Annals of Oncology 26: 149–156, 2015
doi:10.1093/annonc/mdu496
Published online 21 November 2014

Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study

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Received 7 April 2014; revised 12 October 2014; accepted 13 October 2014

Background: Docetaxel/cisplatin/infusional 5-fluorouracil (5-FU; DCF) is a standard chemotherapy regimen for patients with advanced gastric cancer (GC). This phase II study evaluated docetaxel/oxaliplatin (TE), docetaxel/oxaliplatin/5-FU (TEF), and docetaxel/oxaliplatin/capecitabine (TEX) in patients with advanced GC.

Patients and methods: Patients with metastatic or locally recurrent gastric adenocarcinoma (including carcinoma of the gastro-oesophageal junction) were randomly assigned (1 : 1 : 1) to TE, TEF, or TEX. Each regimen was tested at two doses before full evaluation at optimized dose levels. The primary end point was progression-free survival (PFS). Overall survival (OS), tumour response, and safety were also assessed. A therapeutic index (median PFS relative to the incidence of febrile neutropenia) was calculated for each regimen and compared with DCF (historical data).

Results: Overall, 248 patients were randomly assigned to receive optimized dose treatment. Median PFS was longer with TEF (7.66 [95% confidence interval (CI): 6.97–9.40] months) versus TE (4.50 [3.68–5.32] months) and TEX (5.55 [4.30–6.37] months). Median OS was 14.59 (95% CI: 11.70–21.78) months for TEF versus 8.97 (7.79–10.87) months for TE and 11.30 (8.08–14.03) months for TEX. The rate of tumour response (complete or partial) was 46.6% (95% CI 35.9–57.5) for TEF versus 23.1% (14.3–34.0) for TE and 25.6% (16.6–36.4) for TEX. The frequency and type of adverse events (AEs) were similar across the three arms. Common grade 3/4 AEs were fatigue (21%), sensory neuropathy (14%), and diarrhoea (13%). Febrile neutropenia was reported in 2% (TEF), 14% (TE), and 9% (TEX) of patients. The therapeutic index was improved with TEF versus TEX, TE, or DCF.

Conclusion: These results suggest that TEF is worthy of evaluation as an arm in a phase III trial or as a backbone regimen for new targeted agents in advanced GC.

ClinicalTrials.gov Identifier: Trial registration number: NCT00382720.

Key words: antineoplastic agents, combined, platinum compounds, stomach neoplasms, taxoids

introduction

The prognosis for patients with advanced gastric cancer (GC) remains poor with 5-year survival rates of <10% and median overall survival (OS) of <1 year [1]. Palliative chemotherapy improves both survival and quality of life in patients with good performance status [2]. Commonly used cisplatin-based doublets (cisplatin/5-fluorouracil [5-FU], CF) or triplets (cisplatin/epirubicin/5-FU) typically yield response rates of up to 50%; however, progression-free survival (PFS) and OS are poor [3–8].

Recent attention has focused on newer platinum compounds such as oxaliplatin and the oral fluoropyrimidine capecitabine [9]

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and on taxane-containing triplet combinations [10–16]. The combination of docetaxel, cisplatin, and infusional 5-FU (DCF) significantly improved PFS and OS compared with CF [10]. Follow-up studies reported improvements in clinical benefit [17] and quality of life [18]. However, the DCF regimen has been associated with increased toxicity compared with CF [10] and has not been used extensively in clinical practice or as the preferred chemotherapy backbone in clinical trials evaluating new targeted agents. More recent phase II studies reported good efficacy and tolerability with epirubicin/oxaliplatin/docetaxel [13], biweekly docetaxel/oxaliplatin (TE) and infusional 5-FU (TEF) [19], and docetaxel/oxaliplatin/capecitabine (TEX) [11]. A split-dose docetaxel, cisplatin, and leucovorin/fluorouracil regimen was also highly active with reduced toxicity compared with the DCF regimen [20]. The relative benefit : risk profiles of doublet versus triplet therapy in advanced GC remain unknown [21].

This phase II study was conducted to evaluate the efficacy and tolerability of docetaxel plus oxaliplatin with or without infusional 5-FU or capecitabine in patients with advanced GC and to identify a regimen with a better therapeutic index than DCF.

methods

patients

Eligible patients were ≥18 years old with Karnofsky performance status (KPS) >70 and histologically proven metastatic (measurable and/or evaluable) or locally recurrent gastric adenocarcinoma (including carcinoma of the gastro-oesophageal junction). Prior palliative chemotherapy was not permitted. Prior adjuvant (and/or neoadjuvant) 5-FU, cisplatin, and epirubicin were allowed if relapse occurred >12 months after the end of chemotherapy. A period of ≥4 weeks had to have elapsed since the last round of palliative radiotherapy and of ≥3 weeks since last surgery. The main exclusion criterion was the presence of neurosensory symptoms of the National Cancer Institute Common Terminology Criteria for Adverse events (NCI-CTAE) grade ≥2. The study was conducted in accordance with the Declaration of Helsinki (1964). All patients provided written informed consent.

study design and treatments

This was a prospective, multinational, randomized, phase II study comparing TE, TEF, and TEX. The study was conducted in two parts (Figure 1). Part 1 determined the optimal doses for each investigational regimen. Docetaxel was escalated in the TEX arm in an attempt to mimic the dose

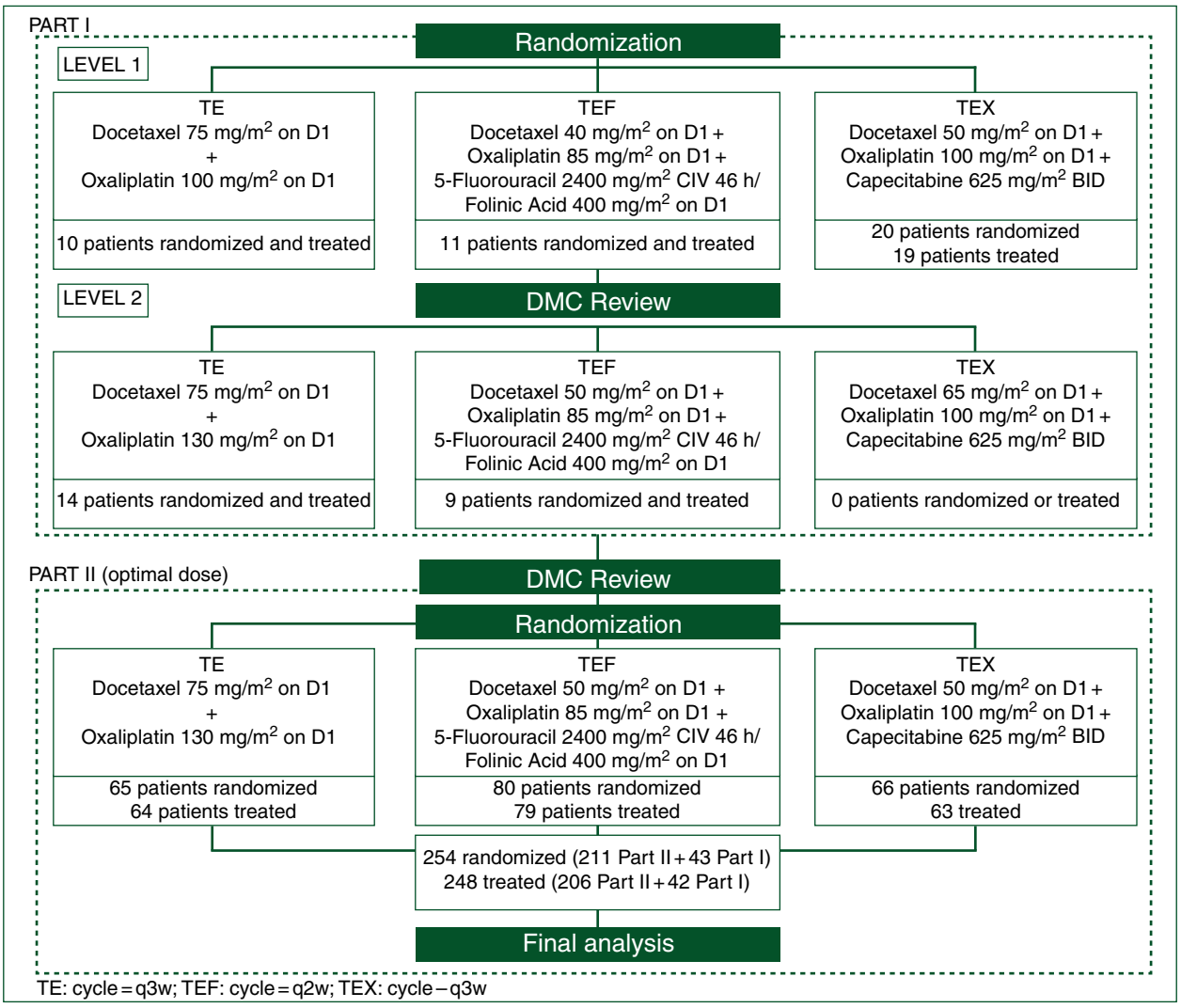


Figure 1. Study design and patient flow.

intensity of docetaxel used in the TAX325 study [10]. In the TE arm, the aim was to use a higher dose of docetaxel (75 mg/m^2) than that used in a previous study of TE in GC (60 mg/m^2 [22]), and it was therefore planned to escalate oxaliplatin starting at a lower dose of 100 mg/m^2 (versus 130 mg/m^2 previously [22]). An Independent Data Monitoring Committee (IDMC) reviewed safety data collected from approximately 10 randomized patients at each of the two dose levels. The efficacy and safety of the optimal dose regimens selected in part 1 were evaluated in part 2.

Patients were randomized centrally using an interactive voice response system, with stratification by country, weight loss (≤5% or >5%), and disease measurability (measurable or evaluable-only lesions). Treatment was administered until disease progression, unacceptable toxicity, or patient withdrawal of consent.

assessments

The primary efficacy parameter was PFS, defined as the time from date of randomization to date of first progression or death from any cause, whichever occurred first. OS was measured as the time from date of randomization to date of death from any cause. Tumour response was evaluated every 8 weeks and classified according to best overall response (World Health Organization criteria). The overall response rate (ORR) included partial and complete responses. Best overall response was the best response designation recorded from the start of treatment until disease progression. Responses were confirmed by two evaluations conducted ≥4 weeks apart. Safety was evaluated by adverse event (AE) reporting and grading (NCI-CTCAE Version 3.0), haematology and laboratory assessments, physical and neurological examinations, vital signs, weight, and performance status.

statistical analyses

In part 1, an estimated 60 patients were required to determine the optimal doses. In part 2, the study size was calculated with an assumed 23% progression-free rate at 12 months, based on results from the V325 study [10]. To obtain a precision of 10% of the 95% confidence interval (CI), an estimated 68 patients per treatment arm were required. The upper limit of the 95% CI was 32.6%, corresponding to a median time-to-progression of 7.4 months. Assuming a drop-out rate of 15%, the target recruitment was 240 patients (80 per arm). Patients treated at the optimal dose in part 1 were included in part 2.

The primary efficacy population was the full analysis population (FAP: all randomized and treated patients analysed in the arm to which they were randomized), with supportive analyses conducted using the intent-to-treat (ITT: all randomized patients) and per protocol (PP: assessable patients [received study treatment and had ≥1 post-baseline tumour assessment] without any major protocol violation) populations.

Table 1. Patient demographics and baseline disease characteristics

Characteristics	TE (N = 79)	TEF (N = 89)	TEX (N = 86)	Total (N = 254)
Mean age, years	59	58	59	59
Male, %	65	69	74	69
KPS, %[a]				
100	24	31	22	26
90	33	39	36	36
80	40	27	38	35
70	1	2	3	2
<70	1	0	0	<1
Site of primary cancer, %[a,b]				
Stomach	90	84	87	87
Gastro-oesophageal junction	37	39	33	36
Organs involved, %[b]				
Lymph node	59	65	62	62
Liver	51	51	44	49
Stomach	41	31	52	41
Lung	19	20	14	18
Omentum/peritoneum/retroperitoneum	11	19	20	17
Oesophagus	6	8	2	6
Visceral cancer only, %[c]	22	24	24	23
Measurable disease, %[a]	87	87	93	89
Weight loss in previous 3 months, %[d]				
≤5%	50	53	52	52
>5%	50	47	48	48
Prior surgery, %[a]	29	39	47	39
Prior radiotherapy, %[a]	5	4	7	6
Prior chemotherapy, %[d]	10	7	12	10

[a]N = 78 for the TE arm.
[b]Patients could have more than one primary site or organ involved.
[c]Cancer located in one or more of the following organs/tissues: brain, oesophagus, stomach, duodenum, small intestine, colon, rectum, liver, pancreas, gallbladder/biliary tract, lung, heart, bladder, kidneys, adrenal glands, prostate, testis, ovary, uterus, eye, and thyroid.
[d]N = 78 for the TE arm; N = 85 for the TEX arm.
KPS, Karnofsky performance status.

The primary end point was PFS. Secondary end points included OS, ORR, and safety. The analyses of efficacy and safety were primarily descriptive and no statistical comparisons between study arms were generated for the end points presented in this report. For PFS and OS, unadjusted Kaplan–Meier estimates were generated along with median values (and 95% CI). A *post hoc* multivariate analysis (Cox proportional hazards model) was conducted to determine whether the TEF regimen was a favourable prognostic factor for PFS and OS; further details of this analysis are provided in supplementary Tables S1 and S2, available at *Annals of Oncology* online. Descriptive statistics are presented for ORR with exact 95% CI determined using the Clopper–Pearson method. The safety data are presented descriptively for the safety population (patients who received at least one dose of study drug at the optimal dose). Statistical calculations were carried out using SAS® version 9.2.

therapeutic index

A *post hoc* analysis was conducted to evaluate overall clinical benefit, which was estimated by calculating a therapeutic index incorporating efficacy (PFS) and a key safety parameter (febrile neutropenia). Median PFS was plotted against the incidence (%) of febrile neutropenia for each of the three regimens investigated in this study and compared with the equivalent data reported previously for DCF and CF [10].

results

Fifty-two sites in the USA and 11 countries in Europe screened and randomized patients. Enrolment occurred between September and December 2006 (part 1) and between March and September 2007 (part 2). Patient disposition and the optimal doses selected by the IDMC are shown in Figure 1. A total of 254 patients were randomly allocated to one of the three treatment arms or to receive the optimal treatment regimen in part 1 and continued with treatment (ITT population). Of these, 248 patients received treatment (full analysis and safety populations). The majority (69%) of patients were male; mean age was 59 years. Baseline disease characteristics were similar across the three treatment arms (Table 1). Overall, 52% of patients had ≤5% weight loss in the 3 months before study entry.

efficacy

For analysis of the primary end point, 64 (82.1%) patients in the TE arm, 55 (62.5%) in the TEF arm, and 58 (70.7%) in the TEX arm were not censored and experienced progression during the study. The proportion of patients with progression was numerically lower with TEF (62.5%) compared with TE (82.1%) and TEX (70.7%). The primary reason for censoring was receiving further anti-cancer therapy. PFS was numerically longer with TEF compared with either TE or TEX (median PFS: 7.66 months [95% CI: 6.97–9.40] versus 4.50 [3.68–5.32] and 5.55 [4.30–6.37] months, respectively; Figure 2A). The progression-free rate at 1 year was also numerically higher with TEF (33.0% [95% CI: 21.6% to 44.5%]) versus both TE (3.9% [0.0% to 9.0%]) and TEX (24.0% [13.3% to 34.8%]).

Median OS was numerically longer with TEF (14.59 [95% CI: 11.70–21.78] months) compared with TE (8.97 [7.79–10.87]

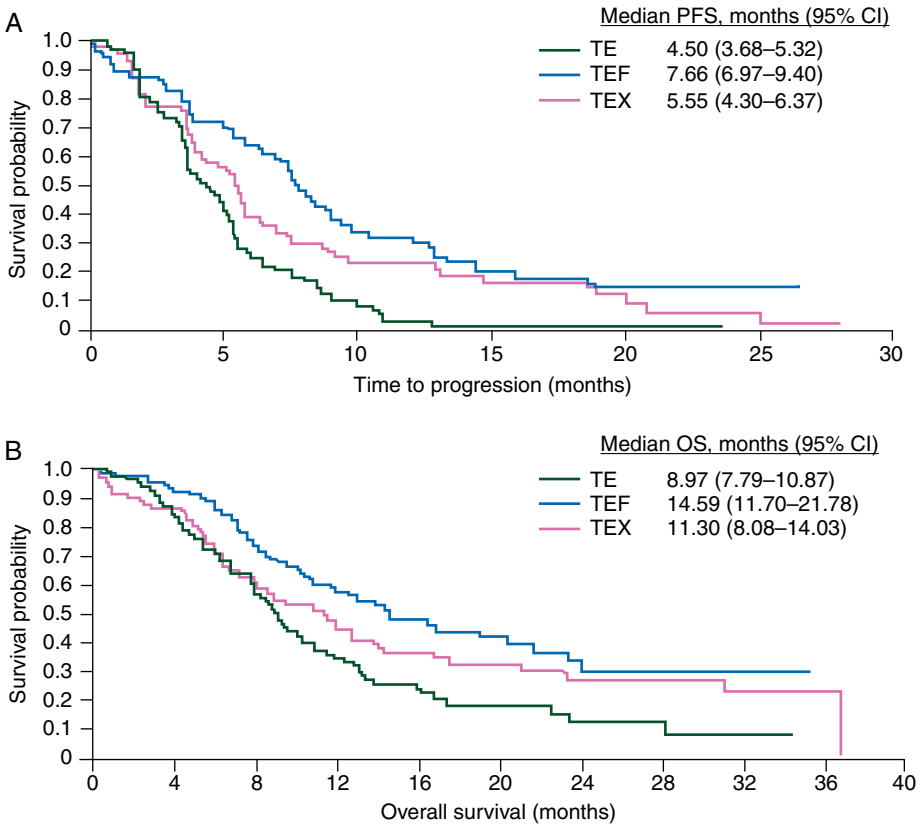


Figure 2. (A) Progression-free survival and (B) overall survival. E, oxaliplatin; F, 5-fluorouracil; OS, overall survival; PFS, progression-free survival; T, docetaxel; X, capecitabine.

months) and TEX (11.30 [8.08–14.03] months; Figure 2B). A numerically greater proportion of patients who received TEF achieved a complete or partial response (46.6% [95% CI 35.9% to 57.5%]) than those who received either TE (23.1% [14.3% to 34.0%]) or TEX (25.6% [16.6% to 36.4%]).

The efficacy results for the FAP were the same qualitatively in the ITT and PP population analyses.

Post hoc multivariate analyses (supplementary Tables S1 and S2, available at *Annals of Oncology* online) showed that treatment with the TEF regimen was a statistically significant favourable prognostic factor for PFS (hazard ratio 0.50 [95% CI 0.36–0.70]; $P = 0.0001$) and OS (hazard ratio 0.60 [95% CI 0.43–0.84]; $P = 0.0031$). Other significant prognostic factors were KPS, site of metastases, prior chemotherapy (PFS and OS), and weight loss in the 3 months before study entry (PFS only).

drug exposure

The median number of treatment cycles administered was 5 (range 1–15), 8 (1–40), and 6 (1–26) in the TE, TEF, and TEX arms, respectively. Cumulative doses, dose intensities, and relative dose intensities are summarized in supplementary Table S3, available at *Annals of Oncology* online. All patients discontinued the treatment; the most common reasons for discontinuation were progressive disease (103 [41.5%]), AEs (59 [23.8%]), and patient withdrawal from treatment (43 [17.3%]).

safety

A description of the AEs reported during the dose-evaluation phase is provided in supplementary data, available at *Annals of Oncology* online: AEs. For patients receiving the optimal doses

Table 2. Adverse events (safety population and optimal dose)

	TE ($N = 78$)		TEF ($N = 88$)		TEX ($N = 82$)	
	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All
Haematological[a]						
Neutropenia[b]	52 (70)	63 (85)	49 (56)	75 (86)	50 (64)	64 (82)
Leukopenia[c]	40 (52)	65 (84)	26 (30)	75 (86)	31 (39)	61 (77)
Anaemia[c]	8 (10)	66 (86)	7 (8)	80 (92)	6 (8)	69 (87)
Thrombocytopenia[c]	6 (8)	16 (21)	4 (5)	16 (18)	6 (8)	16 (20)
Febrile neutropenia	11 (14)	—	2 (2)	—	7 (9)	—
Non-haematological[d]						
Fatigue	19 (24)	52 (67)	12 (14)	62 (70)	20 (24)	54 (66)
Sensory neuropathy	11 (14)	47 (60)	15 (17)	63 (72)	8 (10)	54 (66)
Diarrhoea	15 (19)	48 (62)	10 (11)	59 (67)	6 (7)	54 (66)
Nausea	2 (3)	45 (58)	2 (2)	52 (59)	4 (5)	45 (55)
Alopecia	1 (1)	25 (32)	3 (3)	47 (53)	1 (1)	36 (44)
Anorexia	4 (5)	32 (41)	3 (3)	36 (41)	8 (10)	38 (46)
Vomiting	4 (5)	37 (47)	3 (3)	31 (35)	3 (4)	33 (40)
Abdominal pain	4 (5)	25 (32)	4 (5)	19 (22)	2 (2)	20 (24)
Mucositis, functional/symptomatic	1 (1)	15 (19)	2 (2)	29 (33)	1 (1)	13 (16)
Constipation	2 (3)	13 (17)	0	15 (17)	0	20 (24)
Taste alteration	0	7 (9)	0	24 (27)	0	12 (15)
Dyspnoea	3 (4)	17 (22)	1 (1)	12 (14)	3 (4)	11 (13)
Mucositis, clinical exam	1 (1)	5 (6)	4 (5)	21 (24)	1 (1)	14 (17)
Hand-foot	2 (3)	7 (9)	2 (2)	10 (11)	6 (7)	21 (26)
Nail changes	2 (3)	7 (9)	1 (1)	13 (15)	4 (5)	18 (22)
Limb oedema	0	12 (15)	0	13 (15)	0	12 (15)
Fever	0	14 (18)	0	13 (15)	0	7 (9)
Stomach pain	1 (1)	5 (6)	3 (3)	16 (18)	0	7 (9)
Dysphagia	1 (1)	7 (9)	0	5 (6)	2 (2)	11 (13)
Back pain	3 (4)	7 (9)	1 (1)	6 (7)	2 (2)	9 (11)
Dizziness	0	8 (10)	0	8 (9)	1 (1)	5 (6)
Heartburn	0	4 (5)	0	6 (7)	0	11 (13)
Cough	0	5 (6)	1 (1)	9 (10)	1 (1)	6 (7)
Insomnia	0	8 (10)	0	4 (5)	0	8 (10)
Pulmonary haemorrhage, nose	0	1 (1)	0	13 (15)	0	2 (2)

Data of AEs are denoted as *n* (%).
[a]Laboratory evaluations.
[b]$N = 74$ (TE), $N = 87$ (TEF), $N = 78$ (TEX).
[c]$N = 77$ (TE), $N = 87$ (TEF), $N = 79$ (TEX).
[d]Events with frequency of >10% in any treatment arm.

of study treatment, the proportion reporting at least one treatment-emergent AE was similar across the three arms (TE 97%; TEF 100%; and TEX 96%). Grade 3/4 AEs were reported in 77%, 61%, and 67% of patients in the TE, TEF, and TEX arms, respectively. The frequency of serious AEs was numerically lower among patients treated with TEF (27% [of which 25% were grade 3/4]) than among those treated with TE (45% [37%]) or TEX (44% [38%]).

The most common haematological (laboratory evaluated) and non-haematological AEs are summarized in Table 2. Grade 3/4 neutropenia and leukopenia appeared to be slightly more frequent with TE compared with the other two arms. Febrile neutropenia was reported in 8% of patients overall (TE: 14%; TEF: 2%; and TEX: 9%). The most commonly reported non-haematological grade 3/4 AEs across the three arms were fatigue (21%), sensory neuropathy (14%), and diarrhoea (13%).

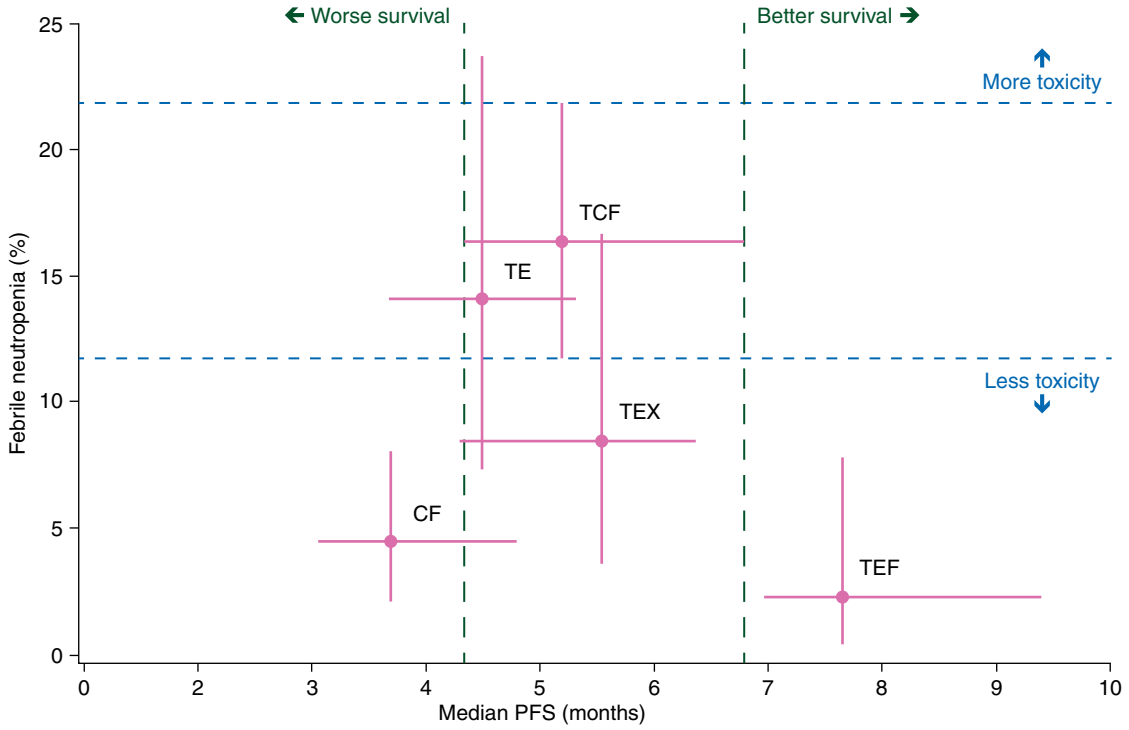
A total of 18 patients experienced AEs that resulted in death (4 [5%], 3 [3%], and 11 [13%] patients in the TE, TEF, and TEX arms, respectively). The majority of deaths (60%) were attributed to disease progression and were not considered to be drug-related.

therapeutic index

The therapeutic index was better with the TEF regimen than with both TEX and TE (Figure 3). TEF also showed an improved therapeutic index when compared with previously published data for DCF and CF [10].

discussion

Although DCF is a standard, effective treatment of advanced or metastatic GC, its use is limited by toxicity. Therefore, it is important to conduct robust, prospective clinical trials to test the tolerability and therapeutic index of potentially less toxic docetaxel/platinum/fluoropyrimidine regimens. In this phase II study, treatment with an optimized TEF regimen was associated with improved PFS, OS, and ORR compared with TE and TEX. A multivariate analysis demonstrated that treatment with TEF (as opposed to either TE or TEX) was a favourable prognostic factor for both PFS and OS. The median OS of >14 months with TEF is substantially better than the 8–9 months' reported in previous international multicentre studies in advanced GC [3–8]. In general, the safety profile of TEF was better than that of the other two regimens, although the incidence of neutropenia and leukopenia was high across the three treatment arms. The improved toxicity profile of TEF, including a lower incidence of febrile neutropenia, relative to TE may have been due to the docetaxel dose schedule used (a lower dose every 2 weeks with TEF versus a higher dose every 3 weeks with TE). This study did not



	GATE			325A	
	TE	TEF	TEX	TCF	CF
Median PFS, month (95% CI)	4.5 (3.5–5.3)	7.7 (7.0–9.4)	5.6 (4.3–6.4)	5.2 (4.3–6.8)	3.7 (3.1–4.8)
Febrile neutropenia, % (95% CI)	14.5 (7.4–23.7)	2.3 (0.4–7.8)	8.5 (3.6–16.7)	16.4 (11.8–21.9)	4.5 (2.2–8.1)

Figure 3. Comparison of therapeutic index for different gastric cancer treatment regimens. Data points (black circles) represent the median PFS (horizontal axis) and incidence of neutropenia (*y*-axis) for each regimen. Solid lines represent the 95% confidence intervals for each data point. The dotted lines are drawn at the 95% confidence limits for PFS and neutropenia with the reference regimen TCF. CF, cisplatin/5-FU; DCF, docetaxel/cisplatin/5-FU; PFS, progression-free survival; TE, docetaxel/oxaliplatin; TEF, docetaxel/oxaliplatin/5-FU; TEX, docetaxel/oxaliplatin/capecitabine.

demonstrate that oral capecitabine may be an alternative to infusional 5-FU. The reason for the lower efficacy (PFS and OS) observed with the capecitabine triplet compared with the 5-FU triplet is not clear, although patient compliance with capecitabine was relatively poor compared with 5-FU (57% versus 100%). Further combination studies with different capecitabine dosing and schedules may be warranted.

Although improved patient survival is usually the primary objective of oncology trials, such improvements may be offset by unacceptable toxicity. For this reason, we evaluated the overall benefit of the regimens investigated in this trial using a therapeutic index relating PFS to a key measure of tolerability, febrile neutropenia. Using this index, TEF was very favourable compared with TE and TEX and also with historical data for DCF and CF, thus providing evidence of an improved benefit : risk profile with TEF compared with the standard treatment in advanced GC.

One possible limitation of this trial was the age of the patient population, which, at a mean of 59 years, is younger than the typical population of patients with GC [23]. This was probably due to the clinical characteristics of the included patients (good performance status and lack of comorbidities). Patient selection is a common limitation in phase II/III trials as demonstrated in previous studies of docetaxel in GC [10, 19, 20]. Nonetheless, the better performance status associated with a younger patient population should be considered when assessing tolerability in this trial. The tolerability of triplet regimens in elderly GC patients is the subject of continued debate [21]. Results of a recent study in elderly patients (≥65 years) with gastro-oesophageal carcinoma suggest that docetaxel-containing triplet regimens are feasible in this age group, although reduced clinical activity and increased toxicity become problematic in patients 70 years of age or older [24].

In conclusion, the results of this trial provide the rationale for a phase III trial evaluating TEF in advanced GC and, based on the relatively favourable safety profile, TEF at the current dose schedule could act as a chemotherapy platform to combine with other novel biologicals.

acknowledgements

The authors thank all patients, coordinators, and investigators who participated in the study.

funding

This work was supported by Sanofi. Editorial assistance was provided by Adelphi Communications Ltd and supported by Sanofi.

disclosure

The institution of EVC has received research funding from Sanofi, the manufacturer of Taxotere® and Eloxatin®. JT has acted as a consultant for Sanofi and has received honoraria from Sanofi. EE-F and SH are employees of and hold stock with Sanofi. All remaining authors have declared no conflicts of interest.

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Annals of Oncology 26: 156–161, 2015
doi:10.1093/annonc/mdu505
Published online 30 October 2014

Genetic features of pulmonary adenocarcinoma presenting with ground-glass nodules: the differences between nodules with and without growth

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Received 19 July 2014; revised 14 October 2014; accepted 15 October 2014

Background: Pulmonary ground-glass nodules (GGNs) include both malignant and benign lesions. Some GGNs become larger, whereas others remain unchanged for years. We have previously reported that smoking history and large diameters are predictors for growth. However, the genetic differences among GGNs remain unclear.

Patients and methods: GGNs with ground-glass component of ≥50% on a thin-section computed tomography scan that were resected between 2012 and 2014 were evaluated for clinicopathological features and the presence of EGFR/KRAS/ALK/HER2 mutations. 'Incidence of 2-mm growth' and 'Time to 2-mm growth' were analyzed according to the mutational status.

Results: Among 104 GGNs in 96 patients, this study included 3 atypical adenomatous hyperplasia (AAH), 19 adenocarcinoma *in situ* (AIS), 27 minimally invasive adenocarcinoma (MIA), and 55 invasive adenocarcinoma (IA). Among the 71 lesions evaluable for growth, 30 GGNs exhibited growth and 5 lesions remained unchanged for ≥2 years before surgery was carried out. We identified mutations or rearrangements in 75% of GGNs (78/104). EGFR mutations were noted in 64% of samples, KRAS in 4%, ALK in 3%, and HER2 in 4%. The remaining 26 quadruple-negative tumors were significantly associated with AAH/AIS ($P < 0.01$) and no-growth ($P < 0.01$) compared with driver mutation-positive tumors, whereas EGFR mutation-positive tumors were correlated with MIA/IA ($P < 0.01$) and growth ($P < 0.01$) compared with EGFR-negative tumors.

Conclusions: Three fourths of resected GGNs were positive for EGFR, KRAS, ALK, or HER2 mutations. Quadruple-negative tumors were associated with a lack of GGN growth, whereas EGFR mutation-positive tumors displayed a correlation with growth.

Key words: ALK, EGFR, ground-glass opacity, HER2, KRAS, lung cancer

introduction

Pulmonary ground-glass nodules (GGNs), hazy lesions on computed tomography (CT) scans that do not obscure underlying bronchial structures or pulmonary vessels [1], are increasingly detected in clinical practice. These lesions include both malignant and benign lesions: lung adenocarcinoma and their preinvasive lesions, focal interstitial fibrosis, inflammation, or hemorrhage [2].

A ground-glass opacity (GGO) proportion of ≥50% has been suggested as a cutoff value for pathological noninvasiveness; the rate of lymph node metastasis ranges from 21% to 26% in ≤3-cm lesions with GGO component of <50% [3–5]. Moreover, the specificities for the diagnosis of pathological noninvasiveness are 96.4% and 98.7% for lesions ≤3 cm with >50% GGO component and lesions ≤2 cm with >75% GGO component,

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