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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

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Background: A phase I–II multicenter trial was conducted to define the maximum tolerated dose (MTD) according to tolerance and toxicity (primary objective), as well as to describe the clinical activity, in terms of response and survival (secondary objectives), of a combination of 5-fluorouracil (5-FU) in protracted continuous intravenous infusion (p.i.v.) with docetaxel and cisplatin for patients with advanced gastric cancer.

Patients and methods: Patients with measurable unresectable and/or metastatic gastric carcinoma, World Health Organization performance status ≤1, normal hematological and renal functions, adequate hepatic function and not pretreated for advanced disease by chemotherapy, received up to eight cycles of a combination of docetaxel on day 1, cisplatin on day 1 and 5-FU p.i.v. on days 1–14 (TCF) every 3 weeks, which was escalated up to the MTD, defined by the occurrence of dose-limiting toxicity in two patients in one dose level.

Results: Fifty-two patients were accrued and treated (43 in the phase I part of the trial and nine additional at the recommended dose level). A median of five cycles/patient was given. The recommended dose of TCF was docetaxel 85 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1 and 5-FU p.i.v. 300 mg/m^2/day on days 1–14. Grade ≥3 toxicities were neutropenia 79%, alopecia 46%, fatigue 23%, mucositis 10%, diarrhea 19%, nausea/vomiting 13%, neurological 4% and palmar-plantar 2%. Ten non-fatal febrile neutropenia episodes were recorded in eight patients. There were no treatment-related deaths. Among 41 patients with measurable disease (79%), we observed one complete and 20 partial responses for an overall intent-to-treat response rate of 51% (95% confidence interval 35–67%). Five patients (20%) had stable disease for ≥12 weeks (four cycles). The median overall survival was 9.3 months.

Conclusions: 5-FU p.i.v. at 300 mg/m^2/day for 2 weeks out of three could be safely added to the docetaxel–cisplatin (TC) combination, but the dose of docetaxel had to be reduced to 75 mg/m^2 in a subsequent phase II trial. This drug regimen seems to be very active in advanced gastric cancer. Comparison with both TC and ECF in a randomized SAKK trial is ongoing.

Key words: chemotherapy, docetaxel, gastric cancer

Introduction

Despite a decline in its incidence, gastric carcinoma remains one of the 10 leading causes of death by neoplasia in Western countries [1]. Surgery remains the treatment of choice for cure. Unfortunately, more than half of patients present with stage III or IV disease, which precludes resection. Up to relatively recently, chemotherapy has generally been considered as ineffective in this disease, and was used as a palliative measure for advanced cases only.

Over the last 6–7 years promising new drug regimens have been proposed in the treatment of this disease. Epirubicin–cisplatin–5-fluorouracil (5-FU) in continuous infusion (ECF) was developed in the UK. Compared with 5-FU–adriamycin–methotrexate (FAMTX) in a phase III randomized trial, ECF yielded a superior response rate (45% versus 21%) and superior median time to pro-

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gression (7.4 versus 3.4 months), with better overall survival. These data led the investigators to propose ECF as standard practice [2]. An intensive weekly chemotherapy called PELF (cisplatin, epirubicin, 5-FU and leucovorin) was studied in Italy and was reported to yield a 62% response rate in a large phase II trial enrolling 105 patients [3]. However, toxicity was substantial, requiring regular use of colony stimulating factors.

Several promising new drugs belonging to the taxane and campothecine groups now have been studied and introduced in the systemic therapy of this disease [4]. Among them, docetaxel (60–100 mg/m^2) as a single agent was shown in three separate phase II studies to yield a response rate of 17–24% [5–7]. These data prompted us to investigate docetaxel in combination with cisplatin (TC) in a phase II trial in gastric carcinoma [8]. With an objective response rate of 56% in 48 treated patients, it was concluded that TC was active in advanced gastric cancer. Despite its relatively high hematotoxicity, this regimen was well tolerated and could be recycled as originally planned in 78% of the cases.

Based on these results we felt TC was promising enough to serve as the core for a new combination involving a third drug. Because of the relatively high hematotoxicity induced by docetaxel, it was felt that only a moderately myelotoxic drug could be added to this regimen without requiring an important dose reduction of docetaxel and cisplatin. 5-FU given in protracted continuous infusion may be an interesting option since it is known to induce very little myelotoxicity, if any. Furthermore, the positive results obtained with the ECF regimen in advanced gastric cancer suggest that protracted continuous infusion might be the most efficient way of administering 5-FU in this disease [9, 10].

A phase I trial exploring the combination of docetaxel and 5-FU showed that docetaxel at 85 mg/m^2 with 5-FU given in continuous infusion over 5 days at 750 mg/m^2/day was tolerable without any major mucosal toxicity or any substantial increase in docetaxel-induced myelotoxicity [11]. This indicates that the addition of 5-FU in protracted continuous infusion to docetaxel and cisplatin may be reasonable and feasible.

We report the results of a phase I–II trial investigating the maximum tolerated dose (MTD), tolerability and, as secondary end point, the efficacy of the combination of docetaxel, cisplatin and 5-FU in protracted continuous infusion (TCF) in inoperable advanced gastric cancer.

Patients and methods

Patients with metastatic or locally advanced adenocarcinoma of the stomach not previously treated palliatively by systemic therapy and not amenable to curative resection were enrolled in this trial. The patients were required to have a World Health Organization (WHO) performance status ≤1, normal blood counts, creatinine clearance ≥60 ml/min, adequate liver function tests [bilirubin <1× upper limit of normal (ULN), AST/ALT <2.5× ULN], no history of anaphylaxis and no peripheral neuropathy of any origin greater than grade 1. Patients with bidimensionally measurable or simply evaluable disease were eligible (elevated tumor markers or unidimensionally measurable disease).

The treatment consisted of docetaxel on day 1 in a 1 h intravenous (i.v.) infusion followed by cisplatin on day 1 in a 4 h i.v. infusion and 5-FU in protracted continuous infusion (p.i.v.) from day 1 to day 14, according to the dose levels described in Table 1. Day 1 of each treatment cycle was given on an in-patient basis in order to ensure correct hyperhydration for cisplatin administration. Patients were to be treated at the same dose level in groups of three. If no dose-limiting toxicity (DLT), defined as grade 4 hematological toxicity with fever (single oral temperature >38.5°C, or three elevations to 38°C during a 24-h period) and/or grade 3 toxicity of any other kind apart from alopecia, occurred, the next three patients were treated at the next higher dose level. If one DLT occurred in cycle one, three additional patients had to be treated at the same dose level. If two or more DLTs occurred at a given dose level, the MTD would be considered to be reached and the dose escalation had to be stopped. The dose just below would be considered to be the recommended dose for future evaluation in phase II trials. All patients received a standard supportive regimen consisting of hyperhydration (3 l of normal saline or 5% dextrose/24 h) during each course of treatment and dexamethasone (Fortecortine®) 8 mg orally administered 12 and 6 h before docetaxel infusion and 8 mg twice daily for an additional 4 days. 5-HT3 inhibitors were used for emesis prophylaxis. The use of hematological growth factors was not permitted during the first cycle of treatment, but was allowed thereafter if needed.

Table 1. Dose escalation scheme

Level	Cisplatin, mg/m^2	Docetaxel, mg/m^2	5-FU p.i.v. 2 of 3 weeks, mg/m^2/day
1	60	70	200
2	60	85	200
3	75	85	200
4	75	85	225
5	75	85	250
6	75	85	275
7	75	85	300
8	75	85	350

p.i.v., protracted continuous infusion; 5-FU, 5-fluorouracil.

After completion of eight cycles of treatment or discontinuation of chemotherapy, disease status was re-evaluated every 3 months. Toxicity was assessed according to WHO grading for each cycle.

The next cycle of treatment could be postponed for no more than 2 weeks to allow the resolution of toxicities. Patients were to be taken off trial treatment in case of delays longer than 2 weeks. A 15 mg dose reduction of docetaxel was mandatory in case of prolonged grade 4 neutropenia (>7 days), grade 4 thrombocytopenia, grade ≥2 liver toxicity and grade 3 cutaneous toxicity. A further 25% dose reduction was foreseen in the event that the same type/grade toxicity was observed in subsequent cycles. If grade 2 neurotoxicity was recorded the dose of docetaxel was to be reduced by 15 mg, along with a 15 mg reduction in cisplatin dose. Cisplatin was reduced when the creatinine clearance dropped below 60 ml/min, and discontinued if it decreased below 40 ml/min. 5-FU was due to be reduced by 50 mg/m^2/day in case of grade 2 diarrhea, mucositis or palmar-plantar syndrome and by 75 mg/m^2/day in case of grade 3 palmar-plantar syndrome and by 100 mg/m^2/day at the occurrence of grade 3 mucositis or diarrhea. Trial treatment was stopped in case of persistent grade 3 liver toxicity, grade ≥3 neuropathy, grade 4 cutaneous toxicity, grade 3 anaphylactoid reaction and if a toxicity recurred despite dose reductions.

The primary objective of the trial was to define the MTD of the regimen under investigation, and all evaluations were purely descriptive. Response, a secondary end point, was assessed according to WHO criteria at the end of every alternate cycle of treatment. Survival, another secondary end point, was determined using the Kaplan–Meier method. The trial was approved by the

Table 2. Patient characteristics

Characteristic	*n* (%)
No. of patients	52
Age, years [median (range)]	58 (30–70)
Sex (male/female)	37/15 (71/29)
WHO performance status (0/1/2)	26/23/3 (50/44/6)
Appetite, good/fair/none	33/15/4 (63/29/8)
Weight change in last 3 months (kg)	
Median (range)	–2 (–15 to +4)
Previous surgery	19 (37)
Previous adjuvant chemotherapy	3 (6)
No. of affected disease sites per patient	
Median (range)	3 (1–5)
Patients with locally advanced disease only	7
No. of disease sites per patient	
1	8
2	15
3	17
≥4	12
Disease sites (measurable and not measurable)	
Lymph nodes	35
Stomach	36
Liver	26
Peritoneum	20
Lung	8
Bone	4
Others	11
Bidimensionally measurable disease	41 (79)

WHO, World Health Organization.

ethics review boards of all participating institutions. All patients gave written informed consent.

Results

Fifty-two patients were enrolled in the trial. One further patient was recruited, but refused participation prior to any trial treatment, and was excluded from all analyses. Patient characteristics are summarized in Table 2. There were 37 males and 15 females, whose performance status was 0 (50%), 1 (44%) and 2 (6%). Thirty-seven per cent of the patients had previously undergone a surgical resection of their primary tumor (total or subtotal gastrectomy), and three (6%) had received neo-adjuvant or adjuvant chemotherapy. At the time of inclusion into the trial, patients had lost a median of 2 kg of weight over the last 3 months. All 52 patients were evaluable for toxicity. Forty-one patients (79%) had bidimensionally measurable disease, whereas 11 had evaluable disease only.

Forty-three patients were accrued during the dose-finding part of the trial and nine additional patients were enrolled to ascertain the safety of the recommended dose level. Table 3 presents the accrual and tolerance per dose level. Twelve patients had to be enrolled in dose level 1 before escalation. This was due to the occurrence in the first six patients enrolled of one episode of febrile neutropenia (FN) and of one occurrence of borderline grade 3 diarrhea. After discussion with the concerned investigators, this latter toxicity was considered to be too ambiguous to consider it as a DLT and consider this dose level as MTD. Therefore, an amendment was issued and submitted to all ethical comittees to allow the accrual of six additional patients at this dose level to resolve these ambiguities and better assess the toxicity. Again, DLTs were observed in two patients, one FN and one with grade 3 self-resolving abdominal pain of uncertain origin. The relationship to the treatment of the latter toxicity remained uncertain. It was therefore decided to start dose escalation. The original protocol was designed with five dose levels. Three additional dose levels incrementing the 5-FU dosage had to be subsequently added, and the MTD was reached at dose level 8 (two DLTs in four patients). Dose level 7 was therefore the recommended regimen with docetaxel 85 mg/m^2 on day 1, cisplatin 75 mg/ m^2 on day 1 and 5-FU 300 mg/ m^2/day on days 1–14.

Table 3. Dose-limiting toxicities (DLTs) according to dose level

Dose levels	No. of patients	DLTs (cycle 1)	Median cycles/ patient
1	12	Febrile neutropenia (*n* = 2)	6
		Grade 3 abdominal pain (*n* = 1)	
		Grade 3 diarrhea (*n* = 1)	
2	6	Grade 3 diarrhea and nausea (*n* = 1)	4
3	6	Febrile neutropenia (*n* = 1)	6
4	3	None	8
5	6	Febrile neutropenia (*n* = 1)	2.5
6	3	None	6
7	3	None	6
8	4	Febrile neutropenia (*n* = 1)	4.5
		Grade 3 mucositis and diarrhea (*n* = 1)	
		≥2 DLTs resulted in stop of dose escalation	

The toxicity analysis is based on 52 patients and 255 cycles of treatment. Overall this regimen was well tolerated and a median of five cycles per patient could be administered. Six patients completed the planned eight cycles of treatment. Twenty-one patients stopped therapy beforehand due to progressive disease, 20 stopped for personal reasons (nine patients), because of toxicity (seven patients) or by physician's decision (four patients), and three were referred to surgery for gastrectomy after response to treatment. Two patients died early from disease. In 55 cycles out of 255 (22%) the treatment was delayed by more than 3 days.

Table 4 summarizes grade 3–4 hematological toxicities per patient and per cycle. Despite the relatively frequent occurrence of

Table 4. Grade 3/4 hematoxicity per cycle and per patient

Hematological toxicity	% of 255 cycles		% of 52 patients	
	Grade 3	Grade 4	Grade 3	Grade 4
Leukocytopenia	19	2	42	8
Granulocytopenia	28	22	27	52
Thrombocytopenia	0	0	0	0

Table 5. Non-hematological toxicity as percentage of 52 patients

Toxicity	Grade			
	1	2	3	4
Nausea/vomiting (%)	33	31	12	2
Diarrhea (%)	33	33	17	2
Mucositis (%)	40	27	8	2
Fatigue (%)	29	42	21	2
Plantar-palmar syndrome (%)	21	8	2	–
Alopecia (%)	10	38	44	2
Neurological (%)	33	12	4	–
Fluid retention[a] (%)	27	2	–	–
Hypersensitivity reaction[a] (%)	23	2	2	–

[a]Grades: 1, mild; 2, moderate; 3, severe.

Table 6. Non-hematological toxicity as percentage of 255 cycles of treatment

Toxicity	Grade			
	1	2	3	4
Nausea/vomiting (%)	29	13	3	0.4
Diarrhea (%)	21	10	4	0.4
Mucositis (%)	18	10	3	0.4
Fatigue (%)	42	20	6	0.4
Plantar-palmar syndrome (%)	6	3	0.4	–
Alopecia (%)	14	33	31	–
Neurological (%)	18	5	1	–
Fluid retention[a] (%)	21	0.4	–	–
Hypersensitivity reaction[a] (%)	20	0.4	0.4	–

[a]Grades: 1, mild; 2, moderate; 3, severe.

grade 3/4 granulocytopenia, only 10 episodes of non-fatal FN were seen in eight patients (15% of the patients, 4% of the treatment cycles). Other main toxicities are reported per patient in Table 5 and per cycle in Table 6. Four patients presented catheter-related complications. One patient presented with an infection of the catheter which had to be removed. The three other patients presented with axillary venous thrombosis which necessitated anticoagulation with coumadine. One patient died from progressive disease 21 days after having received treatment in cycle 3. Another patient died 31 days after his last dose of chemotherapy with evidence of peritonitis secondary to intestinal perforation of unclear origin. There were no other deaths during the treatment period that could be considered to be related to the trial treatment. Other recorded grade 3/4 toxicities were two episodes of transitory loss of consciousness in one patient during cycles 3 and 6, five episodes of self-resolving abdominal pain and epigastralgia of uncertain origin, one episode of subileus, one occurrence of grade 3 hypertonia, and one aggravation of Alzheimer's disease after the first cycle of treatment.

Table 7. Tumor response (patients with bidimensionally measurable disease)

Overall best response	No. of patients (41) (%)
CR	1 (2)
PR	20 (49)
PR not confirmed	3 (7)
SD (for ≥4 cycles)	5 (12)
PD	10 (25)
Not evaluable	2 (5)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

At the end of the dose-finding part of the study, nine additional patients were enrolled to ascertain the safety of the recommended dose level. A separate analysis of the data from the 12 patients treated at the recommended dose level 7 (three patients accrued during the dose-finding part plus nine additional patients) was performed. The toxicity and tolerance were similar to what was observed in the whole trial. Notably, rates of grade 3/4 maximal hematological toxicities were 25%/58% in the 12 patients on dose level 7, and 33%/52% in the whole patient population, while grade 3/4 maximum non-hematological toxicities were 33%/8% and 28%/6%, respectively.

Although this was not an inclusion requirement, 41 patients (79%) had bidimensionally measurable disease, allowing us to make an accurate response rate assessment (Table 7). One complete response (CR) and 23 partial responses (PR), including three unconfirmed, were recorded, for a response rate of 59% [24 of 41 patients; 95% confidence interval (CI) 42–74%]. Five patients had stable disease during at least four cycles of treatment, 10 patients progressed immediately during therapy, and two discontinued treatment after one cycle only due to excessive toxicity. Among the 11 patients with evaluable only disease, six were considered as responding to the treatment. One patient had his primary tumor resected after six cycles of treatment. The median overall survival was 9.3 months (Figure 1) with a 95% CI of 7.7–10.8 months. Forty-seven patients had died at the time of the present evaluation.

Discussion

This trial shows that 5-FU p.i.v. at 300 mg/m^2/day for 2 weeks out of 3 can be added to TC without any alteration of the dose levels of docetaxel and cisplatin. It also confirms the results of our earlier phase II trial with TC regarding the feasibility, the relative good

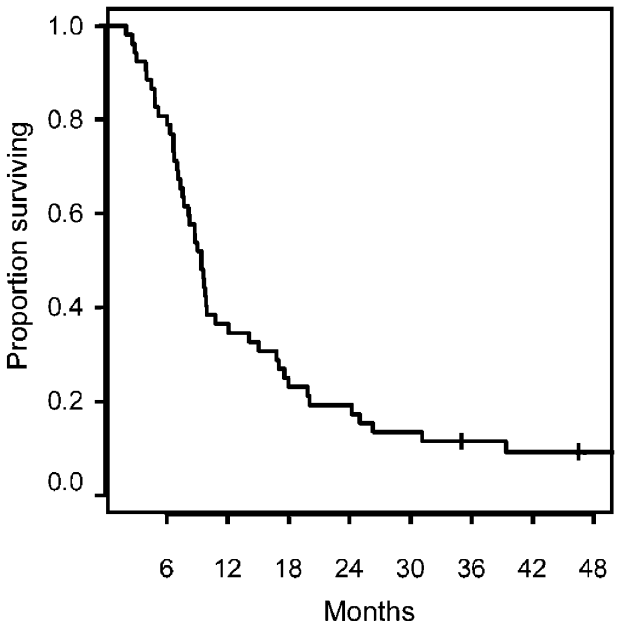

Figure 1. Overall survival of all patients.

tolerability and the activity of docetaxel–cisplatin based combination in advanced gastric carcinoma [8].

As originally expected, the addition of 5-FU p.i.v. to TC did not increase the hematotoxicity compared with what we observed previously with TC alone [8]. Eight of the 52 enrolled patients in this trial presented 10 episodes of non-fatal FN, while we observed nine such episodes in our previous TC trial enrolling 48 patients. With the addition of 5-FU p.i.v., the main changes in the non-hematological toxicity were observed in the occurrence of grade 1/2 diarrhea and mucositis, and in the appearance of plantar-palmar syndrome. All three toxicities are known to be associated with 5-FU. The incidence per cycle of grade 1/2 diarrhea increased from 5%/5% with TC to 21%/10% with TCF, while the occurrence of grade 3 diarrhea rose from 2% to 4%, and grade 4 episodes remained the exception. Similarly, the occurrence of grade 1/2 mucositis went from 13%/4% with TC to 18%/10% with TCF, while grade 3 mucositis went up from 2% to 3% and grade 4 was rarely seen. Plantar-palmar syndrome of some degree occurred in 31% of the patients but was mainly of benign intensity. Only four patients had their 5-FU reduced by 25% because of the occurrence of grade 2/3 plantar-palmar syndrome, and two of them encountered a cycle delay. An unexplained increase in grade 1 fluid retention and hypersensitivity reactions most probably related to docetaxel were also observed. It is interesting to note that, despite these changes of toxicity profile, the median number of cycles of TCF administered per patient was five, as in our previous trial with TC. This suggests that the increase of toxicity did not affect significantly the overall tolerance of and the compliance with the treatment.

The examination of the DLT occurrences during the dose-finding part of the study reported in Table 3 confirms that the hematotoxicity leading to episodes of FN remains the main DLT of this docetaxel-based regimen. FN seems to have occurred in an unpredictable fashion, independently of the dose level considered. Actually, no FN episode occurred in the nine additional patients accrued at level 7 in the confirmatory part of the trial. This might also be the result of an increase in the use of hematological growth factors later in the trial, which were prohibited during the first cycle of the dose-finding part of the study.

Despite the acceptable toxicity results obtained formerly in 48 patients treated with TC and in 40 patients treated with TCF here, both given with docetaxel at 85 mg/m^2, further experience acquired with TC and TCF in our current randomized phase II trial with TC versus TCF versus ECF showed an unexpected higher occurrence of FN episodes with both docetaxel-based regimens (TC and TCF) in the first 30 patients enrolled (SAKK Trials Office, personal communication) [8]. The protocol was then amended and the dose of docetaxel reduced from 85 mg/m^2 to 75 mg/m^2 on day 1 in both TC and TCF, leading to a reduction of FN events. This dosage is also frequently recommended and used by others in combination with cisplatin ± 5-FU in metastatic gastric cancer as well as in other tumors [12–15]. We would therefore recommend using docetaxel at 75 mg/m^2 on day 1 instead of 85 mg/m^2 in both TC and TCF regimens.

Since nearly 80% of the patients had measurable disease, an efficacy assessment could be performed in this patient population. The 51% response rate (CRs plus confirmed PRs) and the median overall survival of 9.3 months are in line with the results already published with TC, and are well within the same range reported by others in metastatic gastric cancer [8, 12, 14]. A formal comparison between TC and TCF is needed to evaluate if the addition of 5-FU to TC translates into an advantage in efficacy, making the risk of moderate additional toxicity linked to it worthwhile. Our randomized phase II trial with TC versus TCF versus ECF is currently ongoing.

In conclusion, the addition of 5-FU 300 mg/m^2 in continuous infusion for 2 weeks out of 3 to docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1 is feasible with only a moderate increase of non-hematological toxicity, which does not seem to affect the overall patient tolerance. This drug regimen seems to be very active in advanced gastric carcinoma, and a further evaluation of efficacy and toxicity is currently underway in a randomized phase II trial of TC versus TCF versus ECF.

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