Cancer Chemother Pharmacol (2015) 76:1285–1295
DOI 10.1007/s00280-015-2872-y

ORIGINAL ARTICLE

Phase 1a/1b and pharmacogenetic study of docetaxel, oxaliplatin and capecitabine in patients with advanced cancer of the stomach or the gastroesophageal junction

Maarten J. Deenen[1,2] · Didier Meulendijks[1,2,3] · Henk Boot[3] · Marie-Cecile J. C. Legdeur[4] · Jos H. Beijnen[5,6] · Jan H. M. Schellens[1,2,6] · Annemieke Cats[3]

Received: 24 June 2015 / Accepted: 8 September 2015 / Published online: 23 October 2015

Abstract
Purpose The prognosis of gastroesophageal cancer is poor, and current regimens are associated with limited efficacy. The purpose of this study was to explore the safety and preliminary efficacy of docetaxel, oxaliplatin plus capecitabine for advanced cancer of the stomach or the gastroesophageal junction (GEJ). Secondary objectives included pharmacokinetic and pharmacogenetic analyses.
Methods Patients were treated in escalating dose levels with docetaxel and oxaliplatin (both on day 1), plus capecitabine b.i.d. on days 1–14 every 3 weeks, to determine the dose-limiting toxicity and maximum tolerated dose (MTD). An expansion cohort was treated at the MTD. A total of ten polymorphisms in pharmacokinetic and pharmacodynamic candidate genes were analyzed and tested for association with treatment outcome.
Results A total of 34 evaluable patients were enrolled. The MTD was docetaxel 50 mg/m^2, oxaliplatin 100 mg/m^2 plus capecitabine 850 mg/m^2 b.i.d. The median number of treatment cycles was 6 (range 2–8). Grade $\geq$ 3 toxicities included neutropenia (24 %), leukocytopenia (15 %), febrile neutropenia (12 %), fatigue (9 %) and diarrhea (6 %). The overall response rate was 45 %; two patients achieved a complete response. Median progression-free survival and overall survival were 6.5 months (95 % CI 5.4–7.6) and 11.0 months (95 % CI 7.9–14.1), respectively. The polymorphisms *ERCC1* 354C>T, *TYMS* 1053C>T and rs2612091 in *ENOSF1* were associated with severe toxicity; *ERCC1* 354C>T and *ERCC2* 2251A>C were associated with poor progression-free survival.
Conclusion Docetaxel, oxaliplatin plus capecitabine are a well-tolerable, safe and effective treatment regimen for patients with advanced cancer of the stomach or GEJ. Pharmacogenetic markers in pharmacokinetic and pharmacodynamic candidate genes may be predictive for treatment outcome.

Keywords Docetaxel · Oxaliplatin · Capecitabine · Gastric cancer · Pharmacogenetics · Pharmacokinetics

Introduction

Gastric cancer is one of the most commonly diagnosed cancers and the third leading cause of cancer death worldwide. It thereby represents a significant global health problem [1]. In Western countries, more than half of the patients with gastroesophageal cancer are diagnosed with

Electronic supplementary material The online version of this article (doi:10.1007/s00280-015-2872-y) contains supplementary material, which is available to authorized users.

✉ Annemieke Cats
a.cats@nki.nl

1 Division of Medical Oncology, Department of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

2 Department of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

3 Division of Medical Oncology, Department of Gastroenterology and Hepatology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

4 Department of Medical Oncology, Medisch Spectrum Twente, Enschede, The Netherlands

5 Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

6 Division of Clinical Pharmacology and Pharmaco-epidemiology, Faculty of Science, Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

advanced disease. In patients with irresectable, advanced disease, treatment options are limited to palliative chemotherapy or best supportive care. Multiple single-agent and combination chemotherapy regimens have been tested for advanced gastroesophageal cancer. A meta-analysis of randomized, controlled trials in patients with advanced gastroesophageal cancer showed that both chemotherapy versus best supportive care, and 5-FU-based combination chemotherapy versus single-agent 5-FU provide superior overall survival and quality of life, though at the cost of increased toxicity [2].

Another anticancer drug that has demonstrated significant antitumor activity in gastroesophageal cancer is docetaxel [3–6]. A randomized phase 3 trial including 445 patients with previously untreated advanced gastroesophageal cancer compared the combination of docetaxel, cisplatin plus 5-FU (DCF) versus the doublet of cisplatin and 5-FU alone. Although DCF appeared superior in all efficacy endpoints, severe toxicity also occurred more frequently with DCF, giving reason for concern to introduce the DCF regimen for the palliative and neoadjuvant treatment of gastroesophageal cancer [7]. Split doses of docetaxel and protracted continuous infusions of 5-FU have been investigated as alternative treatment regimens, with the aim of reducing toxicity but maintaining efficacy [8, 9]. Epirubicin-containing treatment regimens are also widely used, but in comparison with DCF, the latter might be more effective [9]. Although initially proven as a significantly more effective and tolerable treatment regimen compared to older standard treatment regimens, the combination of epirubicin, cisplatin and 5-FU has also shown to result in significant incidences of severe toxicity [10, 11]. A further advantage of a docetaxel-containing regimen over epirubicin is that docetaxel can be combined with trastuzumab in HER2-positive tumors without further precautions, which is not the case for epirubicin given the overlapping cardial toxicity.

Additional important data come from the REAL-2 trial [12]. This randomized study showed both non-inferiority of oxaliplatin over cisplatin, and non-inferiority of capecitabine over 5-FU. In addition, both substitutions resulted in a clinically better tolerable treatment regimen, a more favorable safety profile and increased patient convenience [12]. Because a potential synergy exists between docetaxel and capecitabine, presumably mediated through activation of thymidine phosphorylase by docetaxel [13], we aimed to develop a new, safe, well-tolerable and effective treatment regimen. Here, we describe a phase 1a/1b study in which the safety, feasibility and preliminary efficacy of the combination of docetaxel, oxaliplatin and capecitabine in patients with advanced cancer of the stomach or the gastroesophageal junction (GEJ) were explored. In addition, to gain more insight into clinical pharmacology of this triplet combination, the study also included pharmacokinetic and pharmacogenetic analyses.

Patients and methods

Patients

Patients were eligible if they had histologically or cytologically confirmed, irresectable, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. Further inclusion criteria were as follows: no adjuvant chemotherapy within 12 months before study registration; measurable or non-measurable, evaluable disease; age 18 years or older; WHO performance status of ≤ 2; adequate bone marrow function (i.e., absolute neutrophile count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L and hemoglobin $\geq$6 mmol/L); and adequate hepatic and renal function defined as serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN), serum bilirubin $\leq 1.5 \times$ ULN and ALAT/ASAT $\leq 2.5 \times$ ULN. Patients were excluded if they were known to have central nervous system or leptomeningeal metastases; history of another primary cancer except curatively treated in situ cervical cancer or resected non-melanoma skin cancer; mental disorders not suitable for follow-up; known positive HIV, active hepatitis B or C; and women who were pregnant or lactating, or able to conceive but unwilling to practice effective anticonception. All patients provided written informed consent before enrollment. The study was approved by the Medical Ethics Committees of the participating institutions and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design

This was a multicenter, open-label, phase 1a/1b and pharmacological study conducted at the Netherlands Cancer Institute and the Medical Spectrum Twente (both in the Netherlands). The study was conducted in two phases: phase 1a involved dose escalation to determine the dose-limiting toxicity (DLT) and the recommended maximum tolerated dose (MTD); phase 1b involved an expansion cohort in which patients were treated at the recommended MTD level to further evaluate the safety and to confirm the recommended dose for further phase 2 studies. Secondary endpoints of the study were the preliminary antitumor activity plus pharmacokinetic and pharmacogenetic analyses.

The dose escalation part was performed according to a standard 3×3 phase I design, using six predefined dose levels (Appendix Table 1, online only). Briefly, three patients per dose level were recruited and expanded to six if

one of three patients experienced DLT. Patient recruitment and dose escalation proceeded until DLT was observed in two patients at one dose level. The immediately preceding level at which DLT occurred in maximally one out of six patients was declared the maximum tolerated dose, and the dose recommended for phase 1b. No intrapatient dose escalations were allowed. DLT was defined as any of the following events related to study treatment and occurring during the first cycle: nausea or vomiting grade ≥ 2, neutropenia grade 4 lasting more than 5 days, grade ≥ 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, or any other toxicity grade ≥ 3 (excluding alopecia), all despite best supportive care. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and was assessed at baseline and weekly during the first treatment cycle, and thereafter at every cycle. Tumor measurements were taken at baseline and every other cycle and were evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) [14]. Patients with complete response or partial response required a confirmatory disease assessment at least 4 weeks later. Progression-free survival was defined as time from study registration to the date of first documented disease progression or death, whichever came first. Overall survival was defined as time from study registration to death from any cause.

Study treatment

Docetaxel was administered as a 1-h intravenous infusion in a 250 mL 0.9 % NaCl solution on day 1, followed by a 2-h intravenous infusion of oxaliplatin diluted in 500 mL of a 5 % glucose solution. Capecitabine was administered orally twice daily on days 1–14 followed by 1 week off treatment. Capecitabine was administered within 30 min after a meal or snack, maintaining an interval of preferably 12 h between the morning and evening administration. Treatment cycle duration was 3 weeks. There was no formal limit to treatment duration, but treatment continued until the occurrence of disease progression, death, unacceptable toxicity or patient's request, whichever came first. In the protocol, it was foreseen that 6–8 cycles could be administered and the number of cycles had to be determined in the best interest of the patient.

Premedication consisted of dexamethasone 8 mg p.o. b.i.d. for three consecutive days starting the day prior to day 1 of each cycle. Granisetron 1 mg was given orally twice daily on day 1, and magnesium sulfate 1000 mg and calcium gluconate 1000 mg were administered intravenously before and after oxaliplatin infusion, respectively. Prophylactic hematopoietic growth factors such as granulocyte colony-stimulating factor were not allowed during the study.

Pharmacokinetics

Blood was collected in heparin tubes on day 1 of the first treatment cycle to determine the pharmacokinetics of docetaxel and capecitabine plus its metabolites 5′-dFCR, 5′-dFUR, 5-FU and FBAL. Blood samples for docetaxel were obtained at predose, at the end of infusion and at 6 and 24 h after start of infusion; capecitabine blood samples were obtained at predose and at 0.5, 1, 2, 3, 4, 6 and 8 h after the first morning administration. Plasma levels of docetaxel and capecitabine plus its metabolites were determined using liquid chromatography coupled with tandem mass spectrometry as described previously [15, 16]. The area under the plasma concentration–time curve (AUC) of the individual plasma analytes was calculated as well as the maximum plasma concentrations (C_{max}), time to reach C_{max} (T_{max}) and apparent elimination half-lives ($T_{1/2}$).

Pharmacogenetics

A total of ten genetic polymorphisms within candidate genes were analyzed in order to address potential causes of excessive drug toxicity or differences in (progression-free) survival. To this purpose, whole blood for DNA analysis was obtained prior to start of treatment. The following polymorphisms were assessed: 313A>G (Ile105Val) in glutathione S-transferase P1 (*GSTP1*) and deletion of glutathione S-transferase T1 (*GSTT1*); IVS14 + 1G>A (*DPYD*2A*), 2846A>T (Asp949Val) and 1236G>A (Glu412Glu) within dihydropyrimidine dehydrogenase (*DPYD*); 79A>C (Lys27Gln) in cytidine deaminase (*CDA*); 354C>T (Asn118Asn) in the excision repair cross-complementing group 1 (*ERCC1)*; 2251A>C (Lys751Gln) in the excision repair cross-complementing group 2 (*ERCC2*); 677C>T in methylene tetrahydrofolate reductase (*MTHFR*); 1053C>T in thymidylate synthase (*TYMS*); and rs2612091 within enolase superfamily 1 (*ENOSF1*). Genotypes were determined using TaqMan® real-time PCR assays from Applied Biosystems (Foster City, CA, USA), using PCR followed by Sanger sequencing, or using PCR followed by visualization on agarose gel (methods available upon request). All polymorphisms were tested for associations with toxicity, progression-free survival and overall survival.

Statistical analysis

Descriptive statistics were used for the evaluation of safety, efficacy and pharmacokinetic parameters using SPSS statistics version 17.0. Survival curves were estimated using the Kaplan–Meier method. Associations of polymorphisms with toxicity were assessed using Fisher's exact test, and associations with survival endpoints using log-rank tests.

Results

A total of 37 patients with advanced adenocarcinoma of the stomach or gastroesophageal junction were enrolled in the study. Three patients were considered not evaluable: one due to early withdrawal of consent, and two due to non-treatment-related death within the first treatment cycle, i.e., bacterial meningitis after epidural catheter placement in one patient, and witnessed sudden death following ventricular fibrillation in another patient with preexisting coronary heart disease and diabetes, and were considered non-treatment related. Table 1 shows the baseline patient characteristics of all 34 evaluable patients. In total, 15 patients presented with advanced gastric cancer and 19 patients with advanced cancer of the GEJ. All patients had metastatic disease. A total of 194 treatment cycles were administered, with a median of 6 (range 2–8) treatment cycles per patient. Due to toxicity, the dose of docetaxel was reduced in 6.7 % (95 % CI 2.8–10.6 %) of all cycles, and the dose of oxaliplatin was reduced in 7.2 % (95 % CI 3.2–11.2 %) of all cycles; treatment cycles with capecitabine were not fully completed in 8.8 % (95 % CI 4.8–12.8 %) of all cycles. A total of 11.3 % (95 % CI 6.3–16.2 %) of the subsequent cycles started with delay: in 6.3 % of the cases as a result of toxicity, and in 5.0 % of the cases due to patient desire, intermittent illness or logistic reasons. Treatment delays were required in 10 patients (29 %).

Table 1 Patient baseline characteristics

Characteristics	*n*	%
No. of evaluable patients	34	
Gender		
Male	23	68
Female	11	32
Race		
Caucasian	32	94
Asian	2	6
Median age, years	59	
Range	40–77	
Median body surface area, m^2	2.0	
Range	1.6–2.2	
WHO performance status		
0	20	59
1	13	38
2	1	3
Primary tumor		
Stomach	15	44
Gastroesophageal junction	19	56
Stage		
Locally advanced	0	0
Metastatic	34	100
Prior anticancer therapy		
Chemotherapy	4	12
Gastrectomy	8	24
Chemoradiotherapy	3	9
Radiotherapy to metastatic sites	7	21

WHO World Health Organization

Phase 1a: DLT and MTD

None of the three patients treated at the first dose level presented with DLT. At dose level 2, one of three patients developed neutropenia grade 4 for 5 days, which was considered a DLT. Therefore, an additional three patients were treated at this dose level, in whom no additional DLT occurred. Dose escalation then proceeded to dose level 3, in which two of three patients experienced DLT: one patient with pain grade 3 of hands and feet (no hand-foot syndrome), and one with fatigue and nausea, both grade 3. Given these observations, no additional patients were recruited for dose level 3, and dose level 2 (docetaxel 50 mg/m^2, oxaliplatin 100 mg/m^2 plus capecitabine 850 mg/m^2 b.i.d. on days 1–14) was declared the MTD and recommended dose for phase 1b. An additional 22 patients were treated at this dose in the expansion cohort.

Safety

Table 2 shows the treatment-related adverse events that occurred in 10 % or more of patients. Fatigue was the most commonly observed toxicity (94 %) and was severe (grade 3) in three cases (9 %). Neuropathy was also common (85 %), but never exceeded grade 2. In patients suffering from neuropathy for longer periods of time, treatment could be generally continued with modest (25 %) dose reductions in oxaliplatin. Diarrhea was noted in 62 % of the patients, but was severe (grade 3) in only two patients (6 %). As expected, hematological toxicity was more often severe: grade 3–4 neutropenia and leukocytopenia occurred in 24 and 15 % of the patients, respectively. Febrile neutropenia (grade 3) and decreased hemoglobin (grade ≤ 2) both were reported in 12 % of the patients. No unexpected or fatal toxicities were observed in our study population.

Efficacy

Overall, 31 out of 34 (91 %) patients had measurable disease according to RECIST and were therefore evaluable for response. Two patients achieved a complete response (6 %), and in twelve patients (39 %), a partial response was confirmed, resulting in an objective response rate of 45 % (95 % CI 27–63 %). A total of 14 patients (45 %) had stable

Table 2 Most common treatment-related adverse events of the combination of docetaxel, oxaliplatin and capecitabine

Dose level	Dose level 1		Dose level 2		Dose level 3		Total (all dose levels), *n* (%)		
Number of patients	*n* = 3		*n* = 28		*n* = 3		*n* = 34 (100 %)		
CTC grade	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Any grade
Any toxicity	3	0	28	12	3	2	34 (100 %)	14 (41 %)	34 (100 %)
Fatigue	3	0	25	2	1	1	29 (85 %)	3 (9 %)	32 (94 %)
Neuropathy	3	0	23	0	3	0	29 (85 %)	0	29 (85 %)
Alopecia	2	–	25	–	2	–	29 (85 %)	–	29 (85 %)
Diarrhea	2	0	15	2	2	0	19 (56 %)	2 (6 %)	21 (62 %)
Nausea	2	0	15	0	2	0	19 (56 %)	0	19 (56 %)
Leukocytopenia	2	0	9	5	2	0	13 (38 %)	5 (15 %)	18 (53 %)
Neutropenia	1	0	6	8	1	0	8 (24 %)	8 (24 %)	16 (47 %)
Constipation	1	0	13	0	0	0	14 (41 %)	0	14 (41 %)
Skin toxicity	0	0	14	0	0	0	14 (41 %)	0	14 (41 %)
Lymphocytopenia	1	0	9	1	1	1	11 (32 %)	2 (6 %)	13 (38 %)
Vomiting	1	0	10	0	1	0	12 (35 %)	0	12 (35 %)
Nail changes	1	0	10	0	0	0	11 (32 %)	0	11 (32 %)
Stomatitis	1	0	10	0	0	0	11 (32 %)	0	11 (32 %)
Dysgeusia	1	0	8	0	0	0	9 (26 %)	0	9 (26 %)
Fever	1	0	7	0	0	0	8 (24 %)	0	8 (24 %)
Hand-foot syndrome	1	0	6	1	0	0	7 (21 %)	1 (3 %)	8 (24 %)
Hypoalbuminemia	0	0	8	0	0	0	8 (24 %)	0	8 (24 %)
Pain	0	0	6	0	0	1	6 (18 %)	1 (3 %)	7 (21 %)
Infection	1	0	4	1	0	0	5 (15 %)	1 (3 %)	6 (18 %)
Febrile neutropenia	0	0	0	4	0	0	0	4 (12 %)	4 (12 %)
Anemia	0	0	3	0	1	0	4 (12 %)	0	4 (12 %)

disease, and three (10 %) patients had progressive disease. Of the three patients who had no measurable disease, one patient experienced clinical benefit of treatment, additionally reflected by a strong decrease in tumor marker CA19.9 from 712 kU/L at baseline to 24 kU/L (normal value < 37 kU/L) after completion of six treatment cycles. The median progression-free survival and overall survival were 6.5 months (95 % CI 5.4–7.6 months) and 11.0 months (95 % CI 7.9–14.1 months), respectively (Fig. 1a).

Pharmacokinetics

Table 3 provides the pharmacokinetic parameters of docetaxel and capecitabine plus metabolites. These data are consistent with data previously reported in literature when administered as single agents. No unexpected pharmacokinetic interactions were observed, and the data underscore that therapeutic drug exposure was achieved [17, 18]. Of note, despite the fact that all patients received the same dose of docetaxel (50 mg/m^2), the average AUC of docetaxel appeared lower for patients in dose level 3 compared to patients in dose level 2. The most plausible explanation for this observation is most likely a matter of chance, given the fact that only 3 patients were included in dose level 3 compared to 21 patients with pharmacokinetic data in dose level 2. Furthermore, the individual AUC values in level 3 ranged rather widely, as shown by the relatively high coefficient of variation (51 %),

Pharmacogenetics

From 32 of 34 patients (94 %), blood was obtained for pharmacogenetic analyses. Since only two patients developed gastrointestinal toxicity grade ≥ 3, association tests of polymorphisms with gastrointestinal toxicity (defined as diarrhea, stomatitis, nausea or vomiting) were analyzed as grade 0–1 versus grade 2–3. Hematological toxicity was analyzed as grade 0–2 versus grade 3–4. Table 4 lists the associations of polymorphisms with toxicity.

Homozygous variant allele carriers of the polymorphisms *GSTP1* 313A>G and *ERCC2* 2251A>C experienced severe hematological toxicity significantly more often compared to wild-type or heterozygous patients; variant allele carriers for *CDA* 79A>C experienced severe hematological toxicity more often than wild-type patients. *ERCC1* 354C>T, *TYMS* 1053C>T and rs2612091 in

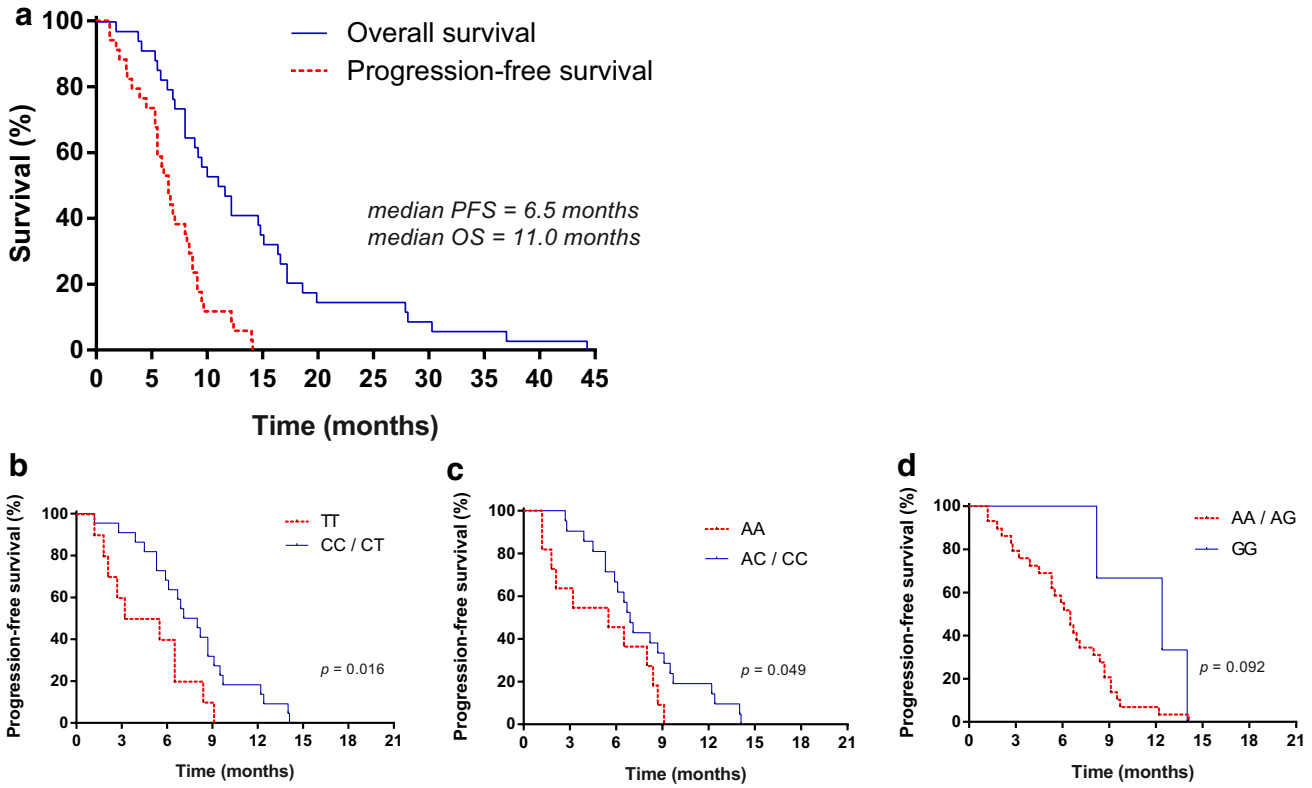

Fig. 1 **a** Progression-free survival and overall survival in patients with advanced cancer of the stomach or gastroesophageal junction treated with the combination of docetaxel, oxaliplatin and capecitabine. **b–d** Progression-free survival by the genotypes *ERCC1* 354C>T, *ERCC2* 2251A>C and *GSTP1* 313A>G, respectively

ENOSF1 were significantly associated with overall severe toxicity.

None of the patients was polymorphic for *DPYD*2A* (IVS14 + 1G>A). However, a patient who was treated in the expansion cohort proved to be heterozygous polymorphic for *DPYD* 2846A>T. In this patient, capecitabine had to be discontinued in the second week of the first treatment cycle, and the patient was hospitalized with febrile neutropenia grade 3. Despite a 1-week delay and a 25 % dose reduction in capecitabine (to 650 mg/m^2 b.i.d.) for the second cycle, febrile neutropenia recurred, which again required hospitalization. After recovery, an additional four cycles could be completed safely at a capecitabine dosage of 500 mg/m^2 b.i.d.

The polymorphisms within *ERCC1* and *ERCC2* were both significantly associated with progression-free survival, and a trend toward better progression-free survival was observed for *GSTP1* 313A>G homozygous variant allele carriers (Fig. 1b). None of the variants was associated with overall survival.

Discussion

The results from this study show that the combination of intravenous docetaxel 50 mg/m^2 and oxaliplatin 100 mg/m^2 on day 1 plus capecitabine 850 mg/m^2 b.i.d. for 14 days in 3-week cycles is a safe, tolerable and effective treatment regimen for patients with advanced adenocarcinoma of the stomach or GEJ. Adverse events that were noted in the 28 patients treated at the MTD were frequent, as is often the case with combination treatment regimens, but remained non-severe and well manageable in most patients. Leukocytopenia and neutropenia were the most common hematological toxicities and were grade $\geq$ 3 in 15 and 24 % of the patients, respectively. Febrile neutropenia occurred in 12 % of the patients, which is less than the 29 % that has been reported for the combination of docetaxel, cisplatin and 5-fluorouracil [7]. Furthermore, adequate systemic exposure of the agents was demonstrated by the pharmacokinetic analysis. With an overall survival of 11 months, this triplet regimen appears a promising basis, and it must be noted, however, that as a phase 1a/1b study, any assertions as to efficacy should be qualified as being preliminary.

Besides the relatively low incidence of severe toxicity, the median number of administered treatment cycles of six was rather high, underscoring that the treatment was also well tolerated over time. In contrast, another current standard first-line triplet treatment regimen using epirubicin, cisplatin and capecitabine reported a median number of only

Table 3 Pharmacokinetic parameters of docetaxel and capecitabine and its metabolites

Drug	PK parameter	Dose level 1			Dose level 2			Dose level 3		
		n	Mean	CV (%)	*n*	Mean	CV (%)	*n*	Mean	CV (%)
Docetaxel	AUC (h*ng/mL)	3	3483	30	21	3902	31	3	2516	51
	C_{max} (ng/mL)	3	1001	28	21	1175	27	3	782	49
	T_{max} (h)	3	1.1	6.4	21	1.1	7.3	3	1.0	1.5
	$T_{1/2}$ (h)	3	13	27	21	16	41	3	16	30
Capecitabine	AUC (h*ng/mL)	2	3724	7.6	22	4281	31	3	2993	21
	C_{max} (ng/mL)	2	2681	23	22	3243	65	3	2107	43
	T_{max} (h)	2	1.6	33	22	1.4	73	3	1.6	32
	$T_{1/2}$ (h)	2	0.4	12	22	0.76	55	3	0.6	38
5′-dFCR	AUC (h*ng/mL)	2	6506	6.9	23	8192	30	3	7093	12
	C_{max} (ng/mL)	2	3342	27	23	3876	45	3	3223	20
	T_{max} (h)	2	1.6	33	23	1.6	68	3	1.6	32
	$T_{1/2}$ (h)	2	0.7	7.9	23	1.0	35	3	0.9	24
5′-dFUR	AUC (h*ng/mL)	2	8260	24	22	7673	29	3	8262	10
	C_{max} (ng/mL)	2	4538	19	22	4198	53	3	4030	33
	T_{max} (h)	2	1.6	33	22	1.7	67	3	1.6	32
	$T_{1/2}$ (h)	2	0.6	15	22	0.9	34	3	0.9	27
5-FU	AUC (h*ng/mL)	2	682	44	20	381	40	3	565	11
	C_{max} (ng/mL)	2	429	13	20	409	72	3	279	39
	T_{max} (h)	2	1.6	33	20	1.5	65	3	1.6	32
	$T_{1/2}$ (h)	2	0.6	17	20	1.0	57	3	1.0	65
FBAL	AUC (h*ng/mL)	2	9521	14	22	14,177	31	3	14,830	20
	C_{max} (ng/mL)	2	2155	7.5	22	2781	28	3	2753	28
	T_{max} (h)	2	2.6	20	22	2.9	29	3	3.9	20
	$T_{1/2}$ (h)	2	2.3	15	22	2.6	33	3	2.4	13

C_{max} maximum concentration, T_{max} time to C_{max}, *AUC* area under the concentration–time curve, *h* hour, *5′-dFCR* 5′-deoxy-5-fluorocytidine, *5′-dFUR* 5′-deoxy-5-fluorouridine, *5-FU* 5-fluorouracil, *CV* coefficient of variation, *FBAL* fluoro-beta-alanine

two administered treatment cycles [10]. The feasibility of this docetaxel, oxaliplatin plus capecitabine regimen is further supported by a low incidence of toxicity-related dose reductions and treatment delays: In this study, 29 % of all patients required treatment delay compared to, for example, much higher reported incidences of 58–64 % for DCF, 53–88 % for ECF, or 60 % for DF [7, 9, 19].

The general prognosis of advanced gastric cancer remains poor and underscores the need for new and better treatment modalities in which safety and administration logistics are of major importance. This triplet regimen has shown an attractive safety profile rarely requiring treatment delays and is also highly convenient in terms of administration logistics. No prehydration is indicated for the administration of oxaliplatin, which is necessary with cisplatin-containing regimens. Furthermore, the use of protracted continuous infusional 5-FU such as used in the FLOT regimen [20] is replaced by treatment with oral capecitabine. Thereby, the need for ports and pumps for prolonged 5-FU administration, which carry a risk of additional treatment complications related to the devices such as thrombosis and infection, is eliminated. The infusions of docetaxel and oxaliplatin can be administered within half a day in an outpatient setting every 3 weeks, while oral treatment with capecitabine is continued in the patient's home setting.

Recently, a few other phase 1 and 2 studies have been conducted using similar triplet combinations (Table 5); however, our study is the first that is supported with pharmacokinetic and pharmacogenetic analyses.

The recommended doses and administration schedules differ per study; most schedules use 3-week cycles and use unsplit dosages of docetaxel and oxaliplatin (i.e., administered only on day 1). The PFS and OS are around 6.5 and 11 months, respectively. The highest overall survival (for Caucasian patients) was achieved in the study by Stein et al. [21], in which relatively high doses of docetaxel and oxaliplatin were used. Herein, a response rate of 43 % was achieved with a median progression-free survival and overall survival of 6.9 and 13 months, respectively. However, the applicability of this regimen might potentially be limited due to the high percentage (30 %) of patients that developed grade $\geq$ 3 diarrhea, probably due to the

Table 4 Associations of genetic polymorphisms with toxicity

Genetic polymorphism	Gastrointestinal toxicity ($n = 32$)			Hematological toxicity ($n = 32$)			Toxicity overall ($n = 32$)		
	Grade 0–1	Grade 2–3	*P*	Grade 0–2	Grade 3–4	*P*	Non-severe	Severe	*P*
	n (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
ENOSF1 rs2612091									
GG/AG	16 (76)	5 (24)	0.123	16 (76)	5 (24)	1.000	15 (71)	6 (29)	0.027
AA	5 (46)	6 (54)		8 (73)	3 (27)		3 (27)	8 (73)	
DPYD 1236G>A									
GG	19 (68)	9 (32)	0.593	21 (75)	7 (25)	1.000	16 (57)	12 (43)	1.000
GA	2 (50)	2 (50)		3 (75)	1 (25)		2 (50)	2 (50)	
DPYD 2846A>T									
AA	21 (68)	10 (32)	0.344	24 (77)	7 (23)	0.25	18 (58)	13 (42)	0.437
AT	0 (0)	1 (100)		0 (0)	1 (100)		0 (0)	1 (100)	
CDA 79A>C									
AA	15 (79)	4 (21)	0.072	17 (90)	2 (10)	0.038	13 (68)	6 (32)	0.149
AC/CC	6 (46)	7 (54)		7 (54)	6 (46)		5 (38)	8 (62)	
TYMS 1053C>T									
CC	14 (83)	3 (17)	0.062	15 (88)	2 (12)	0.106	14 (82)	3 (18)	0.004
CT/TT	7 (47)	8 (53)		9 (60)	6 (40)		4 (27)	11 (73)	
ERCC2 2251A>C									
AA/AC	19 (70)	8 (30)	0.31	23 (85)	4 (15)	0.009	17 (63)	10 (37)	0.142
CC	2 (40)	3 (60)		1 (20)	4 (80)		1 (20)	4 (80)	
ERCC1 354C>T									
CC/CT	12 (55)	10 (45)	0.106	15 (68)	7 (32)	0.38	9 (41)	13 (59)	0.019
TT	9 (90)	1 (10)		9 (90)	1 (10)		9 (90)	1 (10)	
MTHFR 677C>T									
TT/CT	13 (72)	5 (28)	0.465	16 (89)	2 (11)	0.096	13 (64)	5 (36)	0.072
CC	8 (57)	6 (43)		8 (57)	6 (43)		5 (36)	9 (64)	
GSTP1 313A>G									
AA/AG	19 (65)	10 (35)	1.000	24 (83)	5 (17)	0.011	18 (62)	11 (38)	0.073
GG	2 (67)	1 (33)		0 (0)	3 (100)		0 (0)	3 (100)	
GSTT1									
Not NULL	18 (64)	10 (36)	1.000	20 (71)	8 (29)	0.55	15 (54)	13 (46)	0.613
NULL	3 (75)	1 (25)		4 (100)	0 (0)		3 (75)	1 (25)	

ENOSF1 enolase superfamily member 1, *DPYD* dihydropyrimidine dehydrogenase, *CDA* cytidine deaminase, *TYMS* thymidylate synthase, *ERCC1/2* excision repair cross-complementation group 1/2, *MTHFR* methylenetetrahydrofolate reductase, *GSTP1* glutathione S-transferase P1, *GSTT1* glutathione S-transferase T1

relatively high dose intensities [21]. In our study, grade ≥ 3 diarrhea occurred in only 6 % of patients and appears thereby better tolerable.

Although the presented triplet combination has recently also been explored by others, this is the first study which additionally assessed the pharmacogenetics of the docetaxel, oxaliplatin plus capecitabine combination. This analysis revealed several significant associations and, in addition, was helpful in explaining severe toxicity for individual patients. For example, a patient who was hospitalized twice due to severe toxicity showed to be polymorphic for *DPYD* 2846A>T, a variant that is known to result in DPD deficiency and thereby in an increased risk of severe toxicity. Furthermore, homozygous carriers of the *ERCC1* 354C>T variant allele had significantly less severe toxicity, and poor progression-free survival was also reduced. ERCC1 is a key enzyme that is involved in the repair of interstrand cross-links in DNA and in recombination processes, and has been shown to remove platinum-induced DNA adducts. Although *ERCC1* 354C>T (Asn118Asn) is a silent polymorphism, it is associated with reduced mRNA expression and consequently reduced DNA repair capacity [22]. Nonetheless, with regard to its effect on clinical outcome, inconsistent results have been provided. However,

Table 5 overview of phase 1 and 2 studies using docetaxel, oxaliplatin plus capecitabine for advanced gastric cancer

References	Number of patients	Ethnicity	Type of study	Docetaxel	Oxaliplatin	Capecitabine (b.i.d.)	Response rate (%)	PFS (months)	OS (months)
Deenen et al.; current study	34	Caucasian	Phase 1a/1b	50 mg/m^2 day 1	100 mg/m^2 day 1	850 mg/m^2 d1–14 q3w	45	6.5	11.0
Evans et al. [33]	16	Caucasian	Phase 1	30 mg/m^2 days 1, 8	50 mg/m^2 days 1, 8	750 mg/m^2 d1–10 q3w	18	–	–
Sym et al. [34]	21	Korean	Phase 1	60 mg/m^2 day 1	100 mg/m^2 day 1	1000 mg/m^2 d1–14 q3w	79	10.6	15.7
Goel et al. [35]	21	Caucasian	Phase 1	25 mg/m^2 day 1, 8	50 mg/m^2 day 1, 8	625 mg/m^2 d1–14 q3w	29	4.9 (*TTP*)	8.4
Anderson et al. [36], Schonnemann et al. [37]	23	Caucasian	Phase 1	50 mg/m^2 day 1	100 mg/m^2 day 1	625 mg/m^2 d1–21 q3w	35	9.4	12.5
Malik et al. [38]	14	Caucasian	Phase 1	30 mg/m^2 day 1, 8	50 mg/m^2 day 1, 8	675 mg/m^2 d1–14 q3w	57	6.7	10.0
Amarantidis et al. [39]	21	Caucasian	Phase 1	50 mg/m^2 day 1	75 mg/m^2 day 1	750 mg/m^2 d1–7 q2w	29	–	8.5
Stein et al. [21]	70	Caucasian	Phase 1/2	35 mg/m^2 day 1, 8	70 mg/m^2 day 1, 8	800 mg/m^2 d1–14 q3w	43	6.9	13.0
Di Lauro et al. [40]	48	Caucasian	Phase 2	60 mg/m^2 day 1	100 mg/m^2 day 1	625 mg/m^2 d1–21 q3w	52	6.9	12.6
Van Cutsem et al. [41]	82	Caucasian	Phase 2	50 mg/m^2 day 1	100 mg/m^2 day 1	625 mg/m^2 d1–21 q3w	26	5.6	11.3

Drug doses denote the recommended dose level of the triplet combination

b.i.d. twice daily, *d* day, *PFS* progression-free survival, *OS* overall survival, *TTP* time to progression, *q2w* every 2 weeks, *q3w* every 3 weeks

the outcomes of two recent meta-analyses showed that, in line with our study, the variant allele was associated with reduced response rate, and poor progression-free and overall survival in gastric cancer patients treated with oxaliplatin-based chemotherapy [23, 24]. A possible reason for the previous inconsistent results might be the fact that besides a predictive factor in patients treated with chemotherapy, this polymorphism may also have prognostic value in the absence of platinum-containing anticancer drugs; due to a poorer DNA repair capacity in homozygous variant allele carriers, more aggressive tumors may develop through a greater susceptibility for genetic aberrations over time, thereby resulting in a worse outcome [25].

The *ERCC2* 2251A>C polymorphism has been associated with changes in DNA repair capacity [26], and the CC genotype showed to be associated with superior overall survival in esophageal cancer patients treated with platinum-based chemotherapy [25]. However, also for this polymorphism, inconclusive results have been described, and in colorectal cancer, a meta-analysis showed poorer clinical outcomes in variant allele carriers [27]. A definitive conclusion on the predictive effect of chemotherapy in gastric cancer is not yet clearly established and is also affected by a prognostic component, as, similar to ERCC1, the enzyme activity of ERCC2 has shown to affect the natural susceptibility for gastric cancer [28].

GSTP1 is a phase 2 detoxifying enzyme of, amongst others, platinum drugs; the *GSTP1* 313A>G polymorphism reduces GSTP1 enzyme activity and thereby increases the systemic platinum exposure. Indeed, homozygous variant allele carriers experienced more frequently severe hematologic toxicity, and a trend toward superior progression-free survival was observed; this is in line with previous studies in patients with advanced gastric cancer, which showed superior clinical outcome for variant allele carriers of this polymorphism [29, 30]. Similarly, we noticed a significant association of *CDA* 79A>C with hematological toxicity, which has also been associated with thrombocytopenia in NSCLC patients treated with cisplatin and gemcitabine [31]. Furthermore, we could confirm the very recently described association between polymorphism rs2612091 in *ENOSF1* and capecitabine-related toxicity [32]. Altogether, the pharmacogenetic analysis provided useful data, supporting the conduction of further studies in order to confirm their clinical validity.

In conclusion, the combination of docetaxel 50 mg/m^2 and oxaliplatin 100 mg/m^2 on day 1 plus capecitabine 850 mg/m^2 twice daily for 14 days in 3-week cycles is a

safe, tolerable treatment regimen. Thus far, it appears at least as effective as other docetaxel, platinum and fluoropyrimidine triplet combinations for patients with advanced cancer of the stomach or GEJ, but is possibly better tolerated and more convenient for patients. The presented triplet combination is currently being evaluated in a phase 2 trial (ClinicalTrials.gov identifier NCT01359397) in combination with bevacizumab and, in case of HER2 positivity, also with trastuzumab.

Funding The study was funded by an unrestricted Grant from Sanofi-aventis Netherlands B.V. and by the Netherlands Cancer Institute.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the study.

References

1. World Health Organization (2014) World cancer report 2014. http://www.who.org
2. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE (2010) Chemotherapy for advanced gastric cancer. Cochrane Database Syst 3:CD004064
3. Sulkes A, Smyth J, Sessa C, Dirix LY, Vermorken JB, Kaye S, Wanders J, Franklin H, LeBail N, Verweij J (1994) Docetaxel (Taxotere) in advanced gastric cancer: results of a phase II clinical trial. EORTC Early Clinical Trials Group. Br J Cancer 70:380–383
4. Hejna M, Raderer M, Zacherl J, Ba-Ssalamah A, Puspok A, Schmidinger M, Pluschnig U, Brodowicz T, Zielinski CC (2008) Phase II study of docetaxel in combination with oxaliplatin in patients with metastatic or locally advanced esophagogastric cancer previously untreated with chemotherapy for advanced disease: results of the Central European Cooperative Oncology Group Study ESGAS.1.2.001. Anticancer Drugs 19:535–539
5. Roth AD, Maibach R, Martinelli G, Fazio N, Aapro MS, Pagani O, Morant R, Borner MM, Herrmann R, Honegger H, Cavalli F, Alberto P, Castiglione M, Goldhirsch A (2000) Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). Ann Oncol 11:301–306
6. Roth AD, Maibach R, Fazio N, Sessa C, Stupp R, Morant R, Herrmann R, Borner MM, Goldhirsch A, de Braud F (2004) 5-Fluorouracil as protracted continuous intravenous infusion can be added to full-dose docetaxel (Taxotere)-cisplatin in advanced gastric carcinoma: a phase I–II trial. Ann Oncol 15:759–764
7. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA (2006) 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 24:4991–4997
8. Lorenzen S, Hentrich M, Haberl C, Heinemann V, Schuster T, Seroneit T, Roethling N, Peschel C, Lordick F (2007) Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. Ann Oncol 18:1673–1679
9. Roth AD, Fazio N, Stupp R, Falk S, Bernhard J, Saletti P, Koberle D, Borner MM, Rufibach K, Maibach R, Wernli M, Leslie M, Glynne-Jones R, Widmer L, Seymour M, de Braud F (2007) Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 25:3217–3223
10. Guimbaud R, Louvet C, Ries P, Ychou M, Maillard E, Andre T, Gornet JM, Aparicio T, Nguyen S, Azzedine A, Etienne PL, Boucher E, Rebischung C, Hammel P, Rougier P, Bedenne L, Bouche O (2014) Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) Study. J Clin Oncol 32:3520–3526
11. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M (1997) Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15:261–267
12. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
13. Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. Clin Cancer Res 4:1013–1019
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
15. Kuppens IE, van Maanen MJ, Rosing H, Schellens JH, Beijnen JH (2005) Quantitative analysis of docetaxel in human plasma using liquid chromatography coupled with tandem mass spectrometry. Biomed Chromatogr 19:355–361
16. Deenen MJ, Rosing H, Hillebrand MJ, Schellens JH, Beijnen JH (2013) Quantitative determination of capecitabine and its six metabolites in human plasma using liquid chromatography coupled to electrospray tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 913–914:30–40
17. Bruno R, Hille D, Riva A, Vivier N, Bokkel Huinnink WW, van Oosterom AT, Kaye SB, Verweij J, Fossella FV, Valero V, Rigas JR, Seidman AD, Chevallier B, Fumoleau P, Burris HA, Ravdin PM, Sheiner LB (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187–196
18. Reigner B, Blesch K, Weidekamm E (2001) Clinical pharmacokinetics of capecitabine. Clin Pharmacokinet 40:85–104

19. Thuss-Patience PC, Kretzschmar A, Repp M, Kingreen D, Hennesser D, Micheel S, Pink D, Scholz C, Dorken B, Reichardt P (2005) Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study. J Clin Oncol 23:494–501
20. Al-Batran SE, Hartmann JT, Hofheinz R, Homann N, Rethwisch V, Probst S, Stoehlmacher J, Clemens MR, Mahlberg R, Fritz M, Seipelt G, Sievert M, Pauligk C, Atmaca A, Jager E (2008) 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 19:1882–1887
21. Stein A, Arnold D, Thuss-Patience PC, Moehler M, Grothe W, Seufferlein T, Reinacher-Schick A, Geissler M, Hofheinz RD, Schmoll HJ (2014) Docetaxel, oxaliplatin and capecitabine (TEX regimen) in patients with metastatic gastric or gastroesophageal cancer: results of a multicenter phase I/II study. Acta Oncol 53:392–398
22. Yu JJ, Lee KB, Mu C, Li Q, Abernathy TV, Bostick-Bruton F, Reed E (2000) Comparison of two human ovarian carcinoma cell lines (A2780/CP70 and MCAS) that are equally resistant to platinum, but differ at codon 118 of the ERCC1 gene. Int J Oncol 16:555–560
23. Yin M, Yan J, Martinez-Balibrea E, Graziano F, Lenz HJ, Kim HJ, Robert J, Im SA, Wang WS, Etienne-Grimaldi MC, Wei Q (2011) ERCC1 and ERCC2 polymorphisms predict clinical outcomes of oxaliplatin-based chemotherapies in gastric and colorectal cancer: a systemic review and meta-analysis. Clin Cancer Res 17:1632–1640
24. Ma SC, Zhao Y, Zhang T, Ling XL, Zhao D (2015) Association between the ERCC1 rs11615 polymorphism and clinical outcomes of oxaliplatin-based chemotherapies in gastrointestinal cancer: a meta-analysis. Onco Targets Ther 8:641–648
25. Bradbury PA, Kulke MH, Heist RS, Zhou W, Ma C, Xu W, Marshall AL, Zhai R, Hooshmand SM, Asomaning K, Su L, Shepherd FA, Lynch TJ, Wain JC, Christiani DC, Liu G (2009) Cisplatin pharmacogenetics, DNA repair polymorphisms, and esophageal cancer outcomes. Pharmacogn Genom 19:613–625
26. Lunn RM, Helzlsouer KJ, Parshad R, Umbach DM, Harris EL, Sanford KK, Bell DA (2000) XPD polymorphisms: effects on DNA repair proficiency. Carcinogenesis 21:551–555
27. Qian YY, Liu XY, Pei D, Xu JL, Shen H, Chen XF, Liu YQ, Shen LZ, Shu YQ (2014) The XPD Lys751Gln polymorphism has predictive value in colorectal cancer patients receiving oxaliplatin-based chemotherapy: a systematic review and meta-analysis. Asian Pac J Cancer Prev 15:9699–9706
28. Xue H, Lu Y, Lin B, Chen J, Tang F, Huang G (2012) The effect of XPD/ERCC2 polymorphisms on gastric cancer risk among different ethnicities: a systematic review and meta-analysis. PLoS ONE 7:e43431
29. Goekkurt E, Hoehn S, Wolschke C, Wittmer C, Stueber C, Hossfeld DK, Stoehlmacher J (2006) Polymorphisms of glutathione S-transferases (GST) and thymidylate synthase (TS)—novel predictors for response and survival in gastric cancer patients. Br J Cancer 94:281–286
30. Ruzzo A, Graziano F, Kawakami K, Watanabe G, Santini D, Catalano V, Bisonni R, Canestrari E, Ficarelli R, Menichetti ET, Mari D, Testa E, Silva R, Vincenzi B, Giordani P, Cascinu S, Giustini L, Tonini G, Magnani M (2006) Pharmacogenetic profiling and clinical outcome of patients with advanced gastric cancer treated with palliative chemotherapy. J Clin Oncol 24:1883–1891
31. Tibaldi C, Giovannetti E, Vasile E, Mey V, Laan AC, Nannizzi S, Di MR, Antonuzzo A, Orlandini C, Ricciardi S, Del TM, Peters GJ, Falcone A, Danesi R (2008) Correlation of CDA, ERCC1, and XPD polymorphisms with response and survival in gemcitabine/cisplatin-treated advanced non-small cell lung cancer patients. Clin Cancer Res 14:1797–1803
32. Rosmarin D, Palles C, Pagnamenta A, Kaur K, Pita G, Martin M, Domingo E, Jones A, Howarth K, Freeman-Mills L, Johnstone E, Wang H, Love S, Scudder C, Julier P, Fernandez-Rozadilla C, Ruiz-Ponte C, Carracedo A, Castellvi-Bel S, Castells A, Gonzalez-Neira A, Taylor J, Kerr R, Kerr D, Tomlinson I (2015) A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENOSF1 rather than TYMS. Gut 64:111–120
33. Evans D, Miner T, Akerman P, Millis R, Jean M, Kennedy T, Safran H (2007) A phase I study of docetaxel, oxaliplatin, and capecitabine in patients with metastatic gastroesophageal cancer. Am J Clin Oncol 30:346–349
34. Sym SJ, Ryu MH, Kang HJ, Lee SS, Chang HM, Lee JL, Kim TW, Yook JH, Oh ST, Kim BS, Kang YK (2010) Phase I study of 3-weekly docetaxel, capecitabine and oxaliplatin combination chemotherapy in patients with previously untreated advanced gastric cancer. Cancer Chemother Pharmacol 66:373–380
35. Goel G, Jauhri M, Negi A, Aggarwal S (2010) Feasibility study of docetaxel, oxaliplatin and capecitabine combination regimen in advanced gastric or gastroesophageal adenocarcinoma. Hematol Oncol Stem Cell Ther 3:55–59
36. Andersen M, Schonnemann KR, Yilmaz M, Jensen HA, Vestermark LW, Pfeiffer P (2010) Phase I study of docetaxel, oxaliplatin and capecitabine (TEX) as first line therapy to patients with advanced gastro-oesophageal cancer. Acta Oncol 49:1246–1252
37. Schonnemann KR, Yilmaz M, Andersen M, Pfeiffer P (2011) New recommendation of doses in an ongoing phase II study of docetaxel, oxaliplatin and capecitabine as first line therapy in advanced gastro-oesophageal cancer. Acta Oncol 50:151–152
38. Malik I, Bernal P, Byrd J (2010) A phase I study of docetaxel, oxaliplatin, & capecitabine (DOC) as first-line therapy of patients with locally advanced or metastatic adenocarcinoma of stomach and GE junction. Cancer Invest 28:833–838
39. Amarantidis K, Xenidis N, Chelis L, Chamalidou E, Dimopoulos P, Michailidis P, Tentes A, Deftereos S, Karanikas M, Karayiannakis A, Kakolyris S (2011) Docetaxel plus oxaliplatin in combination with capecitabine as first-line treatment for advanced gastric cancer. Oncology 80:359–365
40. Di Lauro L, Vici P, Belli F, Tomao S, Fattoruso SI, Arena MG, Pizzuti L, Giannarelli D, Paoletti G, Barba M, Sergi D, Maugeri-Sacca M (2014) Docetaxel, oxaliplatin, and capecitabine combination chemotherapy for metastatic gastric cancer. Gastric Cancer 17:718–724
41. Van Cutsem E, Boni C, Tabernero J, Massuti B, Middleton G, Dane F, Reichardt P, Pimentel FL, Cohn A, Follana P, Clemens M, Zaniboni A, Moiseyenko V, Harrison M, Richards DA, Prenen H, Pernot S, Ecstein-Fraisse E, Hitier S, Rougier P (2015) Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. Ann Oncol 26:149–156