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ORIGINAL ARTICLE

Simplified FOLFIRI in pre-treated patients with metastatic gastric cancer

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Abstract
Purpose Second-line chemotherapy in patients with metastatic gastric cancer (MGC) pre-treated with cisplatin is not a standard option. We studied a combination of irinotecan, fluorouracil and folates.
Methods Patients progressive to cisplatin-based chemotherapy were enrolled. Irinotecan 180 mg/m^2, folinic acid 200 mg/m^2, and fluorouracil 400 mg/m^2 were given on day 1, immediately followed by fluorouracil 2,400 mg/m^2 46 h continuous infusion (simplified FOLFIRI), every 2 weeks.
Results Between June 2002 and May 2003, 28 patients were treated. Median age was 57 years (range 38–68). Most patients had a distal primary (90%), and metastatic disease (71%). Partial response was obtained in six patients (21%, 95% CI 8–41) and stable disease in eight (21%, 95% CI 13–41). Among the six responsive patients three were refractory to docetaxel. At a median follow-up of 2.9 years median time to progression was 4 months (95% CI: 2–5), and median overall survival was 5 months (95% CI 4–9). Toxicity was mild, without treatment-related deaths or life-treating adverse events.
Conclusions Simplified FOLFIRI was moderately active and well tolerated in unselected patients with MGC pre-treated with cisplatin-based chemotherapy. Its role in patients refractory to taxanes is promising and warrants further investigation.

Keywords FOLFIRI · Metastatic gastric cancer · Irinotecan · Second line chemotherapy

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Introduction

Although decreased in incidence, gastric cancer remains the second cause of cancer-related death worldwide [1]. Epirubicin/cisplatin/fluorouracil (ECF) and cisplatin/fluorouracil (CF) have been used as conventional first-line regimens in MGC over the last decade [2–4]. A recent meta-analysis of chemotherapy in MGC confirmed that the best survival results are achieved with three-drug regimens containing fluorouracil (FU), an anthracycline and cisplatin. Among these regimens using infusion of FU exhibit a lower rate of toxic deaths [5]. Recently, interesting results came from studies with chemotherapeutic regimens including new agents [6–11]. In particular, after two decades of a lack of approved new drugs in gastric cancer therapy, docetaxel has been approved by the FDA as first-line treatment in combination with cisplatin and fluorouracil. This approval was based on the results of the V325 randomized phase III trial, wich showed a higher response rate (37 vs. 25%; chi-square $p = 0.0106$) and a longer time to progression (5.6 vs. 3.7 months; risk reduction 32%, log-rank $p = 0.0004$) for DCF (docetaxel/cisplatin/5-fluorouracil) compared with CF (cisplatin/fluorouracil). With a median follow-up of 23 months, OS was longer with DCF (risk reduction 23%, log-rank $p = 0.0201$). Nevertheless G3-4 toxicity occurred

in 81 and 75% of DCF and CF patients respectively [10]. Other new agents, such as oxaliplatin, oral fluorophirimidine and irinotecan have been studied both as first and second line treatment in MGC [12–24]. In a randomized phase III trial (REAL-2) oxaliplatin, capecitabine and epirubicin (EOX) resulted not inferior to cisplatin, fluorouracil and epirubicin (ECF) in patients with previously untreated esophagogastric cancer [12]. A recent published phase III Japanese trial showed that median overall survival was significantly longer in patients with MGC assigned to S-1 plus cisplatin than in those assigned to S-1 alone [16].

A large phase III trial with irinotecan plus high-dose FU and leucovorin (IF) versus cisplatin and FU (CF) showed a trend to time to progression superiority with IF, as well as a better safety profile [17].

Combined with fluorouracil and folinic acid (FU/FA), irinotecan produced a 22–42% response rate (RR) in previously untreated patients [18–20]. Irinotecan showed activity, mostly combined with cisplatin, also as second-line treatment after conventional upfront chemotherapy [22–24]. Only one report exists showing activity of irinotecan after first-line treatment with new-drug regimens. This phase II study with a combination of irinotecan/5-fluorouracil/leucovorin showed a 21% RR and a median overall survival (OS) of 7.6 months, in patients progressive to taxane and cisplatin-based chemotherapy [25].

We studied a combination of irinotecan and FU/FA (FOLFIRI) in patients with MGC progressing to first-line chemotherapy. Considering that cisplatin is often used as an upfront treatment, we decided to combine irinotecan with FU/FA rather than cisplatin. We chose an infusional rather than bolus regimen on the basis of the better tolerability and efficacy profile reported in colon cancer [26].

We used the "simplified" FOLFIRI due to the acceptable toxicity of this regimen reported in third line therapy in advanced colorectal cancer [27].

Patients and methods

Eligibility criteria

Patients had to meet the following criteria to be eligible for this trial: (1) histologically proven adenocarcinoma of the stomach or gastroesophageal junction; (2) measurable or evaluable metastatic or unresectable locally-advanced disease; (3) disease progression to prior palliative chemotherapy without irinotecan; (4) disease progression within six months from the end of adjuvant/neo-adjuvant chemotherapy without irinotecan; (5) life expectancy of at least 3 months; (6) Eastern Cooperative Oncology Group performance status of 0–2; (7) age between 18 and 75 years; (8) written informed consent; (9) adequate hematologic (WBC > 4,000/mm^3 and or neutrophil count >1.500/mm^3, platelets > 100.000/mm^3), hepatic (AST/ALT < 2.5 times the upper normal limit (UNL) or <5 times the UNL if liver metastasis, bilirubin ≤2 mg/dl) and renal function (serum creatinine ≤1,5 times the UNL); (10) negative pregnancy test; (11) no concomitant uncontrolled medical illness; (12) no history or evidence of brain or meningeal metastases.

Treatment

Treatment was administered through totally tunneled implanted venous catheters (port-a-cath). An elastomeric pump was used for continuous infusion of fluorouracil. Patients received irinotecan 180 mg/m^2 IV given simultaneously to folinic acid 200 mg/m^2 IV over 2 h on day 1, followed by fluorouracil 400 mg/m^2 IV bolus and 46 h infusion of 2,400 mg/m^2 every 2 weeks (simplified FOLFIRI).

Standard antiemetic and anti-diarrhea or other symptomatic therapy was allowed. Corticosteroids were allowed for antiemetic use.

Patients were asked to report any adverse event to the investigator and were monitored at least every 2 weeks for clinical and laboratory toxicity.

Toxicity was graded according to the NCI-CTC scale (version 2). In case of insufficient hematological function (neutrophil count <1,500/mm^3, platelet count <100,000/mm^3), grade ≥2 mucositis, grade ≥2 diarrhea or any clinical toxicity superior to grade 1 (except for alopecia and anemia), the treatment was delayed till recovery. If the patient did not recover within 2 weeks, the treatment was discontinued.

In patients developing grade 2 diarrhea, treatment was resumed with a 25% dose reduction of irinotecan; in cases of grade 3–4 diarrhea all the drugs were reduced by 50%.

Patients developing grade 2 mucositis received a 20% folinic acid and fluorouracil reduction; in case of grade 3–4 mucositis, folinic acid and fluorouracil were resumed at 50% of the dose and irinotecan at 75%.

Patients presenting with a grade 3–4 hematological toxicity, resumed the treatment with a 25% dose reduction of all drugs. If the same grade toxicity reoccurred, chemotherapy was reduced by 50%.

In case of any other grade 3–4 clinical toxicity (except for alopecia), all the study drugs were reduced by 50%.

Treatment was continued for at least four cycles or until disease progression, unacceptable toxicity, patient refusal, or physician decision.

Study evaluations

Baseline and study evaluation included: medical history, physical examinations, complete blood count, assessment

of renal and liver function, ECG, chest X-ray, computed tomography (CT)-scan. Blood cell count, serum creatinine, bilirubin, AST, ALT, lactate dehydrogenase, alkaline phosphatase were measured before each chemotherapeutic administration**.** Tumor markers (carcinoembryonic antigen (CEA) and CA 19–9) were measured at baseline and at every radiological assessment during the study.

A CT-scan was repeated after four cycles of treatment (2 months) or when needed, if disease progression was suspected.

Tumor response, according to response evaluation criteria in solid tumors (RECIST) [28] was assessed after four cycles/2 months. In the case of complete response (CR), patients received two additional cycles and then, if response was confirmed, treatment was stopped; in the case of partial response (PR), chemotherapy was continued for additional 2 months, based on tolerability; in case of stable disease (SD), patients received further four cycles of chemotherapy and then, if a SD was confirmed, they continued treatment with 5-FU continuous infusion alone or stopped treatment based on medical decision. Treatment was stopped after the fourth cycle in case of progressive disease (PD).

Every patient received a questionnaire for quality of life (QoL) at baseline and weekly during the treatment. Quality-of-life assessment was made using the therapy impact questionnaire (TIQ), which has been developed and validated at the National Cancer Institute, Milan, Italy [29]. In comparison with other QoL questionnaires, this instrument offers the advantage of being immediately understandable to Italian patients since it was written in Italian and not translated from English like other QoL instruments.

Objectives

Activity, in terms of response rate (PR and SD), and toxicity, were the primary objectives of this study. Secondary objectives included median time to progression (mTTP), median overall survival (mOS), and QoL.

Statistical methods

We used Simon two-stage minimax design, with $\leq$5% of response rates (RRs) unacceptable and $\geq$25% of RRs acceptable.

For a type one error of 5% and a power of 90%, 15 patients were needed in the first stage and if non response was seen, the study regimen was rejected for response. If one or more responses were observed, the study went on to the second stage and further 10 patients were enrolled. If 3 or fewer responses were obtained in the whole cohort of patients, the study regimen was suspected as ineffective. If $\geq$4 responses were seen, with 5% type 1 error probability, the true RRs was to be greater or equal to 25%.

Results

From June 2002 to May 2003, 28 patients were treated. All patients were evaluated for toxicity. Five patients did not have a radiological evaluation for tumor response due to an early clinical progression occurred within 2 months from the beginning of treatment study. These five patients were included in the progression disease group.

The main characteristics of patients are listed in Table 1. The majority of patients were female (61%), had a distal primary (90%), and metastatic disease (71%). Twenty-four patients were progressive to a first-line chemotherapy, including docetaxel/cisplatin in 11 and ECF in 11. Two patients experienced disease progression during maintenance chemotherapy with mytomicin/fluorouracil and UFT, administered following ECF. Four patients relapsed within 6 months from the end of the neo-/adjuvant chemotherapy.

At study entry 13 patients had early tumor progression during the first-line chemotherapy (refractory), six progressed within four months after obtaining an initial response (resistant), three progressed after 6 months of

Table 1 Patient characteristics

Characteristics	No. of patient (n = 28)
Median age (range)	57 (38–68)
Gender	
Male/Female	11/17
Performance status	
0/1/2	15/10/3
Previous surgery	13
Total gastrectomy/sub-total gastrectomy	7/6
Previous adjuvant chemotherapy	9
ECF/TCF/PELF/FU + FA/MMC + Tegafur	4/1/1/2/1
Disease extent	
Locally advanced/metastatic	0/28
Primary site	
Gastro-esophageal junction/gastric	3/25
Histological sub-type	
Intestinal/non intestinal	5/23
Number of metastatic sites	
1/2/ $\geq$ 3	10/8/10
Sites of disease	
Primary	16
Local lymph nodes	16
Distant lymph nodes	10
Liver	8
Lung	1
Peritoneum	8
Other	5

Table 2 FOLFIRI activity

1st-line regimen	No. of cycles	Response to 1st-line regimen	Response to FOLFIRI
DC	2	PD	PR
ECF	4	SD	SD
ECF[b]	4	–	PD
DC	4	PD	PR
DC	2	PD	PR
DC	6	PR	Not evaluable
ECF	4	PD	PD
DCF	3	SD	PD
ECF	6	PR	PR
DC	6	PR	Early PD
DCF[a]	4	–	SD
ECF[b]	3	–	SD
ECF	4	PD	PR
ECF	4	PR	PD
DCF	4	PR	PD
DCF	6	PR	PR
ECF	4	SD	PD
ECF	6	SD	PD
ECF	2	PD	SD
ECF[a]	4	–	PD
DC	6	SD	PD
ECF	2	PD	SD
ECF	3	PD	SD
DC	6	SD	PD
ECF	3	PR	PD
DC	2	PD	SD
ECF	6	PR	PD
ECF[b]	3	–	SD

D docetaxel, *C* cisplatin, *F* fluorouracil, *E* epirubicin

[a] Neoadjuvant chemoterapy

[b] Adjuvant chemotherapy

maintenance chemotherapy with fluoropyrimidines and two after 8 months from the end of chemotherapy (Table 2).

The mTTP to first line regimen was 3.5 months (range 1–10). In particular it was 4 months and 3 months respectively for docetaxel and antracycline based treatment.

Response

Six out of the 21 patients with measurable disease had a PR, and six a SD. Two out of the seven patients with evaluable disease had a SD as best response. Fourteen patients had a PD. Therefore, with an intention to treat analysis a 21% PR (95% CI: 8–41), 21% SD (95% CI 13–41), and 50% PD (95% CI 31–69) were observed. Four patients with PR were refractory to previous chemotherapy (three to docetaxel-based regimen) and two resistant (Table 2).

Survival

The median TTP was 4 months (95% CI: 2–5). All patients progressed within one year after the end of the "simplified" FOLFIRI chemotherapy and 22 (81.5%) die. Two patients died within two months from the start of study treatment due to disease progression. At a median follow up of 2.9 years all patients died. The median OS was 5 months (95% CI 4–9).

Dose intensity and toxicity

The median number of cycles per patient was five (range 1–14). Three patients received an ab initio reduced dose, based on a physician decision due to poor PS (ECOG 2–3) and/or mild liver/renal failure. The average dose intensity was 70% both for irinotecan and fluorouracil. Dose reduction and treatment delay occurred in 15 and 10% of patients, respectively, mostly due to hematological toxicity. Toxicities are listed in Table 3. No toxic deaths occurred. Non-febrile neutropenia in two patients (7%) was the only grade 4 toxicity. Three patients had a grade 2–3 febrile neutropenia, without clinical infections. Other observed grade 2–3 toxicities were as follows: neutropenia (never febrile) 26% of patients, anemia 7%, diarrhea 11%, nausea 37%, vomiting 15%, stomatitis 22%, fatigue 26%.

Quality of life

Quality of life analysis was not possible due to the poor compliance in filling in the questionnaires, not related to patients' performance status. Thirteen patients filled in the questionnaires at baseline but only nine of them had one questionnaire after 2 months of treatment that matched the baseline. Four out of six patients with PR filled in the questionnaires at study entry and at first assessment of efficacy. In these patients we did not observe a significant change as far as physical symptoms, emotional, cognitive, and relational items are concerned, except for the improvement of fatigue and dysphagia.

Discussion

The 42% disease control (PR + SD) and 5 months mOS obtained in our study, are noteworthy in a context of unselected pre-treated patients with MGC.

The activity of simplified FOLFIRI as a second line treatment is promising, especially if we consider that all patients had received an adequate first line regimen and four of them were refractory to docetaxel-based chemotherapy. This has a practical clinical implication given that docetaxel/cisplatin/fluorouracil (DCF) has recently became

Table 3 Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
	No. of pts	No. of pts	No. of pts	No. of pts
Leukopenia	7 (26%)	2 (7%)	4 (15%)	–
Neutropenia	1 (4%)	3 (11%)	4 (15%)	2 (7%)
Anemia	14 (52%)	2 (7%)	–	–
Nausea	10 (37%)	10 (37%)	–	–
Vomiting	4 (15%)	3 (11%)	1 (4%)	–
Diarrhea	10 (37%)	3 (11%)	–	–
Stomatitis	10 (37%)	2 (22%)	–	–
Fatigue	5 (19%)	7 (26%)	–	–
Hand-foot syndrome	–	1 (4%)	–	–
Paresthesia	1 (4%)	1 (4%)	–	–
Alopecia	1 (4%)			2 (7%)

the reference first-line treatment in MGC. The only report regarding activity of irinotecan/5-FU/LV regimen in patients with MGC who had received taxanes as first-line treatment was by Kim et al. [25], who reported 21% PR, 25% SD, 2.5 months TTP, and 7.6 months OS in 57 patients pre-treated with taxanes and cisplatin. Despite a lower dose intensity (70 vs. 87%), we observed a similar disease control.

The OS of our patients was similar to that reported in two other studies with FOLFIRI as second line [24, 25].

Our regimen showed a favorable toxicity profile. Other authors who studied the FOLFIRI regimen as a second-line treatment in patients with MGC, reported a higher incidence of grade 3–4 toxicity [18, 24]. In particular, the rate of grade 4 neutropenia and gastrointestinal toxicity (nausea, vomiting, diarrhea, stomatitis) was lower in our report than in the other two studies.

The lower toxicity reported in our study compared with that reported in other irinotecan-based trials in MGC could be due to the different way of administering FU (i.e. continuous infusion versus bolus) and/or the dose intensity of irinotecan [15, 20, 21, 24].

The poor compliance for the QoL evaluation does not allow any conclusion. Despite the fact that in some patients partial response was related to improvement of symptoms, this may not be entirely due to chemotherapy and a prospective specific evaluation should be performed in larger series to address this issue. The type and/or the timing of the QoL questionnaire could have had some influence.

In conclusion, simplified FOLFIRI was moderately active and well tolerated as a second-line treatment in unselected patients with MGC pre-treated with a cisplatin-based chemotherapy. Its activity in patients progressive to a docetaxel-based regimen warrants further investigations in this setting. Based on the palliative setting and the often compromised clinical conditions of these patients, a specific QoL questionnaire and easier schedule of evaluation should be proposed, in order to better understand the correlation between tumor response and clinical benefit.

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