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ORIGINAL ARTICLE

Cisplatin plus weekly CPT-11/docetaxel in advanced esophagogastric cancer: a phase I study with pharmacogenetic assessment of XPD, XRCC3 and UGT1A1 polymorphisms

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Abstract
Purpose A multicenter phase I trial to establish the recommended dose of CPT-11/docetaxel plus cisplatin in advanced esophagogastric cancer patients and to correlate the efficacy and toxicity with genetic polymorphisms in DNA repair genes (XPD and XRCC3) and the UGT1A1 gene.
Methods Four dose levels with a fixed dose of cisplatin (60 mg/m^2), day 1, and dose-escalation of CPT-11 (50–70 mg/m^2) and docetaxel (25–30 mg/m^2), days 1 and 8, every 3 weeks were planned. Polymorphisms of XPD (Asp312Asn and Lys751Gln), XRCC3 (Thr241Met) and UGT1A1*28 were examined in baseline peripheral blood.
Results Twenty-eight patients were included at three different dose levels. Dose-limiting toxicities were febrile neutropenia and diarrhea; the recommended dose was established at CPT-11 60 mg/m^2 and docetaxel 25 mg/m^2 plus cisplatin 60 mg/m^2. Objective response was observed in 13 patients (50%). Median time to progression was 6.6 months, and median survival was 11.3 months. Median time to progression was 9.7 months for patients harboring the XRCC3 Met241Met genotype versus 8.4 months for patients with Thr241Met and 3.1 months for those with Thr241Thr (P = .04).
Conclusions CPT-11/docetaxel plus cisplatin is active in patients with advanced esophagogastric cancer. XRCC3 Met241Thr polymorphisms could be a useful marker to predict prognosis in patients treated with a cisplatin-based chemotherapy. However, these results are required to be confirmed with a great number of patients.

Keywords CPT-11 · Docetaxel · Dose-limiting toxicity · Phase I · Polymorphisms

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Introduction

In spite of a certain overall decrease in the incidence of gastric cancer, it remains the second most common cause of cancer death worldwide. Furthermore, in the last 30 years, the number of patients with adenocarcinoma in the distal esophagus and gastroesophageal junction has greatly increased, mainly in western countries [18]. More than 50% of esophagogastric cancer patients are diagnosed with unresectable or metastatic tumors and receive systemic chemotherapy as the standard treatment. Although cisplatin/5-fluorouracil (5-Fu)-based regimens have demonstrated a benefit in terms of quality of life and survival compared with non-cisplatin regimens, outcomes remain suboptimal with response rates of 20–45% and median survival times of 7–9 months [28, 30]. Moreover, the addition of epirubicin or mitomycin to cisplatin/5-Fu led to a modest improvement in activity [20]. In recent years, efforts to improve the

prognosis of advanced gastroesophageal cancer patients have focused on incorporating novel drugs with proven single-agent activity into platinum-based regimens. Single-agent docetaxel and CPT-11 have yielded significant activity in advanced gastric cancer [31]. Moreover, docetaxel/cisplatin reported response rates between 37 and 56% and median survival times ranging from 9 to 10.4 months [19, 21]. Likewise, CPT-11 in combination with cisplatin attained response rates of more than 40% [3, 24] in advanced gastric cancer. Weekly CPT-11 has a good toxicity profile; for example, weekly cisplatin/CPT-11 was active in patients with advanced esophageal cancer with a low incidence of grade 3/4 toxicities [11]. CPT-11 is activated by carboxylesterases to SN-38, a powerful topoisomerase I inhibitor that is inactivated through glucuronidation, which is mediated by the uridine diphosphate glucuronosyltransferase (UGT1A1) enzyme. Interindividual differences in the glucuronidation rates of SN-38 have been linked to a common genetic polymorphism in the UGT1A1 gene [8, 14]. Patients with an additional TA dinucleotide repeat in the promoter region of UGT1A1 ($[TA]_7TAA$) (designated as UGT1A1*28) had significantly reduced transcriptional activity compared to patients with wild-type UGT1A1 ($[TA]_6TAA$). Several studies have suggested that increased SN-38 levels in patients with the UGT1A1*28 genotype can increase both the toxicity and activity of CPT-11 [2, 15].

Inherent to the cytotoxic activity of cisplatin is the formation of DNA adducts that block replication and inhibits transcription. These adducts are repaired by different DNA repair pathways, including nucleotide excision repair (NER) [4] and homologous recombination (HR). Single nucleotide polymorphisms (SNPs) in genes involved in these pathways can impair DNA repair capacity and thus increase cisplatin sensitivity.

The xeroderma pigmentosum group D (XPD) gene is an essential member of the NER pathway. In a case–control study, reduced DNA repair capacity was observed in patients who were homozygous for two wild type XPD SNPs, Lys751Gln at exon 23 and Asp312Asn at exon 10 [25]. In colorectal cancer patients treated with oxaliplatin-based therapy, patients with XPD Lys751Lys had longer survival [17]. The X-ray repair cross-complementing group 3 (XRCC3) gene plays a role in HR, and the XRCC3 Thr241Met SNP has been associated with levels of DNA adducts. Since carriers of XRCC3 Met241Met had higher levels of DNA adducts [16], patients with this genotype could be more chemosensitive to cisplatin-based regimens.

In a previous phase I study [6], we established the recommended dose (RD) of weekly CPT-11 at 70 mg/m^2, followed by docetaxel at 25 mg/m^2, on days 1, 8 and 15 every 28 days. Leukopenia was the dose-limiting toxicity (DLT). A subsequent phase II study in heavily pretreated non-small-cell lung cancer (NSCLC) patients reported interesting activity and a good hematological toxicity profile for this regimen [7]. Based on the significant activity of CPT-11/docetaxel, both alone and in combination with cisplatin, on the feasibility of administering both drugs on a weekly schedule, and on their synergistic activity and non-overlapping toxicities, we designed a phase I study to establish the RD of CPT-11/docetaxel plus cisplatin in patients with advanced esophagogastric cancer and to determine its efficacy and toxicity. In addition, we analyzed XPD, XRCC3 and UGT1A1*28 polymorphisms to correlate the results with activity and toxicity.

Patients and methods

Patient eligibility

Patients with histologically documented locally advanced unresectable or metastatic esophageal and gastric cancer were eligible for inclusion. Prior adjuvant or neoadjuvant chemotherapy completed at least 12 months before enrollment was allowed. Other eligibility criteria included: age >18 years; Karnofsky performance status ≥70%; life expectancy >12 weeks; adequate hematopoietic, (absolute neutrophil count more than 1,500/ml, platelet count more than 100,000/ml and hemoglobin >9 g/dL), hepatic (serum bilirubin level <1.5 mg/dL; aspartate aminotransferase and alanine aminotransferase levels <2.5 times the upper limit of normal and alkaline phosphatase levels <5.0 times the upper limit of normal) and renal (serum creatine level <1.5 mg/dL or creatinine clearance >60 mL/min) functions; absence of brain metastases; no previous malignancy; no clinically evident severe cardiovascular disorders; and no history of any active serious infections. The institutional review board of each participating institution approved the study and all patients gave their signed informed consent.

Treatment Plan

On day 1, patients received CPT-11 (30-min iv) followed by docetaxel (30-min iv), and followed by cisplatin (30-min iv) at the fixed dose of 60 mg/m^2. CPT-11 and docetaxel were administered again on day 8. Four dose levels for CPT-11 and docetaxel were planned (Table 1). Treatment was repeated every 3 weeks. All patients received hyperhydration with 3 L normal saline in 12 h, and dexamethasone 8 mg was administered orally in the evening before chemotherapy, 1 h before docetaxel administration, and on the evening of chemotherapy. Cholinergic symptoms during CPT-11 treatment were treated with subcutaneous atropine 0.25 mg. A prophylactic anti-emetic regimen was given

Table 1 Dose escalation scheme

Dose level	Cisplatin (mg/m^2)	CPT-11 (mg/m^2)	Docetaxel (mg/m^2)	No. of assessable patients
1	60	50	25	8
2	60	60	25	16
3	60	60	30	4
4	60	70	30	–

according to the criteria of each individual center. Patients were instructed to start taking loperamide at the first sign of diarrhea (4 mg initial dose and 2 mg every 2 h for at least 12 h and up to 12 h after the last liquid stool).

Chemotherapy was administered if absolute neutrophil count was >1,500 cells/ml, platelet count was >100,000 cells/ml, and no grade 3/4 non-hematological toxicity was present. If hematologic counts were below these levels on the first day of each cycle, treatment was delayed for 1 week. Patients who required more than a 2-week delay in treatment were withdrawn from the study. The CPT-11 dose was reduced by 20% if grade 3/4 diarrhea occurred. Prophylactic hematopietic growth factor (G-CSF) was given when patients developed grade 4 neutropenia persisting longer than 7 days or accompanied by fever. If a second episode occurred despite the G-CSF therapy, the docetaxel and CPT-11 doses were reduced by 20% in subsequent cycles.

Study design

Three patients were enrolled at each dose level. In the absence of a DLT at the end of the first cycle, the next dose level was opened. If one or two DLTs occurred, three additional patients were enrolled at the current dose level. If no additional DLT occurred, enrollment continued at the next level. The maximum tolerated dose (MTD) was defined as the dose level at which at least three patients developed a DLT during the first cycle of treatment, and the RD was the dose level immediately below the MTD. Expansion of the RD cohort to ten more patients was planned so as to better characterize the pattern of toxicity and confirm the proposed phase II dose.

DLT was defined as follows: grade 4 neutropenia for >4 consecutive days, febrile neutropenia, grade 4 thrombocytopenia, grade 3/4 diarrhea despite loperamide treatment, or any other grade 3/4 non-hematological toxicity (except nausea and vomiting or alopecia).

Sample collection and genotyping

Prior to treatment, venous blood (10 ml) was collected from each subject into tubes containing 50 mmol of EDTA per liter, and genomic DNA was isolated with the QIAmp DNA blood Mini kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. Polymorphisms in XPD Lys751Gln and Asp312Asn, XRCC3 Thr241Met, and UGT1A1*28 were assessed with the 5′ nuclease allelic discrimination assay using an ABI Prism 7900HT Sequence Detection System (Applied Biosystems), as previously described [5, 13].

Statistical analyses

Tumor response was assessed every three cycles of treatment in accordance with the RECIST criteria. Survival time was calculated from the start of chemotherapy to death from any cause Time to progression was calculated from the start of chemotherapy to evidence of disease progression or start of second-line therapy. Each genotype was independently analyzed for association with response to chemotherapy, time to progression and survival time The Kaplan–Meier method was used to create survival curves, and the log-rank test was performed to compare survival times between genotype groups. For each genotype studied, Hardy–Weinberg equilibrium was tested in all patients and at each dose level, both according to the overall response rate and the disease-control rate, using the Chi-square test. The distribution of genotypes according to response rate (complete + partial response vs. stable + progressive disease) was compared using the Chi-square test. All statistical analyses were performed with the SPSS statistical software, version 14.0. All P values are two-tailed.

Results

Patient characteristics

From May 2003 to October 2004, a total of 29 patients from three participating institutions were included in this trial. One patient was considered ineligible because her Karnofsky performance status was <70%. The remaining 28 patients were evaluable for safety and efficacy analyses. Patient characteristics are listed in Table 2. The median age was 59 years (range 28–77 years). Twenty-five patients (89%) were male, and Karnofsky performance status was >80% in 21 patients (75%). Six patients had squamous cell carcinoma, and of the 22 patients with adenocarcinoma, 5 had tumors of the gastroesophageal junction and 15 had tumors located in the stomach. Twenty-five patients (89%) had metastatic disease; 16 of whom had hepatic metastases. Seven patients had previously received neoadjuvant/adjuvant chemotherapy. Twenty-six patients had measurable disease.

Table 2 Patient characteristics

Characteristic	No. of patients	%
Sex		
Male	25	89
Female	3	11
Age, years		
Median	60	
Range	28–77	
Primary tumor site		
Esophagus	8	28
Gastroesophageal junction	5	18
Stomach	15	54
Histology		
Squamous cell carcinoma	6	21
Adenocarcinoma	22	79
Karnofsky performance status		
100%	7	25
90%	14	50
80%	7	25
Metastatic sites		
Liver	16	57
Lymph nodes	8	28
Peritoneum	4	14
Lung	3	10
Others	12	42
No. of organs involved		
1	14	50
2	9	32
>2	5	18
Prior therapy		
Surgery	12	42
Radiotherapy	4	14
Chemotherapy	7	25

Dose escalation and determination of MTD and DLT

Two of six patients enrolled at the first dose level developed a DLT after the first cycle of treatment (one, grade 4 neutropenia; one, grade 3 diarrhea); a third patient also had grade 3 diarrhea but had not complied with the protocol guidelines of early intensive loperamide treatment. Two more patients were then included at this level, for a total of eight patients. These two patients did not suffer a DLT and dose escalation was performed. At the second dose level, one of the three original patients had a DLT (grade 4 neutropenia with grade 3 asthenia); so three additional patients were included at this dose level, with no DLT observed. At the third dose level, three patients experienced a DLT (one, febrile neutropenia with grade 3 diarrhea; one, febrile neutropenia; one, grade 4 diarrhea with grade 3 asthenia). Thus, the MTD dose level was established at the third dose level (CPT-11 60 mg/m^2 and docetaxel 30 mg/m^2 on days 1 and 8 plus cisplatin 60 mg/m^2 on day 1), and the RD was established at the second dose level (CPT-11 60 mg/m^2 and docetaxel 25 mg/m^2 on days 1 and 8 plus cisplatin 60 mg/m^2 on day 1). Ten additional patients were then included at the RD level.

Treatment compliance and toxicity

Twenty-eight patients received 116 cycles of chemotherapy. The median number of cycles was 3.5 overall and 4.5 at the RD level. Twelve patients (42%) completed the planned treatment. Eight patients were withdrawn from study due to toxicity (two at dose level 1, four at dose level 2, and two at dose level 3).

Treatment was delayed on day 1 of 21 cycles (18%) in 13 patients (46%), and on day 8, dose omission was required in 12 cycles (11%) in 10 patients (35%). Dose reduction of CPT-11 and docetaxel on day 1 was necessary in 7% of cycles in 7 patients (25% of patients included at each dose level). The cisplatin dose was reduced in three patients (10%), all at dose level 2. The main reason for dose reduction or delay was hematological toxicity. At the RD level, the relative median dose intensity for CPT-11, docetaxel and cisplatin was 0.91, 0.89 and 0.96, respectively.

Grade 3/4 toxicities at each dose level are listed in Table 3. Nineteen patients (67%) had grade 3/4 neutropenia, and febrile neutropenia occurred in seven patients (25%). Fifty-three percent of patients had grade 3/4 non-hematological toxicities (37, 56 and 75% of patients at dose levels 1, 2 and 3, respectively). Eight patients (28%) had grade 3/4 diarrhea and 11 (38%) had grade 3/4 asthenia. No patient experienced renal failure from cisplatin. There were no treatment-related deaths. At the RD level, grade 3/4 neutropenia occurred in 11 patients (68%), febrile neutropenia in 5 (31%), grade 3 diarrhea in 5 (31%), and grade 3/4 asthenia in 6 (37%).

Patient age was relevant to toxicity. Six of the eight patients (75%) older than 65 years had a DLT. In contrast, six of the 20 patients (30%) younger than 65 years had a DLT ($P = 0.04$).

Efficacy

Among the 26 patients with measurable disease, we observed four complete responses (15%) and nine partial responses (35%), for an overall response rate of 50%. Three of the four patients with complete responses had liver metastases. Of the 16 patients included at the RD level, three patients were withdrawn from the study due to toxicity after the first cycle and were not evaluable for response,

Table 3 Grade 3/4 toxicity by patient at each dose level

Toxicity	Level 1		Level 2		Level 3		Overall	
	3	4	3	4	3	4	3	4
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Neutropenia	3 (37)	1 (12)	3 (18)	8 (50)	2 (50)	2 (50)	8 (28)	11 (39)
Febrile neutropenia	–	–	5 (31)	–	2 (50)	–	7 (25)	–
Anemia	–	–	4 (25)	1 (6)	1 (25)	–	5 (18)	1 (3)
Thrombocytopenia	–	–	3 (18)	–	–	–	2 (7)	–
Non-hematologic toxicity								
Nausea	1 (12)	–	–	–	1 (25)	–	2 (7)	–
Emesis	–	–	1 (6)	–	2 (50)	–	3 (10)	–
Diarrhea	1 (12)	–	5 (31)	–	1 (25)	1 (25)	7 (25)	1 (3)
Stomatitis	–	–	1 (6)	–	–	–	1 (3)	–
Hepatic toxicity	–	–	2 (12)	–	–	–	2 (7)	–
Asthenia	3 (37)	–	5 (31)	1 (6)	2 (50)	–	10 (35)	1 (3)
Dyspnea	–	–	1 (6)	–	–	–	1 (3)	–

and two patients did not have measurable disease but were treated with the planned six cycles of chemotherapy. Eight of the remaining 11 patients (72%) achieved an objective response, including three complete responses.

At a median follow-up of 11.4 months, median time to progression for the 28 patients was 6.6 months (95% confidence interval [CI], 2.8–10.5 months), and median survival was 11.3 months (95% CI, 7.6–15.0 months) (Fig. 1). Survival at 1 and 2 years was 46.4% (95% CI, 28.0–64.8%) and 10.7% (95% CI, 0.0–22.1%), respectively. At the RD level, median time to progression was 6 months (95% CI, 4.2–7.7 months), median survival was 10.7 months (95% CI, 7.1–14.3 months) and the 1- and 2-year survival rates were 43.8% (95% CI, 19.5–68.1%) and 12.5% (95% CI, 0.0–28.8%), respectively. Median survival at dose levels 1 and 3 were 9.1 and 11.3 months, respectively ($P = 0.98$). At the time of writing this article (January 2008), only one patient is alive.

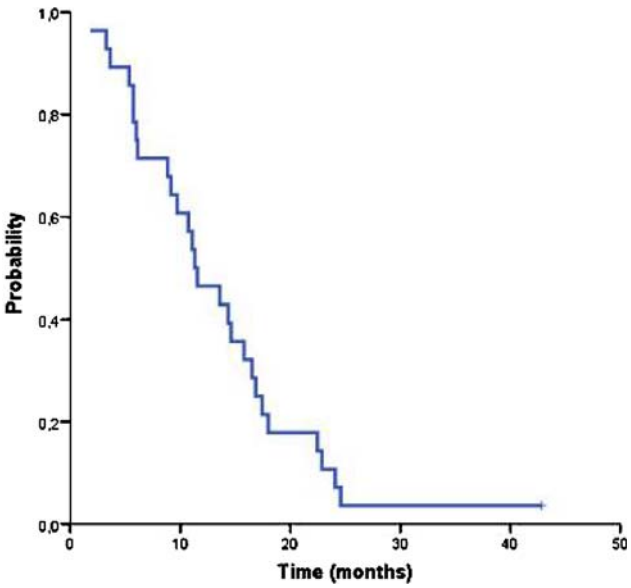

Fig. 1 Overall survival

Assessment of XPD, XRCC3 and UGT1A1 polymorphisms

The distribution of genotypes is shown in Table 4. All polymorphisms were in Hardy–Weinberg equilibrium in all patients and at each dose level. No differences in response rate, time to progression or survival were observed according to XPD Lys751Gln, XPD Asp312Asn or UGT1A1*28 genotypes. However, objective response was attained by all four patients (100%) harboring XRCC3 Met241Met but only one of the six patients (16%) with XRCC3 Thr241Thr and 8 of the 18 patients (44%) with XRCC3 Thr241Met genotypes ($P = 0.06$) (Table 4). A longer time to progression was also observed in patients with XRCC3 Met241Met. Median time to progression was 9.7 months for carriers of XRCC3 Met241Met, 8.4 months for those with Thr241Met and 3.1 months for those with Thr241Thr ($P = 0.042$) (Figs. 2, 3). No significant differences in toxicity were observed according to genotypes of any of the genes analyzed, including UGT1A1*28.

Discussion

The best chemotherapy regimen for patients with advanced esophageal and gastric cancer has not yet been defined. Although a recent meta-analysis [29] of advanced gastric cancer patients reported that combination chemotherapy improved survival in comparison with single-agent chemotherapy, the majority of chemotherapy combinations tested

Table 4 Frequency of genotypes and distribution according to chemotherapy response

Genotypes	Overall Frequency		Objective response[a]		No response[b]		*P*
	N	%	*N*	%	*N*	%	
XPD 312							0.29
Asp/Asp	10	35	6	60	4	40	
Asp/Asn	15	55	5	33	10	66	
Asn/Asn	3	10	2	66	1	33	
XPD 751							0.64
Lys/Lys	9	32	5	55	4	45	
Lys/Gln	17	61	7	41	10	59	
Gln/Gln	2	7	1	50	1	50	
XRCC3 241							0.06
Met/Met	4	14	4	100	0	0	
Met/Thr	18	65	8	44	10	56	
Thr/Thr	6	21	1	16	5	84	
UGT1A1*28							0.14
TA6/TA6	12	42	5	41	7	59	
TA6/TA7	16	58	8	50	8	50	

[a] Objective response = complete or partial response

[b] No Response = stable or progressive disease and non-evaluable patients

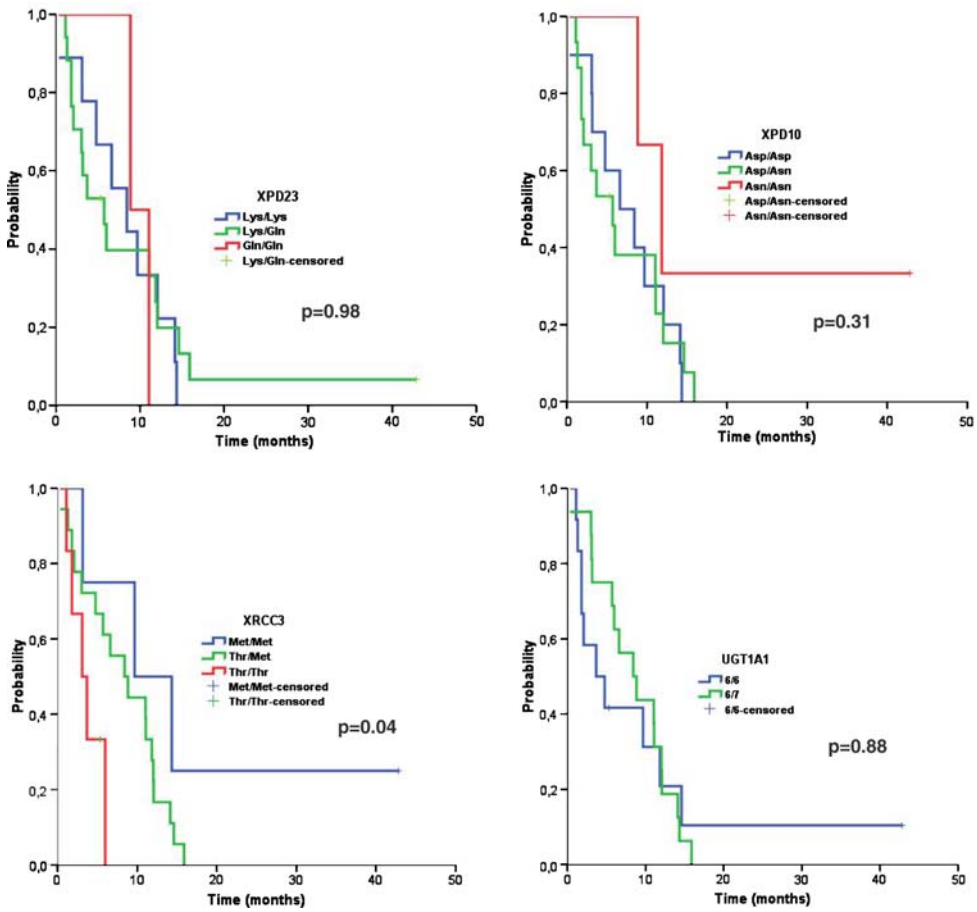

Fig. 2 Time to progression according to genotype

have obtained suboptimal results, with median survival times of only 7–9 months. Docetaxel-based regimens have been widely explored in advanced gastric cancer. In a phase II randomized study [1] comparing docetaxel/cisplatin/5-Fu (DCF) with docetaxel/cisplatin, a better response rate was attained with the triplet combination (43 vs. 26%). In a further phase III trial [27], comparing the DCF triplet with cisplatin/5-Fu, greater benefit was observed in the DCF arm,

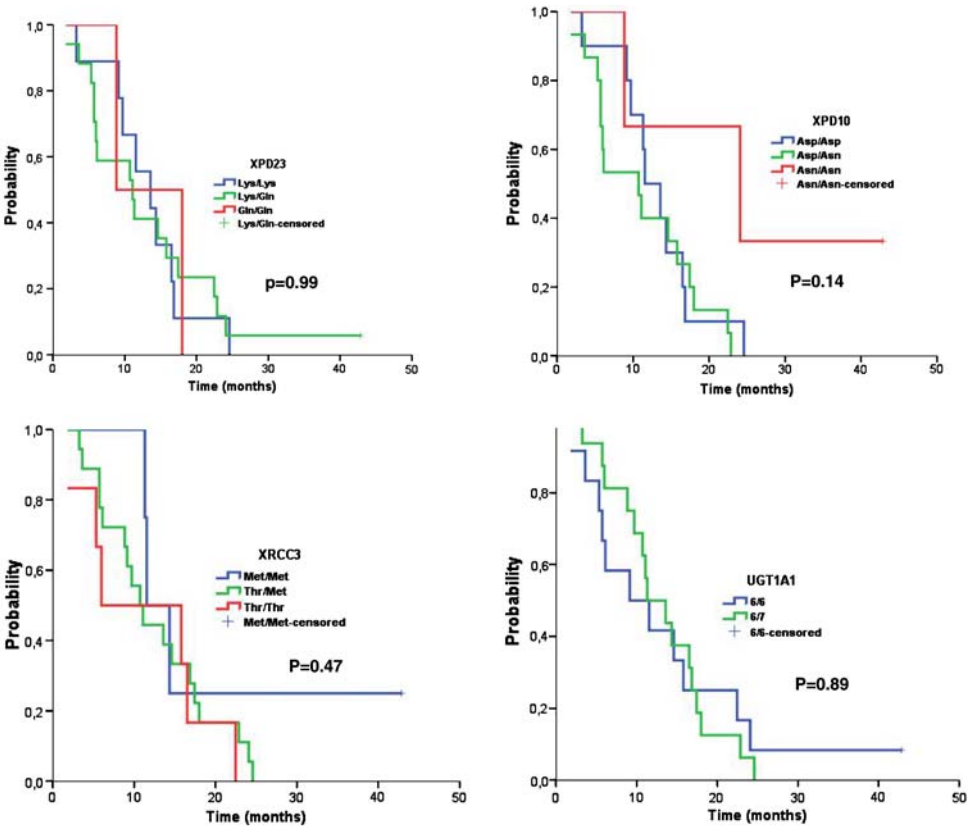

Fig. 3 Survival according to genotype

both in response rate (37 vs. 25%) and median survival (9.2 vs. 8.6 months). DCF can thus be considered a new standard of care in patients with advanced gastric cancer patients, although median survival remains similar to that obtained with classic three-drug regimens [20, 28, 30].

In light of these results, novel regimens need to be explored. In this phase I trial, we have demonstrated the feasibility of adding a third active drug to the cisplatin/CPT-11 combination with a dose-intensity similar to that of cisplatin/CPT-11 alone [3, 24] and a promising antitumor activity. Despite the small number of patients, our results compare favorably with those obtained with the most active cisplatin-based combinations, such as cisplatin/docetaxel with or without 5-Fu [1, 27] or cisplatin/5-Fu/epirubicin [20, 30].

Although the toxicity observed in our study was not negligible, it was within the range of that reported for other docetaxel- or CPT-11-based regimens. Furthermore, 68% of our patients had grade 3/4 neutropenia, and 31% had febrile neutropenia, which is in the line with the toxicities observed with the DCF regimen [1, 27]. In the phase III trial [27], 69% of patients in the DCF arm had an episode of grade 3/4 toxicity, 29% of patients had febrile neutropenia episodes and 49% of patients had severe gastrointestinal toxicity. Interestingly, in patients older than 65 years a significant increase in grade 3/4 infection related to treatment was observed in the DCF arm compared to those patients treated with cisplatin/5-Fu. In our study, 75% of patients older than 65 years had a DLT episode. These results suggest that more aggressive regimens, including those with three-drug combinations, are effective but should be used with caution in older patients.

A wealth of evidence indicates that genetic assessment can predict response to chemotherapy, helping to avoid ineffective treatments and unnecessary toxicities. Studies on lung and colorectal cancer have suggested that reduced DNA repair capacity resulting from SNPs of DNA repair genes is associated with improved survival with platinum-based chemotherapy [5, 10, 13, 17, 25]. However, few studies have addressed the impact of SNPs on chemotherapy efficacy in patients with advanced esophageal and gastric cancer. Recently, when SNPs of 13 DNA repair genes were assessed in 175 advanced gastric cancer patients treated with cisplatin/5-Fu [22], none, including XPD and XRCC3 SNPs, were associated with survival. In fact, several studies analyzing the role of XPD 312 and 751 SNPs have reported contradictory results [5, 10, 13, 17]. In our study, only XRCC3 Met241Met was associated with a higher response rate and a significant improvement in time to progression, although this benefit did not translate to longer survival. These findings are along the same lines as those reported by De las Peñas et al. [5] in NSCLC patients treated with cisplatin-based chemotherapy: of the 14 SNPs analyzed, only XRCC3 was strongly associated with survival. XRCC3 241

polymorphisms were recently associated with clinical outcome in colorectal cancer patients treated with CPT-11-based chemotherapy, possibly as a result of the specificity of the XRCC3 DNA repair function for SN-38 DNA damage [23]. The association between XRCC3 and outcome in the present study may thus be a result of the dual influence of XRCC3 on both cisplatin and CPT-11.

In contrast with some previous studies of CPT-11-treated patients [2, 12, 15], UGT1A1*28 genotype did not correlate with toxicity or efficacy in our patients. This may be due to our limited sample size or the addition of docetaxel and cisplatin to CPT-11. Interestingly, our findings are similar to those of a recent study [26] of 250 colorectal cancer patients treated with CPT-11/5-FU/leucovorin, which reported a slight relevance of UGT1A1*28 to toxicity but without impact on prognosis. Other genetic mechanisms of UGT1A1, such as methylation [9], may also be involved in regulating CPT-11 activity. In general, however, our pharmacogenetic findings should be assessed cautiously, not only because of the small number of patients but also because this was a phase I study where patients were treated with three dose levels. Nonetheless, these exploratory findings merit further investigation with a larger number of patients.

In conclusion, in this phase I study, we have established the RD for weekly CPT-11/docetaxel in combination with cisplatin in advanced esophagogastric cancer. This regimen shows a promising activity that warrants confirmation in a phase II trial; however, the degree of febrile neutropenia observed at the RD level suggests that hematopoietic growth factors should be administered. Furthermore, our findings suggest that XRCC3 assessment can be useful in selecting esophagogastric cancer patients who may have a better outcome to cisplatin-based chemotherapy.

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