The combination of docetaxel, cisplatin, and 5-fluorouracil in advanced gastric cancer: a single-institution experience

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The addition of docetaxel to cisplatin and 5-fluorouracil was shown to confer a survival benefit in patients with advanced gastric cancer (one; AGC), although with increased toxicity. We hereby report our experience with the use of docetaxel, cisplatin, and 5-fluorouracil (DCF). Data on all consecutive patients who received first-line treatment with DCF at our institute were analyzed retrospectively. Twenty-three patients were included. The median age was 63 years. Patients received an average of 10 cycles (range, 1–24). All experienced grade $\geq$ 3 toxicity, requiring hospitalization in 35%. There was one toxic death. The median progression-free and overall survival rates were 10.0 and 12.8 months, respectively; the 2-year and 3-year survival rates were 22 and 17%, respectively. The DCF regimen is indeed associated with substantial toxicity, although manageable. Nevertheless, the observed benefit was remarkable compared with any previous report on chemotherapy in AGC, and should therefore represent a valid treatment option in AGC and a platform for future combinations. *Anti-Cancer Drugs* 23:313–320 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Background

Gastric cancer is the fourth most common cancer worldwide, the second leading cause of cancer-related death among men and the fourth among women, and thus represents a significant global health concern [1]. The disease often presents at an advanced stage and treatment is therefore usually palliative, aiming at improving the quality and quantity of life.

The role of chemotherapy in advanced gastric cancer (AGC) has been established in a number of randomized trials, as well as in a meta-analysis, which demonstrated a significant improvement in overall survival (OS) compared with best supportive care [2]. Nevertheless, the optimal chemotherapeutic regimens are still undetermined and challenging, whereas outcomes such as response rate, toxicity, and OS benefit remain disappointing [3–6]. 5-Fluorouracil (5-FU) and cisplatin (CDDP) based combinations are still the mainstay of treatment in the Western world, although both the commonly used CDDP with continuous infusional 5-FU alone (CF) and with epirubicin (ECF) have yielded only a modest median OS time of 7–10 months [7,8]. Data from the REAL-2 study highlight the role of two other agents, oxaliplatin and capecitabine, in the treatment of AGC [9]. Initial studies have addressed the promising activity of docetaxel in AGC as monotherapy [10–12] and in combination with other agents [13–18]. As docetaxel-based regimens have continued to evolve, the V-325 study group investigated the addition of docetaxel to the standard CF combination (DCF regimen). The initial randomized phase II part of the V-325 study compared the DCF triplet regimen with the doublet regimen of docetaxel/CDDP in patients with AGC [19,20]. The triplet regimen appeared to be superior with regard to the overall response rate (43 vs. 26%) and time to progression (5.9 vs. 5.0 months). These results have paved the way for the subsequent phase III part of the trial. The phase III V-325 trial was an international, multicenter, randomized trial of first-line DCF versus standard CF in 455 patients with AGC. The DCF regimen was superior in terms of the overall response rate (37 vs. 25%, $P = 0.01$), median time to progression (5.6 vs. 3.7 months, hazard ratio = 0.68, $P = 0.0004$), and median OS (9.2 vs. 8.6 months, hazard ratio = 0.77, $P = 0.0201$) [19]. The 2-year survival rate was doubled with DCF (18 vs. 9%). The addition of docetaxel was also associated with improvement of quality of life, with a 44% prolongation of the time of quality of life deterioration ($P = 0.01$). However, DCF was more toxic, leading to a higher rate of grade $\geq$ 3 neutropenia (82 vs. 57%), leukopenia (65 vs. 31%), febrile neutropenia (63 vs. 27%), diarrhea (19 vs. 8%), and neuropathy (17 vs. 6%). The results of the V-325 study have laid the basis for the role of DCF as a first-line treatment option for patients with AGC. The toxicities associated with this regimen, however, have resulted in a general reluctance of the medical community to adopt it.

In light of the apparent effectiveness of the DCF regimen against AGC, we embarked on its use while monitoring

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our patients very closely for toxicities. Herein, we present our experience with the first 23 patients who received DCF at our institution and provide detailed information on our follow-up policy and the performance of the regimen, in terms of safety and efficacy.

Patients and methods

Patients

Patients with histologically confirmed metastatic gastric adenocarcinoma who received first-line treatment with DCF at the Davidoff Cancer Center, Rabin Medical Center, were eligible. Patients had to have an Eastern Cooperative Oncology Group performance status (PS) of at least 2 and adequate bone marrow (white blood cell count $\geq 4000/\mu l$, platelet count $\geq 100\,000/\mu l$), renal [serum creatinine ≤ 1.4 mg/dl and creatinine clearance test (CCT) ≥ 50 ml/min], and liver (bilirubin ≤ 2 mg/dl) functions. As docetaxel is not reimbursed in Israel for AGC, the only selection criterion for treatment with DCF, besides the described eligibility criteria, was the patient's ability to finance the drug, either directly or through a private insurer.

The pretreatment workup included chest and abdominal computed tomography scans, complete blood count, blood chemistry, CCT, and measurement of the epithelial tumor markers carcinoembryonic antigen and CA-19.9.

Treatment protocol

Treatment was administered according to the V-325 protocol: docetaxel (75 mg/m^2 in 1000 cm^3 saline intravenously (i.v.) over 1 h) on day 1, followed by CDDP (75 mg/m^2 in 1000 cm^3 saline i.v. over 90 min) on day 1, and 5-FU (750 mg/m^2/day as continuous i.v. infusion) on days 1–5, every 3 weeks. A permanent venous access (port system) was implanted to enable a continuous infusion of 5-FU. Patients received a standard antiemetogenic protocol for highly emetic regimens, including aprepitant in the later period of the study. Prophylactic growth factors were not administered routinely. Dose reductions were carried out according to the reference protocol, but on many occasions, doses were modified in a more tailored manner. For example, in the case of prolonged grade 2 fatigue, a common condition, minor dose reductions, of 10–15%, were carried out.

Treatment was continued until disease progression or unacceptable toxicity. Prolonged (until progression) 'drug holidays' were considered only after sustained remissions were achieved, generally after a 1-year duration of continuous treatment.

Evaluation of response and toxicity

Evaluation procedures, including physical examination and assessment of toxicity, complete blood count, blood chemistry, CCT, and tumor markers, were repeated every 3 weeks, before each cycle. Toxicity was graded according to the common toxicity criteria-National Cancer Institute version 2. Objective response to treatment, defined by the Response Evaluation Criteria In Solid Tumors criteria (v. 1.0), was evaluated by repeated computed tomography imaging every three or four cycles, by an expert radiologist. Patients were also evaluated at each follow-up visit for clinical benefit (CB) from treatment, defined as the overall change in the patients' general condition. CB was determined according to the change in the patients' PS, weight, and symptoms, regardless of their etiology, that is, regardless of whether their change was disease related or treatment related. Patients were deemed as having a CB if they had an improvement in at least one of these measures without worsening in others.

Statistical analysis

Two survival endpoints were studied: OS and progression-free survival (PFS). OS was defined as the time from the onset of DCF to death due to any cause or the last date the patient was known to be alive. PFS was defined as the time from the onset of DCF to progression or the last date the patient was known to be progression free. OS and PFS were estimated using the product limit method (Kaplan–Meier) [21]. In order to compare the OS or PFS curves of the current study with an earlier one, the log-rank test was performed and two-sided P values were obtained. P values of less than or equal to 0.05 were considered statistically significant. The data collection and analysis were approved by the Institutional Ethics Committee.

Results

Patient characteristics

From January 2006 to November 2008, 23 patients received the DCF regimen at our institution. The patient and tumor characteristics at the onset of DCF treatment are shown in Table 1. The median age was 63 years (range, 28–77), there was a male predominance (78%), and 96% of the patients had PS 0–1. Eighty-eight percent had more than one metastatic site and 56% had visceral involvement. Five patients (22%) had previously undergone surgery for localized disease at diagnosis but none had received adjuvant chemotherapy or radiotherapy.

Treatment delivery

Twenty patients (87%) started treatment at the standard dosage. Three patients received the first cycle at a reduced dosage, due to relative frailty, or without docetaxel, due to bureaucratic delay. All three patients received the classical DCF regimen, at full dosage, from cycle 2 onwards.

Treatment delivery is summarized in Table 2. Patients received an average of 10.7 cycles (range, 1–24), with a total of 245 cycles delivered to the entire group. The median duration of treatment was 8.7 months (range, 0.7–16.0), including three patients in whom treatment was resumed due to disease progression for 3–6 additional

Table 1 Patient characteristics ($n=23$)

	Number	%
Age (year)		
Median (range)	63 (28–77)	
Sex		
Male	18	78.3
Female	5	21.7
Performance status		
0	4	17.4
1	18	78.3
2	1	4.3
Weight loss[a]		
Yes	14	60.9
No	9	39.1
Disease status		
Metastatic at presentation	18	78.3
Metastatic at recurrence	5	21.7
Grade of differentiation		
1–2	3	13.0
3–4	20	87.0
Signet ring cells		
Yes	12	52.2
No	11	47.8
Histological subtype		
Diffuse	5	21.7
Intestinal	2	8.7
NOS	16	69.6
Number of metastatic sites		
1	5	21.7
2	10	43.5
3	8	34.8
Visceral metastases[b]		
Yes	13	56.5
No	10	43.5
Prior treatment		
Surgery	5	21.7
Chemotherapy	0	0
Radiotherapy	0	0

NOS, not otherwise specified.
[a]Weight loss of more than 3 kg.
[b]Involvement of the liver or lungs.

Table 2 Treatment delivery ($n=23$)

	Number	%
Cycles administered		
Mean	10.7	
Median	10.0	
Range	1–24	
Duration of treatment (months)		
Median (range)	8.7 (1.0–16.0)	
Cycles including all three drugs		
Mean	8.2	
Median	7.0	
Range	1–17	
Dose intensity (mg/m^2 week), median[a]		
Docetaxel	19.7	78.8
CDDP	20.0	80.0
5-FU	1026	82.1
Dose reduction (at least once), No. of pts		
Any drug	20	86.9
Docetaxel	19	82.6
CDDP	20	86.9
5-FU	19	82.6
Mean cycle of dose reduction		
First dose reduction of docetaxel	3.0	
First dose reduction of CDDP	2.7	
First dose reduction of 5-FU	3.6	
Maximal dose reduction of docetaxel	5.0	
Maximal dose reduction of CDDP	6.2	
Maximal dose reduction of 5-FU	6.7	
Treatment delay (at least once), No. of pts	10	43.5
Mean cycle of treatment discontinuation		
Docetaxel	10.7	
CDDP	8.2	
5-FU	10.7	
Reason for treatment discontinuation		
Progressive disease	14	60.9
Drug holiday[b]	6	26.1
Toxicity	3	13.0

5-FU, 5-fluorouracil; CDDP, cisplatin; pts, patients.
[a]Actual vs. planned dose intensities (%).
[b]Temporary treatment cessation, without disease progression or unacceptable toxicity.

months after they had previously had a 'drug holiday'. As expected, the number of cycles in which all three drugs were delivered was smaller, with an average of 8.2 cycles per patient (range, 1–17) and a total of 188 cycles for the entire group. Dose reductions were required in 20 patients (87%); on average, the first dose reduction occurred in the third cycle and the maximal dose reduction, that is, the point where no further dose reductions were required, occurred in the sixth cycle. Although CDDP was usually the first drug to be dose reduced, docetaxel was usually the first drug to reach its maximal dose reduction, that is, to be reduced to its lowest dose delivered. Treatment delays, mostly for toxicity, occurred in 10 patients (43%). Despite frequent dose delays and reductions, the overall actual dose intensities of the three drugs were high, ranging between 79 and 82% of the planned dose intensities. The main reason for treatment discontinuation was progressive disease (61%), followed by 'drug holiday' after prolonged remission (26%) and toxicity (13%). CDDP was usually discontinued earlier than 5-FU and docetaxel, on average after 8.2 cycles compared with 10.7 cycles for the other drugs, usually due to the development of peripheral neuropathy.

Safety

All patients were evaluable for toxicity. Grade ≥ 3 adverse events were documented in all patients, but these were usually either uncomplicated neutropenia or nausea and vomiting, which were later controlled effectively by premedication with aprepitant (Table 3). The most common severe (grade ≥ 3) hematological toxicity was neutropenia (78%), complicated by fever in 22% of the patients, followed by leukopenia (48%). The use of granulocyte colony-stimulating factors, either as primary or as secondary prophylaxis, was relatively uncommon (22%). The most frequent severe nonhematological toxicities were nausea (52%) and vomiting (48%), but the extent of these toxicities was substantially reduced at the later period of the study, with the routine use of aprepitant. Other common severe nonhematological toxicities were diarrhea, stomatitis, fatigue, and neurotoxicity (39, 30, 30, and 35%, respectively).

There was one treatment-related death (4%), presumably due to propagating thrombosis around the central catheter. Hospital admissions or treatment discontinuation due to toxicity occurred in 35 and 13% of the patients, respectively.

Table 3 Most common toxicities ($n=23$)

	Any grade	Grade 3 or 4
Toxicity	Number[a] (%)	Number[a] (%)
Hematological		
Neutropenia	22 (95.6)	18 (78.3)
Neutropenic fever	5 (21.7)	5 (21.7)
Leucopenia	19 (82.6)	11 (47.8)
Anemia	21 (91.3)	3 (13.0)
Thrombocytopenia	7 (30.4)	1 (4.3)
Bleeding	2 (8.7)	0 (0.0)
Nonhematological		
Nausea	23 (100.0)	12 (52.2)
Vomiting	19 (82.6)	11 (47.8)
Fatigue	16 (69.6)	7 (30.4)
Diarrhea	15 (65.2)	9 (39.1)
Stomatitis	15 (65.2)	7 (30.4)
Neurotoxicity	10 (43.5)	8 (34.8)
Anorexia	9 (39.1)	3 (13.0)
Creatinine	5 (21.7)	0 (0.0)

[a]Number of patients experiencing the toxicity.

Efficacy

Twenty-two patients were evaluable for response; one patient, who discontinued treatment after one cycle due to toxicity, was not evaluated for response. Complete response (CR) was documented in four patients (18%) and partial response (PR) in nine (41%). No formal confirmation of response according to Response Evaluation Criteria In Solid Tumors was obtained, but as assessed clinically, CR and PR lasted for over 4 weeks in most patients. Seven patients (32%) had stable disease (SD) for at least 2 months. Therefore, the objective response rate (CR + PR) was 59% and the disease control rate (CR + PR + SD) was 91%. Some of the responses were very durable. Accordingly, five patients (22%) enjoyed prolonged 'drug holiday' periods, lasting for a median of 20 months (range, 7–53 +), including two (9%) that remain in unmaintained CR 42 + and 53 + months from diagnosis, respectively.

Clinical improvement in pain was noted in 67% of the patients, weight gain in 32%, and overall improvement in PS, that is, decrease in the initial PS score, in 48%. Altogether, 19 of the 21 symptomatic patients at the initiation of DCF (90%) derived CB from this treatment.

At the time of analysis, with a median follow-up of 44 months (range, 33–53), 19 patients (82%) have died of the disease, two (9%) are alive with disease, and two (9%) remain in prolonged unmaintained CR. The median OS of the entire group was 12.8 months (range, 1.7–61 + months) and the median PFS was 10.0 months (range, 1.3–61 + months). The 2-year OS rate reached 22% and the 3-year OS rate was 17%.

Comparison with a historical control

We recently reported our experience in treating 45 AGC patients using a combination of 5-FU and leucovorin (LV) weekly, and CDDP biweekly, known as the C-AIO regimen [22]. This regimen served as the standard protocol at our institution until it was recently replaced by DCF. The C-AIO regimen consisted of a weekly treatment for a total of 6 weeks, followed by a 2-week rest period. To confirm the safety of the regimen, the first 18 patients received lower doses of the drugs (5-FU 2000 mg/m^2, LV 500 mg/m^2, CDDP 40 mg/m^2), whereas the other 27 patients received the standard doses (5-FU 2600 mg/m^2, LV 500 mg/m^2, CDDP 50 mg/m^2).

The difference between the two patient cohorts, the earlier C-AIO group and the present DCF group, was the fact that those in the DCF group were not reimbursed for the docetaxel; thus, the C-AIO group could serve as a historical control, yet without randomization or initial statistical planning. As expected, the patients' characteristics in both cohorts were similar, although there were more men (78 vs. 55%) and patients with good PS (96 vs. 76%) in the DCF group (Table 4). DCF was clearly superior to C-AIO in all outcome endpoints ($P < 0.05$ for all endpoints). For example, the median PFS and OS were 10.0 versus 5.6 months ($P = 0.004$) and 12.8 versus 8.2 months ($P = 0.008$), respectively. The Kaplan–Meier estimates for OS and PFS are shown in Figs 1 and 2. Nevertheless, DCF was more toxic, with higher rates of severe toxicities (100 vs. 48%) and hospitalizations (35 vs. 22%). Despite this, there was no apparent difference in the rates of toxic deaths or treatment discontinuations.

Discussion

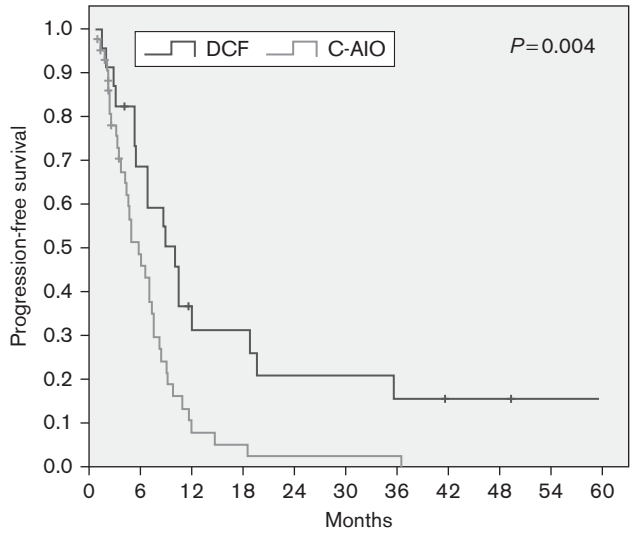
Docetaxel is clearly a potent drug against AGC, as demonstrated by a series of phase II studies and a pivotal

Table 4 Comparison between the DCF and the C-AIO regimens at RMC

	C-AIO ($N=45$)	DCF ($N=23$)
Patient and tumor characteristics		
Median age (years)	67	63
Male	55%	78%
Performance status 0–1	76%	96%
Metastatic disease	98%	100%
Poor differentiation	78%	87%
Toxicity		
Grade $\geq$ 3 toxicities		
Any	48%	100%
Neutropenia	20%	78%
Leukopenia	15%	48%
Neutropenic fever	9%	22%
Anemia	4%	13%
Nausea	22%	52%
Vomiting	15%	48%
Diarrhea	15%	39%
Stomatitis	2%	30%
Hospitalizations	22%	35%
Toxic deaths	0%	4%
Discontinuation because of toxicity	13%	13%
Outcome		
Response rate	33%	59%
Median PFS (months)	5.6	11.4
Median OS (months)	8.2	13.8
2-year survival	2%	26%
3-year survival	0%	17%

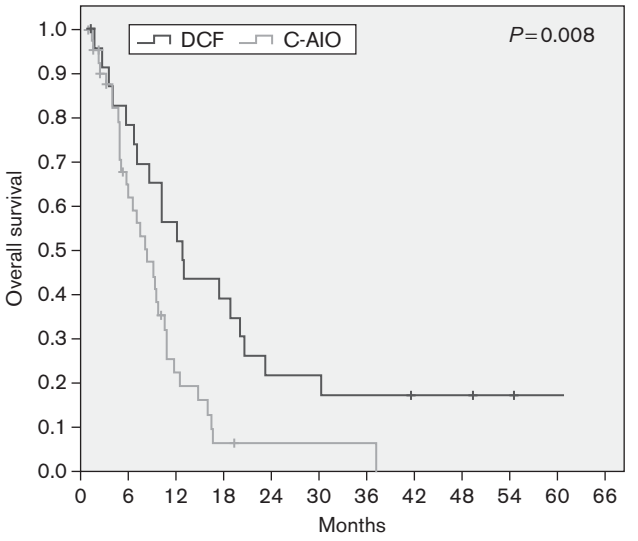
C-AIO, weekly 5-fluorouracil and leucovorin, and biweekly cisplatin; DCF, docetaxel, cisplatin and 5-fluorouracil; OS, overall survival; PFS, progression-free survival; RMC, Rabin Medical Center.

Fig. 1



DCF versus C-AIO: progression-free survival. C-AIO, weekly 5-fluorouracil and leucovorin, and biweekly cisplatin; DCF, docetaxel, cisplatin and 5-fluorouracil.

Fig. 2



DCF versus C-AIO: overall survival. C-AIO, weekly 5-fluorouracil and leucovorin, and biweekly cisplatin; DCF, docetaxel, cisplatin and 5-fluorouracil.

phase III study, V-325 [10,11,13–19]. The randomized V-325 study has shown that the addition of docetaxel to the standard CF regimen resulted in superiority of the triplet regimen, DCF, in all efficacy endpoints, particularly doubling of the 2-year survival rate (18 vs. 9%), although at the cost of a higher toxicity profile [19]. In light of the significant toxicity of DCF, and despite the appreciation of its high potency against AGC, the medical community remained largely reluctant to adopt the DCF regimen, and the role of docetaxel in this disease remains to be defined.

Impressed by the efficacy of DCF in the V-325 study, we assumed that we could manage to overcome its toxicity by closely monitoring our patients and adjusting treatment as needed. With this policy, DCF has become our standard regimen. The current study is a retrospective analysis of our experience with the initial 23 AGC patients treated with DCF at our institution. The aim of this analysis was to evaluate this regimen outside the framework of a clinical study, and, more importantly, to test our working hypothesis that by close patient follow-up, we should be able to exploit the benefits of DCF and minimize its toxicity. Our study largely confirms previous data on the activity and toxicity of DCF. Using a very recent historical control ($n = 45$), a cohort of consecutive patients treated at our institution by our former standard regimen, C-AIO (a combination of 5-FU and LV weekly, and CDDP biweekly), DCF was found to be substantially more effective, although more toxic (Table 4). With similar patient and tumor characteristics, all efficacy outcomes in this exploratory comparison were considerably superior in the DCF cohort. Most importantly, only DCF was associated with a small, yet distinct cohort of long-term survivors, reflected by the 22% 2-year survival and 17% 3-year survival rates observed with this regimen. Although DCF was associated with significantly higher rates of grade ≥ 3 toxicities and hospitalizations, this did not translate into higher rates of toxicity-related deaths or treatment discontinuations.

In light of the substantial toxicity of DCF, various attempts have been made to lessen its toxicity by modifying its dose and schedule. Comparing the results of DCF in our study, DCF in V-325, and several DCF modifications (Table 5), two main observations arise. First, the activity noted in our study is in the upper range of earlier reports. Most studies reported a median PFS of 5–6 months and a median OS of 9–11 months. Our results, median PFS and OS of 10.0 and 12.8 months, respectively, are considerably higher and are similar to only those reported by Lorenzen *et al.* and Shah *et al.* [23,24]. However, as opposed to ours, both studies included selected phase II populations and also patients with esophageal cancer. Second, similar to the efficacy, even the toxicity in our study is in the upper range of previous reports. Of note, all three studies with docetaxel administration every 3 weeks, including ours ([19,25], current study), were associated with higher rates of severe toxicities, most notably neutropenia, compared with weekly or biweekly DCF modifications. Although most DCF modifications to date involved introducing changes in the regimen's mode of administration, recent reports describe the potential benefits of replacing CDDP by oxaliplatin [26] or of replacing 5-FU by capecitabine [27]. On the basis of nonrandomized phase

Table 5 Different docetaxel-based triplet regimens in advanced gastric cancer

Author[a] (year) (Ref)	Regimen	No. (met.)	ORR (%)	PFS (months)	OS (months)	Neutr. grade ≥ 3 (%)	Neutr. fever (%)	Hospitalizations (%)	Toxic deaths (%)
Van Cutsem *et al.* [19]	*Standard DCF (Q:3w)* Docetaxel 75 mg/m^2, day 1 CDDP 75 mg/m^2, day 1 5-FU 750 mg/m^2, days 1–5	221 (96%)	37	5.6	9.2	82	29	NA	4
Lorenzen *et al.*[b,c] [23]	*C-AIO-based (Q:7w)* Docetaxel 40 mg/m^2, days 1, 15, 29 CDDP 40 mg/m^2, days 1, 15, 29 5-FU 2000 mg/m^2, weekly	60 (60%)	47	8.1	15.1	22	5	NA	NA
Shah[b] *et al.* [24]	*De Gramont-based (Q:2W)* Docetaxel 40 mg/m^2, day 1 CDDP 40 mg/m^2, day 3 Leucovorin 400 mg/m^2, day 1 5-FU 400 mg/m^2, day 1 5-FU 1000 mg/m^2, days 1,2	30 (NA)	50	8.6	14.9	38	4	20	0
Park *et al.* [25]	*Low-dose DCF (Q:3w)* Docetaxel 50 mg/m^2, day 1 CDDP 80 mg/m^2, day 1 5-FU 1200 mg/m^2, days 1–3	47 (100%)	40	4.6	9.7	68	26	NA	2
Tebbut *et al.* [27]	*Weekly DCF (Q:3w)* Docetaxel 30 mg/m^2, days 1,8 CDDP 60 mg/m^2, day 1 5-FU 200 mg/m^2, days 1–21	50 (96%)	47	5.9	11.2	10	6	NA	0
Overman *et al.* [28]	*Weekly DCF (Q:8w)* Docetaxel 20 mg/m^2, weekly $\times 6$ CDDP 20 mg/m^2, weekly $\times 6$ 5-FU 350 mg/m^2, weekly $\times 6$	95 (66%)	34	4.1	8.9	4	0	23	0
Current study	*Standard DCF (Q:3w)* Docetaxel 75 mg/m^2, day 1 CDDP 75 mg/m^2, day 1 5-FU 750 mg/m^2, days 1–5	23 (100%)	59	10.0	12.8	78	22	35	4

C-AIO, weekly 5-fluorouracil and leucovorin, and biweekly cisplatin; CDDP, cisplatin; DCF, docetaxel, cisplatin and 5-fluorouracil; 5-FU, 5-fluorouracil; met., metastatic disease; NA, not available; Neutr., neutropenia; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

[a]The first study (Van Cutsem *et al.*) was a phase III study; the rest (Lorenzen *et al.*, Park *et al.*, Tebbut *et al.*, and Shah *et al.*) were phase II studies, apart from the last two (Overman *et al.*, current study), which were retrospective.

[b]The study also included patients with esophageal cancer.

[c]PFS and OS of patients with metastatic disease.

II data, such strategies clearly represent additional alternatives to the original DCF regimen.

There are several potential explanations for the high activity of DCF in our study. The first derives from the obvious limitations of small retrospective studies like ours, with the potential patient selection and biases. For example, our cohort included patients who purchased docetaxel on their own, patients who may be relatively healthier and more motivated than the average. Indeed, 96% of our patients had a good PS at the onset of treatment. Second, the close monitoring and intensive treatment modifications, together with a more 'tailored' dose reduction strategy, enabled prolonged exposure to DCF. For example, our patients received a median of seven cycles of the triplet regimen compared with six in V-325. In most other studies, patients were treated even for less than 3 or 4 months [23,25,27,28]. The effect of the close monitoring on overall treatment exposure is further supported by the higher rate of toxicity-related treatment discontinuations in V-325 compared with our study (27 vs. 13%). Finally, close monitoring also enables early detection of progressive disease and initiation of second-line treatment. Although second-line information in AGC is very limited, as much as 80% of our patients were able to receive salvage treatment upon progression. A pooled analysis of data from 1080 patients from phase III studies testing 5-FU-based regimens suggested that only about 20% of the patients with AGC who progress on first-line treatment go on to receive second-line treatment [29]. The impact of salvage treatment in AGC was suggested by the recent randomized phase III trial that demonstrated a survival benefit in second-line treatment with irinotecan over best supportive care [30].

The high rate of severe toxicities in the present study, compared with others, including V-325, may at least in part reflect the different pattern of data collection between multi-institutional and multinational phase III studies and studies summarizing a single institution's experience, like the current one. In support of this is the fact that the objective toxicities in V-325, for example, are very similar to ours, whereas the rates of subjective toxicities, such as gastrointestinal adverse reactions, are much higher in our study. In line with this is the much higher rate of treatment discontinuations due to toxicity in V-325 (27 vs. 13%). Nevertheless, although the toxicity noted in the present study seems to be within the overall

range of other triweekly DCF-based regimens [19,27], we cannot exclude the possibility that the strict drug administration in our study, for longer periods, may result in somewhat higher overall toxicity.

This study provides some insight into possible ways to minimize adverse effects from the toxic, yet highly effective DCF regimen. Although all patients experienced some grade ≥ 3 toxicity, most of them managed to continue treatment for long periods (median = 8.7 months) while gaining CB (90%). Very few discontinued treatment because of toxicity (13%), and there was one death, which may have been treatment related. In our view, the key to achieving these results is close patient monitoring, which enables early detection of toxicities and immediate dose modifications. This is manifested by the frequent dose reductions, in 87% of patients, and the fact that, on average, these were already initiated in the third cycle and reached their maximum in the sixth; the last four or five cycles usually did not require any additional dose reductions. Despite these dose reductions, the dose intensities of all drugs were high, approximating 80% of those intended. This may guide us in further development of DCF. If administering 80% of the planned dose intensities of DCF provided high activity of this regimen in our study, apparently not inferior to any other mode of delivering it, then perhaps this should be the dose intensity to aim for in future trials. The fact that the best results so far with DCF-based chemotherapy were obtained using regimens that deliver about 80% of the dose intensities of docetaxel and CDDP in the parent regimen, supports this hypothesis (Table 1).

Another interesting finding from the current study is the ability of some of our patients to enjoy prolonged periods of 'drug holidays'. As described (Patients and Methods), our policy was to offer temporary treatment cessation, until disease progression, after extended remissions, of around 12 months. We were surprised by the fact that five of the six patients (83%) who initiated 'drug holidays' in our cohort remained in unmaintained remissions long afterward, for a median of 20 months. Furthermore, two patients (9% of the study group) remain without disease progression approximately 4 years from diagnosis. We are not aware of any other information on the optimal duration of chemotherapy, nor on the role of 'drug holidays', in AGC. Our findings, although intriguing, only emphasize the need for more extensive data on these issues.

In summary, the DCF regimen is indeed associated with a high rate of side effects in our experience, but these are usually controllable. In our small cohort, we observed an impressive activity of DCF, in the higher range reported for this or any other chemotherapeutic regimens in this disease. Possible ways to maximize its benefit and minimize its toxicity were suggested. In our view, DCF should represent a valid treatment option in AGC and a platform for future regimens.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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