RESEARCH ARTICLE

Low-Dose Docetaxel/Cisplatin - Leucovorin and 46 Hour Infusional Fluorouracil in Metastatic Gastric Carcinoma

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Abstract

Background: Phase II and III trials of docetaxel, cisplatin and fluorouracil (DCF) have shown superior efficacy versus cisplatin and fluorouracil alone but with high rates of hematologic toxicity in metastatic gastric cancer cases. To reduce toxicity while maintaining the efficacy of DCF, we investigated low dose docetaxel (D), cispatin (C) - leucovorin and fluorouracil (De Gramont regimen). Patient and methods: Chemotherapy-naïve patients with metastatic gastric cancer (MGC) received D 60 mg/m^2 on day 1 and cisplatin 30 mg/m^2 on day 1-2 and the De Gramont regimen (Folinic acid 400 mg/m^2 on day 1 and 5-FU 2400 mg/m^2/46h continuous infusion) every 3 weeks. The primary endpoint was response rate. Results: One hundred twenty patients with a median age of 52.5 years (range, 32-78) received a median of 6 cycles (range, 2-12 cycles). Of the 120 evaluable patients, 4 showed complete remission and 36 achieved a partial response. The overall response rate was 56.6%. Twenty eight patients (23.3%) showed stable disease and 52 (43.3%) progression. The median time to progression was 7 months (95%CI 6-7.9). The median overall survival was 15 months (95%CI 13.7-16.2). The most frequent hematological toxicity was leucopenia, which occurred at grade ¾ intensity in 24 patients (20%). Conclusions: Low-dose DC- De Gramont regimen is active in MGC with a tolerable toxicity profile.

Keywords: Cisplatin - docetaxel - fluorouracil - gastric cancer - Turkey

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Introduction

Patients with inoperable gastric cancer may benefit from palliative chemotherapy. However, to date, there is no generally accepted standard regimen. Single chemotherapy drugs, e.g. cisplatin, 5-fluorouracil (5-FU), and doxorubicin, have long been considered as active drugs (Ajani et al., 2005), and more recently agents such as docetaxel, paclitaxel, irinotecan and oxaliplatin have been added to the list.

A number of controlled studies of two-drug combination chemotherapys, especially cisplatin-containing regimen, have shown a significant improvement in median survival and quality of life compared with best supportive care (Bang et al., 2002;Ajani et al., 2003). Of these, 5-FU and cisplatin combination (FP) has been considered as an active and safe regimen for a long time (Colevas et al., 1998).

Many trials using combinations of three drugs have been conducted to improve treatment results further in advanced gastric cancer. One of the three-drug combination is adding docetaxel, a novel semi-synthetic taxoid, to "5-FU+cisplatin" (DCF). According to the recent randomized phase III studies the DCF regimen is superior to the FP and epirubicin+cisplatin+5-FU (ECF) regimens in terms of response rate, time to progressions and overall survival as a first –line treatment in advanced gastric cancer (Colevas et al., 1999).

In both of these trials (V325 and SAKK), however, DCF was associated with higher rates of hematologic toxicities than FP or ECF (Glimelius et al., 1997; Colevas et al., 1999). There had been several combination methods regarding these three drugs. These combinations had been studied actively in head and neck cancer (Fleming, 1982; Geen and Weiss, 1992; Kim et al., 1993; Janinis and Panagos, 2000; Janinis et al., 2001). In various

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combinations, docetaxel could usually be used up to 70-80 mg/m^2, cisplatin up to 7080 mg/m^2 and 5-FU up to 4000 mg/m^2 per cycle with manageable toxicity. We wanted to minimize toxicity the treatment and use the de Gramont regimen with DC so that the regimen can be used on a day every 3 weeks. Among these methods, Janitis et al. used docetaxel 80 mg/m^2 on day 1, cisplatin 40 mg/m^2 on days 3 and 3, and 5-FU 1000 mg/m^2 by 24 h continuous infusions on days 1-3 every 4 weeks in head and neck cancer (Geen and Weiss, 1992).

Furthermore, since drug toxicity profiles usually differ some what in ethnic groups, we wanted to determine the safety of the modified DCF regimen for use in Turkish patients with gastric cancer

DCF combination warrants a modification of dose schedule. Because this relatively high hematotoxicity is due primarily to docetaxel, we conducted a retrospectively study of low dose docetaxel (60 mg/m^2 on day 1, every 3 weeks) and cisplatin (60 mg/m^2 on days 1 and 2, every 3 weeks) combined with de Gramont regimen (Folinic acid 400 mg/m^2 on day 1 and 5-FU 2400 mg/m^2/46h continuous infusion every 3 weeks) in patients with metastatic gastric cancer to find a regimen that maintained efficacy while minimizing toxicity.

Materials and Methods

Patient population

From may 2006 to April 2010, 120 patients with advanced gastric cancer were entered in this study. Eligibility criteria included histologically proven unresectable or metastatic gastric adenocarcinoma, no prior chemotherapy or radiotherapy for metastatic disease, World Health Organization (WHO) performance status 0-2, age 18 years or more, a life expectancy of at least 12 weeks, absence of a second primary malignant tumor, and no severe organ dysfunction, coronary insufficiency, or uncontrolled infections. Patients were also required to have bidimensionally measurable disease by computed tomography (CT) scans. Laboratory criteria included adequate bone morrow (absolute granulocyte count 1500/dl and platelets >100000/dl), renal (serum creatinine levels <1.5 mg/dl), and hepatic (serum bilirubin levels <1.5mg/dl) and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values <4 times the upper normal limits) functions.

Treatment schedule

The chemotherapy regimen consisted of: docetaxel 60 mg/m^2 intravenous infusion over 1 h on day 1, cisplatin 30 mg/m^2 intravenous infusion over 1h on day 1 and 2, folinic acid 400 mg/m^2 on day 1 and 5-FU 2400 mg/m^2/46h continuous infusion with infusions pump every 3 weeks. We used a dexamethasone 16 mg intravenous push 15 min before chemotherapy infusion on days 1 and 2. Also, pre- and post cisplatin hydration with dextrose was performed on days 1 and 2. A serotonin antagonist was used as an antiemetic. Treatment was repeated every 3 weeks until disease progression, patients refusal or unacceptable adverse reactions. Prophylactic administration of granulocyte-colony stimulating factor (G-CSF) was not allowed.

Dose modifications

Chemotherapy was delayed until neutrophils were recovered (>1500/μl) or platelets reached >100000/ μl, or until resolution of any significant non-hematological toxicity. Doses of all drugs were reduced by 25% in subsequent cycles in the case of National Cancer Institute-Common Toxicity Criteria grade 4 neutropenia or grade 3-4 thrombocytopenia lasting for >3 days, or in the case of febrile neutropenia, which was treated with granulocyte colony-stimulating factor and antibiotics. The dose of all drugs was reduced by 25% in subsequent cycles in the case of National Cancer Institute-Common Toxicity Criteria grade 3-4 mucositis and in the case of poor performance status.

Evaluation

Pretreatment evaluation included a determination of medical history; physical examination; complete blood cell (CBC) count with differential, platelet count, blood chemistry; gastroendoscopy; chest radiograph; and computed tomographic (CT) scan of the abdomen. During the first 2 chemotherapy cycles, CBC with differential and platelet count was performed weekly, and then every 3 weeks. Blood chemistry was examined every 3 weeks. A CT scan was acquired every 3 cycles or if clinically indicated to evaluate response to treatment. Complete response(CR), partial response (PR), stable disease (SD), and progressive disease (PD) were defined according to the standard World Health Organization criteria. Data from patients who received at least 1 cycle of chemotherapy were included in the safety analysis. Toxicities were graded using the NCI CTC (version 2.0).

Statistical analyses

Sample size was determined using a two stage design, as described by Fleming (Mavroudis et al., 2000). With 72 evaluable patient, a null hypothesis for the true response rate of 15% and an alternative hypothesis of 35%, the type I error α was less than 5% and the type II error ß was less than 10%. Categorical date were presented in with frequencies and percentages. Continuous data were summarized using median, minimum and maximum values. Confidence intervals were calculated at the 95% level. Time dependent parameters were analyzed using the Kaplan–Meier method and 95% confidence interval for the median was reported (13). Considering safety analysis, worst NCI-CTC version 2.0 grade was reported by patient and by cycle on all treated patients.

Results

Patient characteristics

From January 2008 to June 2010, 120 patients (76 men, 44 woman) were enrolled in the study. The patient characteristics are listed in Table 1. The median age of the patients was 52 years (range 32-78). Eighty patients (67%) had performance status 0 or 1. All patients had measurable metastatic lesions, and metastatic sites were located in the liver in 42 patients (35%), lymph node in 34

Table 1. Patient Characteristics

Characteristics		n	(%)
No.of patients		120	
Age (year)	Median	52.5	
Range		32-78	
Gender	Male	76	(63.3)
	Female	44	(36.7)
ECOG Performance status	0-1	80	(67.0)
	2	40	(33.0)
Metastatic site	Liver	42	(35.0)
	Lymph nodes	33	(27.5)
	Peritoneum	26	(21.7)
	Lung	2	(1.7)
	Peritoneum –liver	4	(3.3)
	Liver-lung	4	(3.3)
	Peritoneum-lung-liver-ovary	4	(3.3)
	Ovary- Lymph nodes	5	(4.2)

Table 2. Response

Response	No.of patients	(%)
Complete response (CR)	4	(3.3)
Partial response(PR)	36	(30.0)
Stable disease(SD)	28	(23.3)
Progressive disease(PD)	43	(43.3)

Table 3. Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicity				
Leucopenia	8 (6.7)	28 (23.3)	20 (16.7)	4 (3.3)
Anemia	24 (20.0)	8 (6.7)	4 (3.3)	
Thrombocytopenia	12 (10.0)		12 (10.0)	
Non-hematological toxicity				
Vomiting	20 (16.7)	44 (36.7)	8 (6.7)	
Diarrhea	12 (10.0)	12 (10.0)	4 (3.3)	
Mucositis		12 (10.0)		

patients (28.3%), peritoneum in 26 patients (21.7%), and others in 18 patients (15%). Seventeen patients (14%) had multiple metastases involving 2 or more organ systems.

Drug exposure

A total of 732 chemotherapy cycles administered (mean 6 cycles per patients, range 2-12). Treatment was extended to twelve cycles in a patients with a partial response who expressed a wish for further therapy. The dose was reduced in 44 (5.9 %) cycles. The most common reason for dose reduction was cytopenia. Other causes were decreased real function and poor performance status.

Efficacy

Efficacy data are shown in Table 2. Of the 120 evaluable patients, 4 patients showed complete remission and 36 patients achieved partial response. The overall response rate was 56.6%. Twenty eight patients (23.3%) showed stable disease and 52 patients (43.3%) progressive disease. The response to chemotherapy did not differ significantly according to the sex, age (younger than 65 years versus older), performance status (ECOG 0 and 1 versus 2) and metastatic sites. The median time to progression was 7 months (95%CI 6-7.9). The median overall survival was 15 months (95%CI 13.7-16.2). These

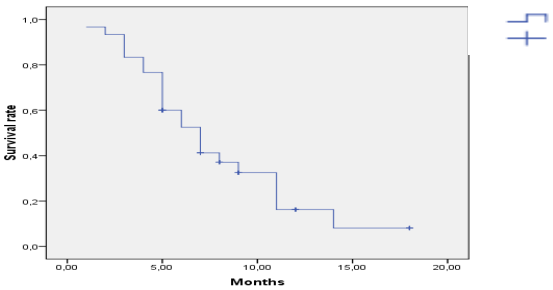

Figure 1. PFS for All Treated Patients

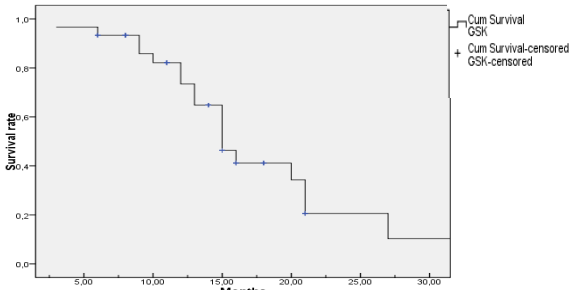

Figure 2. OS for All Treated Patients

are shown in Figure 1 and 2. Among the patients who responded to chemotherapy, no one underwent surgery.

Adverse reactions

The toxicity profile is summarized in Table 3. The most frequent hematological toxicity was leucopenia, which occurred at grade 3/4 intensity in 24 patients (20%). Febrile neutropenia occurred in 5 patients (4.1%). Grade 3/4 thrombocytopenia occurred in 12 patients (10%) and grade 3/4 anemia was observed in 4 patients (3.3%). Nonhematologic adverse events were moderate. The most common grade 3/4 nonhematologic toxicity was nausea-vomiting (6.7%), followed by diarrhea (3.3%). There were no toxic deaths to chemotherapy.

Discussion

Patients with inoperable gastric cancer may benefit from palliative chemotherapy. There are many regimens consisting of a single drug, two-drug combination, three-drug combination and even more. However, at present, there is no 'standard' chemotherapy regimen generally accepted. Traditionally, the combination of 5-FU and cisplatin has been considered active and safe (overall response rate up to 50%, time to progression 5.4 months, overall survival <1 years).

Docetaxel is a novel semi-synthetic taxoid, which has demonstrated activity against human gastric carcinoma cell lines in vitro and in vivo (Preusser et al., 1988). The use of this agent for the treatment of patients with advanced or metastatic gastric cancer resulted in a response rate of 15-24% when it was given as first line therapy (Pyrhonen et al., 1995; Ridwelski et al., 2001; Roth et al., 2004) and 18-24% when given as a second line therapy (Roth et al., 2000).

Various drug combination schedules were used in these trials. As mentioned earlier, the DCF regimen used by Ajani et al. (2005) was a 5-day regimen, which included

docetaxel 75mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5-FU 750mg/m^2/day administered by continuous infusion on days 1-5 every 3 weeks.

Our study showed a high response rate (56.6%) and a promising overall survival (OS) of 15 months in patients with advanced gastric cancer receiving low-dose DC- De Gramont regimen.

The V325 trial demonstrated an incremental benefit of adding docetaxel to the reference FP regimen as first line therapy in patients with advanced or locally recurrent gastric cancer (Colevas et al., 1999). However, the high incidence of hematologic toxicities may be a limitation for the broad use of this highly active regimen. Modification of DCF may result in a less intense and more tolerable treatment. Myelosuppression, the most significant side effect, can be minimized when docetaxel is administered on low dose (60 mg/m^2). Due to these observations, we evaluated low-dose scheduling of DC combined with de Gramont regimen. Based on experiences in a single arm phase II study and the results of a randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC 40953), the cisplatin–FU-leucovorin combination was considered as the backbone chemotherapy regimen (Sulkes et al., 1994; Tanaka, 1996).

In patients with metastatic gastric cancer, low-dose DC- de Gramont regimen compares favorably with the results of other docetaxel-containing combinations (Wilke et al., 1996; 1998; Vanhoefer et al., 2002; Thuss-Patience et al., 2005; Van Cutsem et al., 2006). With an overall response rate (ORR) of 56.6%, an encouraging median time to treatment progression (TTP) of 7 months, and a median OS of 15 months in patients with metastatic disease, the activity of the low-dose DC- de Gramont regimen exceed the study hypothesis. As patient characteristics (such as performance status and age) are in the same range as in previously reported trials (Wilke et al., 1996; Van Cutsem et al., 2006).

The low-dose DC-de Gramont regimen resulted in much less severe hematologic toxicity and consequently fewer episodes of serious infection, compared to the high incidence of grade 3/4 neutropenia seen with 3-weekly administration of DCF (Wilke et al., 1996; Thuss-Patience et al., 2005). Prophylactic G-CSF support was not given in our study and has therefore not contributed to the lower incidence of hematologic toxicity.

With the exception of severe neutropenia, which occurred in 20% of all patients, other hematologic and non-hematologic toxicities were infrequent or mild to moderate in severity. Furthermore, there were no treatment related deaths. Besides our efforts to reduce the toxicity of the DCF regimen by low-dose DC- de Gramont.

In these recently presented trials the third generation platinum compound oxaliplatin and the oral fluoropyrimidine capecitabine proved to be equal in terms of efficacy but were associated with slightly reduced toxicity and better tolerability compared to cisplatin and infusional fluorouracil, respectively.

Our study also shows that the low-dose DC- de Gramont schedule had at least similar antitumor activity as previously reported docetaxel-containing triple therapies in metastatic gastric cancer. With a 1-year survival rate of 73% and an estimated 2-year survival rate of 20.6% in metastatic disease, the low-dose DC-de Gramont regimen appears to be a reasonable treatment approach in this setting. These promising efficacy date are consistent with the 1- and 2-year survival rates (40% and 18%,respectively) reported in the DCF arm of the V325 study (Wilke et al., 1998).

In conclusion, the low-dose DC- de Gramont regimen is an active treatment with high efficacy in terms of tumor response rate, TTP and OS. In patients with metastatic disease the considerably high survival rate of 15 months supports further investigation of the schedule. Low-dose DC- de Gramont regimen was well tolerated, with moderate and manageable myelotoxicity. Compared to previously published studies, the reduction in hematologic toxicity may translate into quality of life advantages. The low- dose DC- de Gramont regimen would be an appropriate comparator with other newly established reference regimens in advanced gastric cancer, and should be further investigated in large-scale randomized trials.

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