Cancer Chemother Pharmacol (2011) 67:41–48
DOI 10.1007/s00280-010-1281-5

ORIGINAL ARTICLE

Sequential chemotherapy with dose-dense docetaxel, cisplatin, folinic acid and 5-fluorouracil (TCF-dd) followed by combination of oxaliplatin, folinic acid, 5-fluorouracil and irinotecan (COFFI) in metastatic gastric cancer: results of a phase II trial

Matteo Dalla Chiesa · Gianluca Tomasello · Sebastiano Buti · Rodrigo Kraft Rovere · Matteo Brighenti · Silvia Lazzarelli · Gianvito Donati · Rodolfo Passalacqua

Received: 18 August 2009 / Accepted: 9 February 2010 / Published online: 5 March 2010

Abstract
Purpose To evaluate a new strategy of two sequential, intensified chemotherapy regimens in metastatic gastric cancer.
Patients and methods Chemo-naïve patients with metastatic gastric cancer were enrolled to receive 4 cycles of TCF-dd (docetaxel initially 85 mg/m^2 and cisplatin initially 75 mg/m^2 on day 1 [later modified due to toxicity: 70 and 60 mg/m^2 respectively], l-folinic acid 100 mg/m^2 on days 1 and 2, 5-fluorouracil 400 mg/m^2 bolus and then 600 mg/m^2 as a 22 h continuous infusion on day 1 and 2, every 14 days). Subsequently, patients with CR, PR or SD received 4 cycles of COFFI (oxaliplatin 85 mg/m^2, irinotecan 140 mg/m^2, l-folinic acid 200 mg/m^2, 5-fluorouracil bolus 400 mg/m^2 on day 1 followed by 2,400 mg/m^2 as a 48 h continuous infusion, every 14 days). In both regimens pegfilgrastim 6 mg subcutaneously on day 3 was included.
Results Forty consecutive patients were enrolled. TCF-dd regimen achieved an ORR of 55% (95% CI, 40–70). Twenty-three patients proceeded to COFFI. After this regimen the ORR was then increased to 60% (95% CI, 45–75). Among the 21 patients treated with TCF-dd after the protocol amendments, main grade 3–4 toxicities were: neutropenia (29%), thrombocytopenia (19%), asthenia (24%) and diarrhea (14%). COFFI caused grade 3–4 neutropenia (all not febrile) and diarrhea in 35% and 17% of patients respectively.
Conclusions A sequential strategy with TCF-dd followed by COFFI is very active and may be of special interest in selected patients.

Keywords Sequential chemotherapy · Irinotecan · Oxaliplatin · Docetaxel · Cisplatin · 5-Fluorouracil · Gastric cancer

Introduction

Gastric cancer is the second leading cause of cancer related death in the world [1]. It accounts for more than 20 deaths per 100,000 population annually in East Asia, Eastern Europe, and parts of Central and South America [2]. Surgical resection is the main curative treatment option in the early setting of this disease, with 5-year survival rates of 58% to 78% and 34% reported for stage I and II, respectively [3]. Unfortunately, in the western world, most patients are diagnosed when the tumor is inoperable. In this setting, chemotherapy remains the best treatment option [4].

Many cytotoxic agents, such as platinum compounds, anthracyclines, fluoropyrimidines, taxanes and irinotecan, in various combinations, have demonstrated significant efficacy in patients with metastatic gastric cancer, regarding disease free and overall survival [4–12].

However, in spite of these improvements, most patients with metastatic disease will develop drug resistance in a

Presented in part at 44th annual meeting of the American society for clinical oncology, May 31–June 3, 2008, Chicago, IL (J Clin Oncol 26: 2008 [May 20 Suppl; abstr 4570]).

M. Dalla Chiesa (✉) · G. Tomasello · S. Buti · R. K. Rovere · M. Brighenti · S. Lazzarelli · G. Donati · R. Passalacqua
Departments of Medical Oncology and Biostatistics, Azienda Ospedaliera di Cremona, Cremona, Italy
e-mail: mdallachiesa@yahoo.it

M. Dalla Chiesa
Medical Oncology Division, Azienda Istituti Ospitalieri, Viale Concordia 1, 26100 Cremona, Italy

few months after starting treatment and median survival still remains below 12 months in most trials.

Three decades ago, Norton and Simon reported, in a mathematical model, that the rate of tumor regrowth increases as the tumor shrinks in response to chemotherapy [13].

The Norton-Simon hypothesis [14] predicts either that a rapid reduction of tumor burden could best be achieved by shortening the interval between the cycles, and that the resistance might be overcome by switching from initial chemotherapy to new one.

Based on this hypothesis, many dose-dense regimens and sequential schedules have been developed in various tumors, with mixed results [15–18].

In advanced gastric cancer, studies with intensified weekly or biweekly [19–23] combinations or sequential [24–26] chemotherapies have reported encouraging results.

In the present study we tested a new strategy with the sequence of two intensified biweekly regimens, in order to avoid the emergence of drug resistance.

For the first part of the sequence, a combination of docetaxel, cisplatin and 5-fluorouracil (TCF) was chosen, which is currently considered a valid option in the first-line setting [7].

In order to increase the dose intensity, we have reduced to two weeks the interval between each cycle; furthermore, we have modulated the 5-fluorouracil with folinic acid, according to the studies by de Gramont and colleagues in colorectal carcinoma [27].

For the second part of the sequence, a combination of oxaliplatin, irinotecan, folinic acid and 5-fluorouracil was chosen, based on previous phase II trials that reported high activity in metastatic gastric cancer [22, 23].

Patients and methods

Patients

The inclusion criteria for this study were: histologically confirmed metastatic gastric cancer, at least one measurable metastatic lesion, age $\leq$80 years, an ECOG performance status (PS) $\leq$1, adequate hepatic, renal, haematological and cardiac function and written informed consent.

Prior adjuvant chemotherapy and radiotherapy were allowed, provided that terminated by at least 6 months before the enrollment in the study.

Major exclusion criteria were: prior palliative chemotherapy, either bone metastases or pleural/peritoneal effusion as the sole disease site, pregnancy, breast-feeding, child-bearing potentiality without use of any contraception, any other current or prior malignancy (with the exception of excised cervical carcinoma in situ or squamous cell skin carcinoma) and psychiatric conditions considered as making it difficult or impossible to apply the therapeutic program.

The study was approved by the local ethical committee and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Chemotherapy administration and dose reductions

Dose-dense TCF (TCF-dd) regimen consisted of: docetaxel (Taxotere®; Sanofi-Aventis, Paris, France) 85 mg/m^2 over 1-h intravenous (i.v.) infusion on day 1, cisplatin 75 mg/m^2 on day 1 (1 h i.v. infusion), levo-folinic acid 100 mg/m^2 administered in 5% glucose over 2-h i.v. on day 1 and 2, followed by 5-fluorouracil 400 mg/m^2 bolus i.v. on day 1 and 2 and then 5-fluorouracil 600 mg/m^2 as a continuous i.v. infusion over 22 h on day 1 and 2.

Pegfilgrastim (Neulasta®, Amgen, Thousand Oaks, CA, USA) 6 mg was administered on day 3, subcutaneously, at the end of 5-fluorouracil continuous infusion.

As a precaution, we decided per protocol to reduce by 30% all the chemotherapeutic agents for patients aged $\geq$65 years, on the basis of our clinical practice about polichemotherapy regimens in metastatic gastric cancer.

Hematological and non hematological toxicities encountered in the first 6 patients, prompted us to make an amendment to the protocol and thereby we reduced docetaxel dose to 75 mg/m^2.

Because of persistent toxicities, mainly hematological and constitutional symptoms (severe asthenia) we decided, after the 19th patient treated, to further reduce docetaxel (70 mg/m^2) and cisplatin (60 mg/m^2) doses.

Antiemetic treatment (5-hydroxytryptamine receptor antagonist type and dexamethasone), appropriate hydration and premedications were always administered before the infusion of chemotherapy.

In the event of toxicity, the following dose reductions and treatment delays were planned: in case of insufficient hematological function (neutrophil count <1,500/mm^3 and/or platelet count <100,000/mm^3), and/or non-hematological toxicities grade >1 on day 15 of any cycle, treatment was delayed until resolution.

If toxicities lasted longer than two weeks, the treatment was continued, after recovery, with a dose reduction of 20%, but always keeping the 2-week schedule.

In the event of febrile neutropenia, grade 4 not febrile neutropenia lasting longer than five days, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, there were 25% dose reductions of each drug.

The same dose reduction was indicated for grade 3 and 4 non-hematological toxicity.

Treatment was repeated every 14 days and it was continued for 4 cycles (one cycle = 15 days) in absence of disease

progression, unacceptable toxicity, patient refusal, or at physician's discretion.

At the end of the TCF-dd treatment, patients were re-evaluated and those with complete response (CR), partial response (PR) or stable disease (SD) received COFFI: irinotecan (Campto®, Aventis Pharma, Rainham Road South, Dagenham, UK) 140 mg/m^2 in saline solution over 1-h i.v. infusion on day 1, followed by oxaliplatin (Eloxatin®, Laboratoires Thissen, Braine-L'alleud, Belgium) 85 mg/m^2 and levofolinic acid 200 mg/m^2 administered simultaneously in 5% glucose over 2-h i.v. on day 1, followed by 5-fluorouracil 400 mg/m^2 bolus i.v. on day 1 and then 5-fluorouracil 2,400 mg/m^2 as a continuous i.v. infusion over 48 h.

Also in this case, pegfilgrastim was administered at the end of 5-fluorouracil continuous infusion and patients aged ≥65 years received a 30% dose reduction.

In the event of toxicity, the following dose reductions and treatment delays were planned: in case of insufficient hematological function (neutrophil count <1,500/mm^3 and/or platelet count <100,000/mm^3), and/or gastrointestinal toxicities grade >1 on day 15 of any cycle, treatment was delayed until resolution; if gastrointestinal toxicities lasted longer than two weeks, the treatment was then discontinued.

In the event of febrile neutropenia, grade 4 not febrile neutropenia lasting longer than five days, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, there were 25% dose reductions of each drug.

The same dose reduction was indicated for grade 3 and 4 gastrointestinal toxicity. For ototoxicity or neurotoxicity grade ≥ 2, oxaliplatin was discontinued.

Treatment was repeated every 14 days and it was continued for 4 cycles (one cycle = 15 days) in absence of disease progression, unacceptable toxicity, patient refusal, or at physician's discretion.

Study assessments

Upon study entry, a medical history was taken, and all of the patients underwent a physical examination, an evaluation of ECOG PS, blood chemistry tests, a chest X-ray and a computed tomography scan of the abdomen and of all measurable and assessable sites. A bone scan, a magnetic resonance imaging scan and an ultrasound endoscopy were carried out only if indicated.

The patients subsequently underwent a physical examination and laboratory tests (blood cell count, serum creatinine, bilirubin, aspartate aminotransferase [ALT], alanine aminotransferase [AST]) before each cycle. The tumor markers carcinoembryonic antigen (CEA) and CA 19.9 were measured at baseline and every month.

Instrumental evaluations of the lesions present at study entry were carried out after 4 cycles of TCF-dd (or at least 2 cycles in case of early stopping), a second time after 4 cycles of COFFI (or at least 2 cycles in case of early stopping) and then every 2 months until disease progression or withdrawal from study medication, on the basis of the RECIST criteria [28].

In addition, survival was monitored every 2 months in each patient leaving the study.

Adverse events, including neurosensory toxicity, were classified according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical analysis

This was a monocentric, non-randomized phase II study. The efficacy analyses were based on the intent-to-treat population. The primary objective was the activity evaluated as overall response rate (ORR): CR plus PR. Secondary endpoints were safety, time to progression (TTP) and overall survival (OS).

On the basis of an ORR of 37% for patients who received DCF or TCF regimens in previous recent randomized trials [6, 7] we expected a 50% ORR with the TCF-dd regimen and a further increase of 20% ORR by the addition of COFFI.

We have estimated that 23 evaluable patients receiving both TCF-dd and COFFI were required to accept this hypothesis as being true [29] in order to guarantee a power of the study of 0.80 and significance of 0.05.

We have also projected that an extra amount of 10–15 patients had to be enrolled, considering the expected drop out after TCF-dd regimen, due to progression of disease (per protocol), toxicity and other causes.

Descriptive statistics was reported as proportions and medians. Kaplan-Meier estimates were used in the analysis of time-to-event variable and the 95% confidence interval (CI) for the median time to event was computed.

The dose intensity (DI) was calculated according to Hryniuk method [30]. The relative DI was calculated as the ratio of the DI actually delivered to the DI planned by the protocol.

Results

Patients' characteristics

Forty consecutive patients were enrolled into this study from November 2004 to April 2008.

Patients' characteristics are listed in Table 1. Median age was 64 years (range 40–80 years); the majority were male (73%) and had an ECOG PS of 0 (70%).

All patients had histologically confirmed adenocarcinoma.

Table 1 Patients' characteristics

	No.	%
Enrolled patients	40	100
Sex		
Male	29	73
Female	11	27
Age (years)		
Median	64	
Range	40–80	
ECOG PS		
0	28	70
1	12	30
Primary tumor site		
Esophagogastric junction	8	20
Stomach	32	80
Histological diagnosis		
Adenocarcinoma	40	100
G1	0	0
G2	16	40
G3	18	45
Unknown	6	15
Prior gastrectomy	18	45
Disease sites		
Distant lymph nodes	23	58
Stomach	22	55
Liver	20	50
Peritoneum	15	38
Bone	6	15
Lung	5	13
Prior adjuvant chemotherapy	4	10
Prior adjuvant radiotherapy	2	5

The most common disease sites were distant lymph nodes (58% of patients), liver (50%), peritoneum (38%), bone (15%) and lung (13%).

Eight patients (20%) had their primary tumor at the esophagogastric junction. Forty-five percent of patients underwent prior gastrectomy, the rest had metastatic disease as first diagnosis.

Four patients (10%) had received prior adjuvant chemotherapy. Two patients (5%) had received prior adjuvant radiotherapy.

Chemotherapy delivery

The exposure to study medications is listed in Table 2.

A median of 4 cycles (range 1–4) of TCF-dd per patient were administered.

Sixteen patients (40%) completed the planned 4 cycles without any delay nor dose reductions.

Four patients received less than 4 cycles (see below for further details).

Median actual DI was 42.5 mg/m^2/week (range 21.2–42.5; relative DI = 1.0, range 0.5–1.0) for docetaxel and 37.5 mg/m^2/week (range 18.7–37.5; relative DI = 1.0, range 0.5–1.0) for cisplatin in the first 6 patients treated at the initial doses (docetaxel 85 mg/m^2 and cisplatin 75 mg/m^2). After the protocol amendments, in which the docetaxel dose was reduced to 70 mg/m^2 and cisplatin dose was reduced to 60 mg/m^2, median actual DI was 35 mg/m^2/week (range 14–35; relative DI = 1.0, range 0.4–1) for docetaxel, 30 mg/m^2/week (range 12–30; relative DI = 1.0, range 0.4–1) for cisplatin and 1,000 mg/m^2/week (range 400–1,000; relative DI = 1.0, range 0.4–1) for 5-fluorouracil.

Twenty-three patients were treated with COFFI and a median of 4 cycles (range 2–4) per patient was administered.

Nine patients (39%) completed the planned 4 cycles without any delay nor dose reductions.

Three patients received less than 4 cycles of COFFI: one experienced severe gastrointestinal toxicity after 3 cycles, the second developed clinical progression of disease after 2 cycles and the other refused to continue the treatment after 3 cycles.

Median actual DI was 64 mg/m^2/week (range 43.7–70; relative DI = 0.92, range 0.62–1) for irinotecan, 39 mg/m^2/week (range 26.5–42.5; relative DI = 0.92, range 0.62–1) for oxaliplatin and 1,280 mg/m^2/week (range 875–1,400; relative DI = 0.92, range 0.62–1) for 5-fluorouracil.

Efficacy

Thirty-six patients were evaluable for response to the TCF-dd regimen. There were two treatment related deaths (one patient died after 1 cycle because of bowel perforation and another because of septic shock due to febrile neutropenia) and two early suspensions (one patient discontinued the treatment because of severe allergic reaction to docetaxel in the 2nd cycle and another interrupted after 3 cycles because of severe gastrointestinal and hematological toxicity, without instrumental evaluation of disease).

After 4 cycles of TCF-dd, 2 CR (5%), 20 PR (50%), 9 SD (22%) and 5 disease progressions (12%) were observed, for an ORR of 55% (95% CI, 40–70), as shown in Table 3.

The activity rate achieved after the administration of COFFI is listed in Table 4. The two CR observed after TCF-dd were maintained after COFFI. Among the 20 patients with PR after TCF-dd, 2 achieved CR, 6 had a further improvement of response, 6 maintained PR, 2 progressed and 4 did not start COFFI (1 early death not related to the disease nor to the treatment, 1 protocol violation, 1 patient refusal and 1 for other reasons).

Table 2 Chemotherapy delivery

	TCF-dd	COFFI
No. of treated patients	40	23
No. of patients who completed 4 cycles without delay nor dose reductions (%)	16 (40)	9 (39)
No. of patients who received less than 4 cycles (%)	4 (10)	3 (13)
No. of patients with dose reduction (%)	10 (25)	6 (26)
No. of patients with at least 1 cycle delay (%)	21 (53)	13 (57)
No. of patients with at least 1 cycle delay and dose reduction (%)	9 (23)	5 (22)
Median no. of cycles per patient (range)	4 (1–4)	4 (2–4)
No. of planned cycles	160	92
No. of delivered cycles (%)	151 (94)	88 (96)
No. of delayed cycles (%)	61 (40)	21 (24)
No. of cycles with dose reduction (%)	15 (10)	16 (18)
Median dose intensity[a] (mg/m^2/week)	Docetaxel 35	Irinotecan 64
	Cisplatin 30	Oxaliplatin 39
	5-Fluorouracil 1.000	5-Fluorouracil 1.280
Median relative dose intensity[a] (range)	Docetaxel 1 (0,4-1)	Irinotecan 0,92 (0,6-1)
	Cisplatin 1 (0,4-1)	Oxaliplatin 0,92 (0,6-1)
	5-Fluorouracil 1 (0,4-1)	5-Fluorouracil 0,92 (0,6-1)

[a] Refers to 21 patients treated after the protocol amendments

Table 3 Activity of TCF-dd regimen—intention to treat analysis

	No.	%
CR	2	5
PR	20	50
ORR	22	55 (95% CI, 40–70)
SD	9	22
PD	5	13
NE	4	10

TCF-dd Docetaxel, cisplatin, 5-fluorouracil modulated with folinic acid—dose-dense, *CR* Complete response, *PR* partial response, *SD* stable disease, *ORR* overall response rate (CR + PR), *PD* progressive disease, *NE* not evaluable

Among the 9 patients with SD after TCF-dd, 2 achieved PR, 2 maintained stable disease, 1 progressed and 4 did not start COFFI (1 protocol violation, 1 patient refusal and 2 for other reasons).

The ORR in the 23 patients who received both TCF-dd and COFFI was 60% (95% CI, 45–75).

Two patients with multiple liver metastases maintained CR for 16 and over 36 months respectively. Two patients with peritoneal macrometastases maintained CR for 11 and over 12 months respectively. At a median follow-up of 19 months (95% CI, 16–23), median TTP was 8.6 months (95% CI, 6.2–9.3) and median OS was 10.7 months (95% CI, 8.4–15.6). The 1-year OS was 31%. These survival figures refer to patients who received both regimens.

Table 4 Activity of the sequence TCF-dd followed by COFFI—intention to treat analysis

	No.	%
CR	4	10
PR	20	50
ORR	24	60 (95% CI, 45–75)
SD	7	17
PD	5	13
NE	4	10

TCF-dd docetaxel, cisplatin, 5-fluorouracil modulated with folinic acid—dose-dense, *COFFI* combination of oxaliplatin, folinic acid, 5-fluorouracil and irinotecan, *CR* complete response, *PR* partial response, *SD* stable disease, *ORR* overall response rate (CR + PR), *PD* progressive disease, *NE* not evaluable

Safety

Toxicities experienced during treatment are listed in Tables 5 and 6.

All patients were evaluable for toxicity. Among the 21 patients treated with TCF-dd after the protocol amendments, grade 3–4 neutropenia and thrombocytopenia rates were 29% and 19% respectively. Febrile neutropenia occurred in 10% of patients. Most frequent grade 3–4 non-hematological toxicities were: asthenia (24%), diarrhea (14%) and hypokalemia (14%).

Eight patients (35%) treated with COFFI developed grade 3–4 neutropenia (all not febrile); however, two

Table 5 Toxicity of TCF-dd before and after the protocol amendments according to NCI-CTC version 3.0 criteria

	Before the amendments		After the amendments	
	No. of patients	%	No. of patients	%
Treated	19	100	21	100
Neutropenia				
Grade 1–2	6	32	1	5
Grade 3–4	13	68	6	29
Febrile neutropenia	6	32	2	10
Thrombocytopenia				
Grade 1–2	10	53	3	14
Grade 3–4	7	37	4	19
Anemia				
Grade 1–2	14	74	7	33
Grade 3–4	4	21	1	5
Nausea/vomiting				
Grade 1–2	9	47	9	43
Grade 3–4	2	11	3	14
Diarrhea				
Grade 1–2	9	47	5	24
Grade 3–4	5	26	3	14
Asthenia				
Grade 1–2	2	11	9	43
Grade 3–4	9	47	5	24
Stomatitis				
Grade 1–2	3	16	3	14
Grade 3–4	2	11	1	5
Hypokalemia				
Grade 1–2	6	32	4	19
Grade 3–4	4	2	3	14
Hypocalcaemia				
Grade 1–2	4	21	3	14
Grade 3–4	5	26	0	0
Creatinine elevation				
Grade 1–2	8	42	1	5
Grade 3–4	0	0	0	0

patients did not receive erroneously for the first cycle any primary prophylaxis with granulocyte colony stimulating factors. Grade 3–4 diarrhea occurred in 17% of patients.

Discussion

In this study we have tested for the first time in advanced gastric cancer a strategy consisting of two sequential, intensified chemotherapy regimens.

The ORR of 55%, obtained after 4 cycles of TCF-dd rose to 60% after 4 cycles of COFFI.

This result is interesting and also confirms those of previous phase II trials of sequential chemotherapy in this setting, which have shown an increase of activity by introducing non cross-resistant drugs [24–26].

However the administration of 8 cycles of chemotherapy might have lead to the good response rates registered; for this reason we believe that this issue deserves to be clarified by the means of a randomized study.

Despite the dose reduction of cisplatin and docetaxel after the study started, the activity of the TCF-dd regimen was apparently not compromised: in fact, among the first 19 treated patients, the ORR was 47% compared to 62% observed among the 21 patients subse-

Table 6 Toxicity of COFFI according to NCI-CTC version 3.0 criteria

	No. of patients	%
Treated	23	100
Neutropenia		
Grade 1–2	0	0
Grade 3–4	8*	35[a]
Febrile neutropenia	0	0
Thrombocytopenia		
Grade 1–2	7	30
Grade 3–4	2	9
Anemia		
Grade 1–2	4	17
Grade 3–4	1	4
Nausea/vomiting		
Grade 1–2	4	17
Grade 3–4	1	4
Diarrhea		
Grade 1–2	8	35
Grade 3–4	4	17
Asthenia		
Grade 1–2	3	13
Grade 3–4	1	4
Stomatitis		
Grade 1–2	1	4
Grade 3–4	0	0
Creatinine elevation		
Grade 1–2	0	0
Grade 3–4	0	0

[a] Two patients did not receive erroneously for the first cycle any primary prophylaxis with granulocyte colony stimulating factors

quently treated after the protocol amendments (data not shown).

The increase of activity in our study is less than we expected at the time of the trial design; probably the 70% ORR foreseen was too optimistic.

Moreover we think that the results obtained from this sequential therapy should be balanced with the potential toxicity and financial burden of the heavy regimens administered. It is then of paramount importance the proper selection of patients which may potentially have benefit.

The TTP and OS were not primary end-points, however they deserve some considerations.

A median TTP of 8.6 months is longer than those achieved by other regimens considered among the most effective in advanced gastric cancer, such as ECF [5], DCF [6] and TCF [7].

Notwithstanding, due to a relatively small sample size and a non-randomized design, it is not possible to draw definitive conclusions from this result. Despite the fact that we have found a long TTP, the median OS of 10.7 months was not impressive. This could be explained by the fact that only patients with distant metastases were included in our study. In addition, the 1-year OS was 31%.

It is also important to show the clinical course of the four patients with CR: of the two patients with multiple liver metastases, one is still in CR after 36 months of follow-up and the other has relapsed after 16 months. Of the two patients with peritoneal macrometastases, one is still in CR after 12 months of follow-up and the other has relapsed after 11 months.

Regarding the toxicity, some remarks are deserved. The TCF-dd regimen was unacceptably toxic at the initial dosing schedule, especially concerning the gastrointestinal and hematological toxicities and lethargy.

Undoubtedly it would have been more correct to perform first a dose-escalation phase I study to determine the recommended dose of cisplatin and docetaxel.

After the protocol amendments, the toxicity was significantly reduced in the 21 patients subsequently treated. However, constitutional symptoms and hematological toxicity were still not negligible.

At the reduced doses the TCF-dd regimen was feasible, as 10 patients (48%) completed the planned 4 cycles without any delay nor dose reductions (data not shown).

The toxicity of COFFI, mainly represented by diarrhea and neutropenia, was acceptable and comparable to that found in previous phase II studies with this combination [22, 23]. Another point that must be discussed is that unfortunately, no quality of life questionnaires were responded by the enrolled patients. It would have been undoubtedly additive valuable information, also when considering this approach instead of the "classic" strategies in this disease.

Nevertheless, on the basis of aforementioned considerations, we think that a sequential strategy with TCF-dd for 4 cycles followed by COFFI for 4 cycles is feasible, effective and deserves to be tested in well designed randomized trials. It may be of special interest in patients with symptomatic disease in need of a rapid reduction of tumor burden as well as in the neoadjuvant setting in order to achieve better response rates.

It also may be of special interest the addition of biological agents to enhance the efficacy of this strategy, which will be our next subject of research.

Conflict of interest The author(s) indicated no potential conflicts of interest.

References

1. Kamangar F, Dores GM, Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137–2150

2. Parkin DM, Bray F, Ferlay J et al (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
3. Lim L, Michael M, Mann GB et al (2005) Adjuvant therapy in gastric cancer. J Clin Oncol 23:6220–6232
4. Wagner AD, Grothe W, Haerting J et al (2006) Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 24:2903–2909
5. Webb A, Cunningham D, Scarffe JH et al (1997) Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15:261–267
6. Van Cutsem E, Moiseyenko VM, Tjulandin S et al (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 24:4991–4997
7. Roth AD, Fazio N, Stupp R et al (2007) Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 25:3217–3223
8. Cunningham D, Starling N, Rao S et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
9. Al-Batran SE, Hartmann JT, Probst S et al (2008) Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 26:1435–1442
10. Kang YK, Kang WK, Shin DB et al (2009) Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 20:666–673
11. Dank M, Zaluski J, Barone C et al (2008) Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 19:1450–1457
12. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
13. Norton L, Simon R, Brereton HD et al (1976) Predicting the course of Gompertzian growth. Nature 264:542–545
14. Norton L, Simon R (1986) The Norton-Simon hypothesis revisited. Cancer Treat Rep 70:163–169
15. Fizazi K, Zelek L (2000) Is one cycle every three or four weeks' obsolete? A critical review of dose-dense chemotherapy in solid neoplasms. Ann Oncol 11:133–149
16. Vasey PA (2003) Resistance to chemotherapy in advanced ovarian cancer: mechanisms and current strategies. Br J Cancer 89(Suppl 3):S23–S28
17. Grossi F, Aita M, Follador A et al (2007) Sequential, alternating, and maintenance/consolidation chemotherapy in advanced non-small cell lung cancer: a review of the literature. Oncologist 12:451–464
18. Ocana A, Hortobagyi GN, Esteva FJ (2006) Concomitant versus sequential chemotherapy in the treatment of early-stage and metastatic breast cancer. Clin Breast Cancer 6:495–504
19. Cascinu S, Labianca R, Alessandroni P et al (1997) Intensive weekly chemotherapy for advanced gastric cancer using fluorouracil, cisplatin, epi-doxorubicin, 6S-leucovorin, glutathione, and filgrastim: a report from the Italian Group for the Study of Digestive Tract Cancer. J Clin Oncol 15:3313–3319
20. Lordick F, Lorenzen S, Stollfuss J et al (2005) Phase II study of weekly oxaliplatin plus infusional fluorouracil and folinic acid (FUFOX regimen) as first-line treatment in metastatic gastric cancer. Br J Cancer 93:190–194
21. Louvet C, Andre T, Tigaud JM et al (2002) Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 20:4543–4548
22. Chiesa MD, Buti S, Tomasello G et al (2007) A pilot phase II study of chemotherapy with oxaliplatin, folinic acid, 5-fluorouracil and irinotecan in metastatic gastric cancer. Tumori 93:244–247
23. Lee J, Kang WK, Kwon JM et al (2007) Phase II trial of irinotecan plus oxaliplatin and 5-fluorouracil/leucovorin in patients with untreated metastatic gastric adenocarcinoma. Ann Oncol 18:88–92
24. Cascinu S, Graziano F, Barni S et al (2001) A phase II study of sequential chemotherapy with docetaxel after the weekly PELF regimen in advanced gastric cancer. A report from the Italian group for the study of digestive tract cancer. Br J Cancer 84:470–474
25. HC Yeh K, Lu Y et al (2006) Phase II study of sequential non-cross-resistant chemotherapy using weekly 24-hour infusion of cisplatin, high-dose 5-fluorouracil and leucovorin (P-HDFL) followed by weekly docetaxel and irinotecan (DI) for recurrent or metastatic gastric cancer: an interim analysis. J Clin Oncol 24:18S (Suppl; abstr 14063)
26. F Loupakis, Masi G, Bursi S et al (2007) Phase II study of sequential chemotherapy with cisplatin (P) in combination with infusional 5FU/LV (PFL) followed by irinotecan (Ir) + 5FU/LV (IrFL) followed by docetaxel (T) + 5FU/LV (TFL) in patients (pts) with metastatic gastric carcinoma (MGC) by the Gruppo Oncologico Nord-Ovest (GONO). J Clin Oncol 25:18S (Suppl; abstr 15059)
27. de Gramont A, Bosset JF, Milan C et al (1997) Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 15:808–815
28. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
29. A'Hern RP (2001) Sample size tables for exact single-stage phase II designs. Stat Med 20:859–866
30. Hryniuk WM, Goodyear M (1990) The calculation of received dose intensity. J Clin Oncol 8:1935–1937