: carboplatin, docetaxel, and capecitabine; EOX: epirubicin, oxaliplatin and capecitabine; OS: overall survival.

Safety

Related grade 3 or 4 treatment-emergent AEs occurred in 86% of patients on CTX and 69% on EOX. Treatment-emergent grade 3 or 4 AEs occurring in ≥5% are summarized in Table 2. Grade 3 or 4 neutropenia occurred in 82.4% of patients on CTX and 52.9% of patients on EOX. Febrile neutropenia occurred in 31.4% of patients on CTX and 13.7% of patients on EOX. In the CTX-arm 49% of patients had at least one hospital admission during the course of treatment. The first admission most commonly occurred after the first cycle

Table 2. Related hematologic and non-hematologic toxicities in >5% (NCIC CTC version 4.0).

Treatment (no. of patients)	CTX ($n = 51$)		EOX ($n = 51$)	
	Grade 3–4		Grade 3–4	
Toxicity	No.	%	No.	%
Hematology				
Neutropenia	42	82.4	27	52.9
Febrile neutropenia	16	31.4	7	13.7
Anemia	3	5.9	0	0
Non-hematologic				
Diarrhea	4	7.8	0	0
Fatigue	3	5.9	0	0
Peripheral neuropathy	0	0	5	9.8
Nausea	0	0	3	5.9

CTX: carboplatin, docetaxel, and capecitabine; EOX: epirubicin, oxaliplatin and capecitabine.

of chemotherapy (76%) and had febrile neutropenia as the most common reason (56%). In the EOX-arm 29% of patients had at least one hospital admission during the course of treatment. The first admission most commonly occurred after the first cycle of chemotherapy (60%) and had febrile neutropenia as the most common reason (33%). The number of deaths occurring within 30 days of the last intravenous administration of chemotherapy was 3 (5.9%) with CTX and 3 (5.9%) with EOX. No deaths were ascribed to chemotherapy.

Quality-of-life

Thirty-two patients (65.3%) in the CTX-arm were eligible for QoL analysis pertaining to question 30 (global health status) in QLQ-C30. The median time to definitive deterioration was 5.8 months (95% CI 4.5−7.1). In an unplanned analysis of 44 eligible patients in the CTX-arm, the median time to definitive worsening of ECOG performance status was 5.9 months (95% CI 5.0−6.9).

Discussion

Based on the study results, CTX was rejected for further study as the 1-year survival rate of 34.7% fell below the defined threshold for rejection of 40%. In addition, CTX was toxic with 31.4% of treated patients affected by febrile neutropenia.

Regarding the efficacy parameters, 1-year survival (CTX 34.7%; EOX 36.7%) and median overall survival (CTX 9.8 months; EOX 10.2 months), CTX appears similar to EOX but SEED was not a comparative study. The EOX-arm served as an internal control to validate the outcomes of the CTX-arm. The reference for EOX is the REAL-2 trial where one-year survival and median overall survival were reported higher at 46.8% and 11.2 months, respectively [9]. However, in the REAL-2 trial more patients had non-metastatic disease than in SEED (REAL-2 EOX-arm: 24.3%; SEED EOX-arm: 14%). The difference in median PFS in SEED (CTX 6.1 months; EOX 5.1 months) is likely explained by the longer interval between scans in the CTX-arm.

The wider implications of this study concern the issue of docetaxel in the first-line setting when combined with 5-FU- and platinum-based chemotherapy. It is known that DCF on a 3-weekly schedule is superior to CF in terms of time-to-progression, overall survival, and response rates but toxicity prevents its widespread application [4]. Modified triplets with docetaxel combined with 5-FU and either cisplatin (mDCF) or oxaliplatin (FLOT) on 2-weekly schedules have been reported in phase 2 trials to be highly active with low toxicity rates [14,15]. CTX might be considered another potentially useful variant of DCF but given the results of SEED, it appears that CTX is not less toxic than DCF. This is even though less treatment is given with a reduced dose of docetaxel (in CTX 60 mg/m^2; in DCF 75 mg/m^2) and less frequent chemotherapy infusions (CTX 4-weekly; DCF 3-weekly). Probably, the utilization of carboplatin which is more myelotoxic than cisplatin or oxaliplatin undercuts the potential toxicity benefit of less docetaxel.

A number of trials show that the risks of triplets *versus* doublets outweigh the potential benefits. In the FLOT65+ randomized trial elderly patients with metastatic esophagogastric adenocarcinoma did not gain benefit from docetaxel, oxaliplatin, and 5-FU (FLOT) compared to 5-FU and oxaliplatin (FLO) but had more toxicity [16]. Recently, a large randomized phase 3 trial in patients with metastatic gastric cancer showed that 2-weekly docetaxel, cisplatin and S-1 compared to cisplatin and S-1 increased toxicity, in particular grade 3 or 4 neutropenia, without adding benefit [17]. Similarly, it has been observed that the addition of epirubicin to FU and platinum increases toxicity without increasing response rates or overall survival compared to FOLFOX [18]. Real-world evidence of the utilization of chemotherapy in clinical practice confirms these findings [19,20].

The abovementioned studies [4,16,17] and SEED, therefore, indicate that the addition of docetaxel to FU and platinum for palliation should not be a recommendation for all patients. A doublet of FU and platinum (CAPOX, FOLFOX, or CF) is appropriate for most patients treated with palliative intent. In situations when a response is needed in select patients (fit and in good performance status) a triplet regimen with docetaxel, FU and platinum can be considered. This is in accordance with international guidelines, e.g., NCCN [3]. For triplet therapy in the metastatic setting we prefer the FLOT-regimen that has become standard in the perioperative setting for resectable esophagogastric adenocarcinoma [21].

In conclusion, first-line CTX did not show sufficient efficacy in terms of one-year survival to merit recommendation for further study in this randomized, non-comparative, phase 2 trial. In addition, CTX was too toxic with a high rate of febrile neutropenia. This trial adds to current knowledge of docetaxel combined with platinum and 5-FU in the first-line setting: that the combination is associated with increased toxicity and its use should be limited to fit patients in need of a response.

Disclosure statement

The authors have declared no conflicts of interest.

ORCID

Peter C. Petersen http://orcid.org/0000-0002-2337-4377
Ivan Vogelius http://orcid.org/0000-0002-8877-1218
Jon K. Bjerregaard http://orcid.org/0000-0003-1088-7242
Lene Baeksgaard http://orcid.org/0000-0003-4662-5164

References

[1] Wagner AD, Syn NLX, Moehler M, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2017;8: CD004064.
[2] Smyth EC, Verheij W, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(5):v38–v49.
[3] National Comprehensive Cancer Network (NCCN). Gastric cancer. Version 1.2020 – March 19, 2020. [accessed on 6 May 2020].
[4] Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. J Clin Oncol. 2006; 24(31):4991–4997.
[5] Petrelli F, Tomasello G, Ghidini M, et al. Modified schedules of DCF chemotherapy for advanced gastric cancer: a systematic review of efficacy and toxicity. Anticancer Drugs. 2017;28(2): 133–141.
[6] Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20(4):666–673.
[7] Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the arbeitsgemeinschaft internistische onkologie. J Clin Oncol. 2008; 26(9):1435–1442.
[8] Park YH, Lee JL, Ryoo BY, et al. Capecitabine in combination with oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer. Cancer Chemother Pharmacol. 2008;61(4):623–629.
[9] Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008; 358(1):36–46.
[10] Gadgeel SM, Shields AF, Heilbrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. Am J Clin Oncol (CCT). 2003;26(1):37–41.
[11] Einzig A, Kelsen DP, Cheng E, et al. Phase II trial of carboplatin in patients with adenocarcinomas of the upper gastrointestinal tract. Cancer Treat Rep. 1985;69(12):1453–1454.
[12] Ujmajuridze Z, Ehrnrooth E, Lassen E, et al. Efficacy of carboplatin, docetaxel and capecitabine (CTX) in the treatment of patients with advanced or metastatic upper gastrointestinal tract carcinomas. A retrospective analysis. J Clin Oncol. 2008;26(15_suppl):abstr 15629.
[13] Fleming TR. One-sample multiple testing procedure for phase II clinical trials. Biometrics. 1982;38(1):143–151.
[14] Shah MA, Janjigian YY, Stoller R, et al. Randomised multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. J Clin Oncol. 2015;33(33):3874–3879.
[15] Al-Batran SE, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol. 2008;19(11):1882–1887.
[16] Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internististische Onkologie (FLOT65). Eur J Cancer. 2013;49(4):835–842.
[17] Yamada Y, Boku N, Mizusawa J, et al. Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG 1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol. 2019;4(7):501–510.
[18] Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol. 2016;34(23):2736–2742.
[19] Dijksterhuis WPM, Verhoeven RHA, Slingerland M, et al. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: a real-world evidence study. Int J Cancer. 2020;146(7):1889–1901.
[20] Baumgartner R, Taghizadeh H, Jomrich G, et al. Utilization and efficacy of palliative chemotherapy for locally advanced or metastatic gastroesophageal carcinoma. Anticancer Res. 2020;40(2):965–975.
[21] Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948–1957.