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ORIGINAL ARTICLE

Oxaliplatin, irinotecan, and fluorouracil/folinic acid in advanced gastric cancer: a multicenter phase II trial of the Southern Italy Cooperative Oncology Group

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Abstract
Purpose This phase II trial assessed the tolerability and efficacy of a triplet of oxaliplatin, irinotecan, and fluorouracil/folinic acid in advanced gastric cancer.
Methods Patients with unresectable or metastatic gastric cancer, unexposed to palliative chemotherapy, received oxaliplatin 85 mg/m^2 iv and irinotecan 150 mg/m^2 iv on day 1, 6S-folinic acid 250 mg/m^2 iv and fluorouracil 750 mg/m^2 iv on day 2, every 2 weeks. Response rate (RR) was assessed after a minimum of four cycles, and treatment continued up to 12 cycles.
Results Sixty-three patients were treated, with a median of eight (range 1–12) cycles/patient. Two complete and 19 partial responses were registered (RR 33% [95% CI, 22–46%]). Median progression-free survival was 7.5 (95% CI, 5.6–9.4) months, and median overall survival was 12.1 (95% CI, 10.8–13.4) months. Most common grade ≥3 toxicities were neutropenia (59%), febrile neutropenia (7%), vomiting (20%), and diarrhoea (10%). All-grade neurotoxicity affected 33% of patients.
Conclusions Oxaliplatin, irinotecan, and fluorouracil/folinic acid administered every 2 weeks are safe and active in advanced gastric cancer.

Keywords Gastric cancer · Fluorouracil · Irinotecan · Oxaliplatin · Triplet regimen

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Introduction

Gastric cancer is still a significant global health problem [1]. In metastatic patients, chemotherapy may provide a substantial palliation, and can improve survival and quality of life compared to best supportive care [2], and fluorouracil, alone or associated with folinic acid, represents the cornerstone for the treatment of this disease [2]. A recent meta-analysis showed that combination regimens achieve better survival outcomes than fluorouracil monotherapy, and that regimens containing fluorouracil, anthracyclines and cisplatin are the most effective [3]. Indeed, epirubicin, cisplatin and infusional fluorouracil (ECF) regimen is one of the most widely used in Europe, while in US the standard regimen has remained for a long time cisplatin and infusional fluorouracil (CF) [2, 4–7].

Activity of irinotecan in advanced gastric cancer was seen in 18–23%, regardless of prior chemotherapy [8, 9]. Irinotecan has shown synergistic or additive activity with fluorouracil in vitro and in vivo [10–13]. Recently, weekly irinotecan plus infusional fluorouracil/folinic acid (IFF) was randomly compared with cisplatin plus fluorouracil given every 4 weeks. The IFF regimen produced a greater response rate (RR) (32 vs. 25%), and demonstrated a marginally significant superior progression-free survival (PFS) (5.0 vs. 4.2 months, $P = 0.088$), but not overall survival (OS) (9.0 vs. 8.7 months) in comparison with the reference regimen, showing a better toxicity profile [14].

The combination of oxaliplatin and fluorouracil/folinic acid has been extensively investigated in metastatic gastric cancer patients [15–20]. Recently, a trial comparing oxaliplatin, fluorouracil and folinic acid versus cisplatin, fluorouracil and folinic acid showed greater RR (34.8 vs. 24.5%), and a trend towards improved PFS (5.8 vs. 3.9 months, $P = 0.077$) but not OS (10.7 vs. 8.8 months) for the oxaliplatin-arm, with less serious adverse events (9 vs. 19%) [21]. Interestingly, a schedule-dependent interaction has been observed for oxaliplatin followed by fluorouracil, which was more synergic than the reverse sequence in cancer cell lines, either sensitive or resistant to fluorouracil [22]. In addition, in vitro experiments have demonstrated that the oxaliplatin and fluorouracil combination is more cytotoxic when fluorouracil is utilized as a short rather than prolonged exposure [23].

Synergistic cytotoxicity has been observed on human gastric cancer cell lines exposed to oxaliplatin followed by SN-38 (the active metabolite of irinotecan) [24]. Moreover, non-overlapping dose-limiting toxicities of oxaliplatin and irinotecan justify their combination in clinical practice. Indeed, some phase II trials on oxaliplatin and irinotecan have shown promising activity (RR 50–58%, PFS 5.3–5.5 months) [25, 26].

This background represents a strong rationale for combining all these three active drugs in the treatment of advanced gastric cancer patients. We have already assessed this triplet in pre-treated patients with metastatic gastrointestinal carcinomas [27, 28]. Here we report on the safety and activity of this regimen in untreated gastric cancer patients.

Patients and methods

Patient selection and initial work-up

The aim of this study was to estimate the RR of oxaliplatin, irinotecan, and fluorouracil/folinic acid in advanced gastric cancer patients. Secondary end-points were safety, failure-free survival (FFS), PFS, and OS of patients.

Eligibility criteria were as follows: histologically proven diagnosis of adenocarcinoma of the stomach or gastro-oesophageal junction; age >18 years; performance status (PS) $\leq$2 of the Eastern Cooperative Oncology Group (ECOG) scale; unresectable or metastatic disease; measurable lesion(s); no previous exposure to palliative chemotherapy; discontinuation of fluorouracil-based (Machover or De Gramont regimen) adjuvant treatment for at least 6 months; absolute neutrophil count (ANC) $\geq$2,000 mm^{-3}, platelet (PLT) count $\geq$100,000 mm^{-3}, haemoglobin level $\geq$9.5 g/dl; bilirubin level $\leq$1.5$\times$ upper normal limit (UNL), serum alanine-aminotransferase and aspartate-aminotransferase $\leq$2.5$\times$ UNL in the absence of liver metastasis, or $\leq$5$\times$ UNL in the presence of liver metastasis; normal renal function. Exclusion criteria were: life expectancy <12 weeks; uncontrolled metabolic disorders or active infection; severe cardiac arrhythmia, uncontrolled congestive cardiac failure, severe ischemic heart disease, or acute myocardial infarction in the last 6 months; cerebral metastasis; other concomitant or previous malignant tumour. Patients gave written informed consent to participate into this study, which was approved by the Independent Ethics Committee of the National Tumour Institute of Naples.

At entry, physical examination, blood cell count with ANC and PLT counts, routine biochemistry, chest x-ray, and ECG were carried-out. Esophagogastric endoscopy was performed when indicated. Measurable lesions were assessed with CT or MRI scan.

Treatment plan

Oxaliplatin 85 mg/m^2 iv (2-h infusion), followed by irinotecan 150 mg/m^2 iv (60-min infusion) on day 1, and 6S-folinic acid 250 mg/m^2 iv (2-h infusion), followed by fluorouracil 750 mg/m^2 iv (bolus) were given on day 2. Cycles were repeated biweekly for a minimum of four cycles, and up to 12 cycles. Prophylactic treatment with anti-HT3 for emesis, and with atropine for cholinergic syndrome, was mandatory.

No prophylactic granulocyte colony-stimulating factor (G-CSF) was prescribed, but its use was mandatory for treating febrile neutropenia, and for preventing further episodes in subsequent cycles.

Treatment was recycled in the presence of ANC $\geq$1,500 mm^{-3} and PLT count $\geq$100,000 mm^{-3}, and recovery of any extra-haematological toxicity. After an episode of grade 4 haematological toxicity, or grade $\geq$3 non-haematological toxicity, subsequent cycles were administered with a 25% dose-reduction of all cytotoxic drugs. The same dose-reduction was applied from initial cycle for patients aged >70 years, or having previously suffered from severe toxicity during adjuvant chemotherapy; if treatment was tolerated, doses could be escalated in subsequent cycles. In the presence of transient neurotoxicity, no oxaliplatin dose-reduction was applied. In the presence of persistent neuropathy, oxaliplatin was reduced to 75%, while it was definitely discontinued for grade 4 neurotoxicity.

Assessment of toxicity

Blood cell count was performed weekly, while biochemistry, clinical and neurologic examinations were performed at every cycle. Acute toxicity was graded according to WHO toxicity criteria [29], while neurotoxicity was graded according to Lévi scale [30], and the worst toxicity suffered by each patient during the whole treatment was recorded.

Assessment of activity

Measurement of disease lesions with CT or MRI scans was repeated after every four cycles, and response was classified according to WHO criteria [27]. Responses were confirmed after a minimum of 4 weeks from initial documentation. RR was calculated on patients treated with at least one cycle (intent-to-treat [ITT]) population, and on those receiving at least four cycles (per-protocol population [PPP]). FFS was calculated from the date of registration to the date of discontinuation of treatment for progression, toxicity, refusal, or death, whichever occurred first. PFS was calculated from the date of registration to the date of tumour progression, or death. OS was calculated from the date of registration to the date of death for any cause, or last follow-up. After discontinuation of study treatment, patients were followed every 2 months to assess the disease status and survival. Second-line treatment was left to the attending physician's choice.

Statistical considerations

Sample size was defined according to minimax design of Simon [31], selecting a 0.05 alpha error, and a 0.20 beta error. Minimum RR (p_0) was set at 30%, while the alternative hypothesis (p_1) was a 45% RR. Consequently, more than 25 responses should be achieved in a total of 65 patients.

Descriptive statistics were reported as proportions with their exact 95% confidence intervals (95% CI). Time-to-event probabilities were estimated using the Kaplan–Meier method [32], computing the median and 95% CI.

Results

Enrolment

From July 2005 to March 2008, 65 eligible patients were included in this study by 11 SICOG investigators. Main characteristics are listed in Table 1. Notably, 28 (43%) patients were aged $\geq$65 years, and 16 (25%) patients were

Table 1 Main characteristics of enrolled patients

Characteristics	No.	%
Eligible patients	65	100
Males	45	69
Females	20	31
Median age (years)	61	
Range (years)	26–81	
Site of primary		
Stomach	54	83
Gastroesophageal junction	11	17
Previous surgery	27	42
Previous adjuvant chemotherapy	7	11
Locally advanced	5	6
Metastatic	60	94
Number of disease sites		
1	7	11
2	19	29
3+	39	60
Site of metastasis		
Lymph nodes	40	62
Liver	39	60
Lung	16	25
Peritoneal	16	25
Other[a]	7	11
Performance status		
0	30	46
1	34	52
2	1	2
Previous weigh loss >5%	32	49
Baseline CEA >5 ng/mL	33	51
Baseline CA 19.9 > 37 U/mL	30	46
Baseline alkaline phosphatase >UNL	18	28

UNL upper normal limit

[a] Ovary (4), kidney (1), skin (1), spleen (1)

aged ≥70 years. All but four patients had metastatic disease, and most (60%) had ≥3 sites. Significant weight loss was reported for nearly half of patients. All but one patient had an excellent (ECOG 0, 46%) or good (ECOG 1, 52%) PS.

Treatment delivery

Two patients, due to worsening of clinical conditions, did never receive study treatment, leaving 63 patients assessable for safety and efficacy. Overall, 525 cycles were delivered, with a median of eight (range 1–12) cycles/patient. Early drop-out (before four cycles) occurred in ten patients, because of progression (six cases), severe toxicity (two cases), or withdrawn of consent (two cases). Therefore, 53 (84%) patients received at least four cycles as per-protocol. Table 2 reports the treatment disposition. Of note, nearly half of patients were treated with ≥10 cycles. Fifty-three (84%) patients went off treatment for progression, four (6%) for toxicity, and six (10%) for refusal due to subjective treatment intolerance. Treatment ranged from 0.5 to 9.1 months (median 4.8 months).

Twenty-two (35%) patients initiated the treatment with reduced doses, because of age (16 cases) or previous severe toxicity from adjuvant chemotherapy (6 cases), while 15 (24%) patients had a dose-reduction over the first four cycles. Absolute (and relative) median dose-intensity was 28 mg/m^2 per week (66%) for oxaliplatin, 50 mg/m^2 per week (66%) for irinotecan, and 259 mg/m^2 per week (69%) for fluorouracil. Median (range) cumulative doses of oxaliplatin, irinotecan, and fluorouracil were 516 (47–767) mg/m^2, 888 (83–1,412) mg/m^2, and 4,571 (273–9,771) mg/m^2, respectively.

Toxicity

Six (9%) patients died within 2 months from their enrolment, all because of progression. No treatment-related fatality was reported. Main side effects of treatment are listed in Table 3. Severe neutropenia affected 56% of patients (grade 4, 35%). It more often occurred in aged ≥65 years (69%) than in younger (54%) patients. Febrile neutropenia occurred in only 7% of patients. Five patients received G-CSF during the treatment. Severe anaemia and thrombocytopenia were negligible. Grade 3 diarrhoea, and grade 3 neuropathy occurred in 10 and 2% of patients, respectively (no grade 4 was recorded). Despite prophylactic anti-emetic treatment, 66% of patients complained of some gastric disturbance after chemotherapy, but these symptoms were severe in only 20% of them.

Table 2 Treatment disposition

Treatment	No.	%
Total delivered cycles	513	100
Median cycles/patient	8	
Range	1–12	
Patients treated with ≥2 cycles	57	90
Patients treated with ≥4 cycles	53	84
Patients treated with ≥6 cycles	46	73
Patients treated with ≥8 cycles	43	68
Patients treated with ≥10 cycles	27	43
Patients treated with ≥12 cycles	22	35

Table 3 Main side effects reported during treatment

Toxicity	WHO grade		
	1–2%	3–4%	All grade (%)
Neutropenia	15	56	71
Febrile neutropenia	5	7	12
Thrombocytopenia	32	0	32
Anaemia	49	5	54
Nausea/vomiting	46	20	66
Diarrhoea	39	10	49
Stomatitis	14	0	14
Alopecia	25	15	40
Fatigue	14	0	14
Neurologic	29	2	31
Hepatic	8	2	10
Renal	0	2	2

Activity

A complete response (CR) was registered in a 55-year-old male with inoperable lung metastases and baseline CEA serum level of 253 ng/mL, in whom disappearance of lung nodules and normalization of CEA level occurred after 2 months of treatment. CR persisted for 3 months; thereafter disease recurred, and the patient eventually died after 19.4 months. Another CR was achieved in a 63-year-old female with unresected gastric primary, nodal and peritoneal spread, who showed disappearance of disease after 5 months of treatment; she recurred and eventually died 9 months after initial therapy. Nineteen patients achieved a partial response; therefore, RR was 33% (95% CI, 22–46%) in ITT analysis (Table 4), and 40% (95% CI, 26–54%) in PPP analysis. Responses were registered after a median of 10 (range 4–36) weeks, and had a median duration of 30 (range 4–114 weeks) weeks.

In addition, four patients showed minor tumour shrinkage. Noteworthy, among non-responding patients, 8 of 20 (40%) with baseline abnormal CEA or CA 19.9 serum level showed a decrease >50% of these values during therapy.

Overall, tumour control (response or disease stabilization) was achieved in 51 (81%; 95% CI, 69–90%) patients.

Table 4 Activity according to intent-to-treat analysis

Responses	No.	%
Complete response	2	3
Partial response	19	30
Stable disease	30	47
Progressive disease	6	10
Not assessed	6	10
Treated patients	63	100

RR was not associated with age, sex, or PS. Indeed, RR was 31% in subjects aged ≥65 years, and 35% in younger ones; similarly, RR was 31% in males, and 35% in females; it was 27% for patients having a PS of 0, and 39% among patients having a PS ≥ 1. Other pre-treatment characteristics did not adversely affect achievement of response.

Ten of 24 (42%) patients, in whom dose-intensity was above the median value for all three drugs, achieved a response, as opposed to 11 of 39 (28%) patients treated with a with a lower dose-intensity ($P = 0.204$).

Three of four patients with initially unresectable disease underwent radical gastrectomy; moreover, 14 patients received second-line chemotherapy (docetaxel alone four cases; docetaxel plus cisplatin one case; capecitabine five cases; ECF two cases; oxaliplatin, fluorouracil and folinic acid two cases).

At the time of this report, after a median potential follow-up of 22 months, median FFS was 6.2 (95% CI, 3.9–8.5) months. At that time, 48 (74%) patients had shown a disease progression. The estimated median PFS survival was 7.5 (95% CI, 5.6–9.4) months (Fig. 1). Forty-two (65%) patients eventually died, and the estimated median OS was 12.1 (95% CI, 10.4–13.8) months; 1- and 2-year OS probabilities (±SE) were 51% (±0.7%) and 20% (± 0.6%), respectively (Fig. 2).

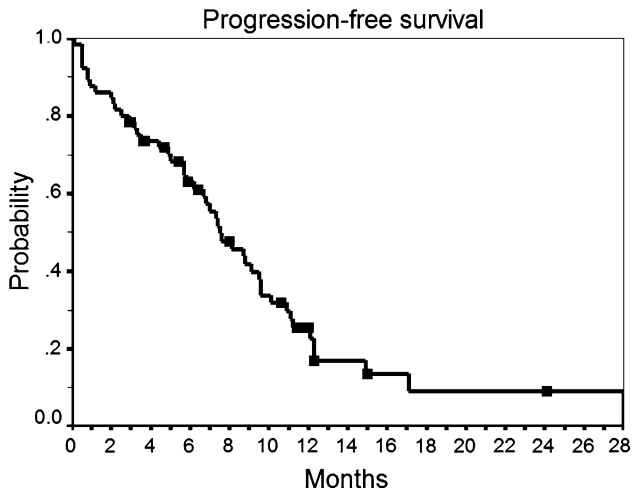

Fig. 1 Kaplan–Meier estimate of progression-free survival

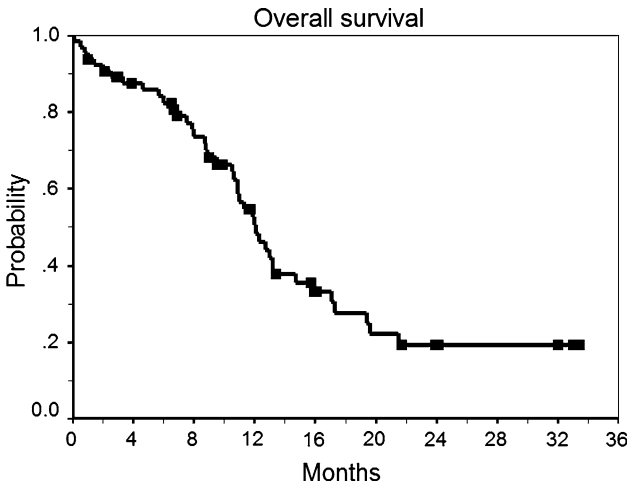

Fig. 2 Kaplan–Meier estimate of overall survival

Discussion

Treatment of advanced/metastatic gastric cancer remains still challenging. For many years, fluorouracil and cisplatin have been the only active agents for this disease, and a doublet of these compounds has been the reference regimen for treating these patients [1]. However, considering the results of recent trials [5–7], triplets have gained consensus as a standard treatment for advanced gastric cancer [2, 4].

The triplet tested in our trial showed a 33% RR according to intent-to-treat analysis, while this figure rose to 40% as per-protocol analysis. Although this activity was inferior to those achieved by other doublets [10–13, 15–20, 25, 26], and lower than that hypothesized in the study design, we would stress that this result was obtained in a series reflecting the gastric cancer population commonly seen in the clinical practice. Moreover, activity of our regimen was comparable in elderly and younger patients, and no other baseline demographic or clinical characteristic appeared to significantly affect probability of response.

Activity of our regimen was also mirrored by a long median PFS of 7.6 months, likely due to the high fraction (81%) of patients achieving disease control. Median OS (12.1 months) was also longer than expected for this kind of patients, and the probability of being alive at 2 years was 20%. In this regard, we would underscore that, considering the prognostic factors of our series, two-thirds of patients should have a moderate (43%) or poor risk (23%) score, which in a retrospective multivariate analysis were associated with median OS of 4.1 and 7.4 months, respectively [33].

For an indirect comparison, we would recall the performance of ECF regimen, which demonstrated superiority over the FAM in terms of RR (45 vs. 21%), FFS (median 7.4 vs. 3.4 months), OS (median 8.9 vs. 5.7 months), and

quality of life [5]. Also with ECF or its variants, substituting oxaliplatin for cisplatin (EOF), or oral capecitabine for fluorouracil (ECX), median OS was inferior to 10 months. Only the double drug substitution in the EOX regimen was associated with a prolongation of median OS (11.2 months) in comparison with the ECF regimen, but the 2-year OS was still around 20%. Moreover, no advantage in overall quality of life of patients was reported [6].

On the other hand, addition of docetaxel to cisplatin and fluorouracil (DCF regimen) demonstrated to significantly increase RR (37 vs. 25%), PFS (median 5.6 vs. 3.7 months), and OS (median 9.2 vs. 8.6 months) of patients in comparison with the CF regimen. However, also in this case, the gain in median OS was marginal, with a more striking difference at 2-year observation (18 vs. 9%), questioning the advantage of an early introduction in frontline of docetaxel, which surely increased the occurrence of febrile neutropenia and neutropenic infections, especially in patients aged ≥65 years [7].

Tolerability of our triplet was acceptable, because only 16% of patients withdrew early from the study for toxicity or refusal, while 68% of patients received at least eight cycles. The most common severe side effect of this treatment was neutropenia (59%); its occurrence compared favourably with that reported with DCF regimen (82%) [7], but was greater than that produced by ECF (36–42%) [5] or EOX (28%) [6]. Notably, due to the low cumulative dosage of oxaliplatin actually delivered in our trial, grade 3 neurotoxicity was infrequent.

Due to preventive or mandated dose-reductions applied in our study to 35 and 24% of patients, respectively, dose-intensity for all three cytotoxic drugs was suboptimal (around two-third of the planned one). Since there was a (non-significant) trend towards a higher RR for patients receiving a greater dose-intensity, we may speculate that tolerability, and possibly activity, of our regimen could be improved by the prophylactic delivery of G-CSF, at least in elderly patients.

Recently, Lee et al. assessed a three-drug combination of oxaliplatin, irinotecan, and 48-h infusion fluorouracil every 2 weeks in 48 metastatic gastric cancer patients with relatively favourable characteristics (median age 54 years; no patient aged ≥70 years; 85% with only 1 or 2 involved organs). They reported a 68% RR, and a median PFS of 9.6 months [34]. Therefore, despite a higher RR, median PFS was only 2-month longer than that obtained in our study. Neutropenia (assessed every 2 weeks during treatment) affected 52% of patients, and incidence of grade 3 vomiting and diarrhoea was 44 and 10%, respectively. Therefore, the all-infusional delivery of fluorouracil in this triplet did not seem safer than fluorouracil bolus. However, it remains to be explored whether oral capecitabine (mimicking a prolonged infusion of fluorouracil) could represent a preferable component of this triplet. Some preliminary experiences demonstrated the feasibility of such combination in metastatic colorectal cancer [35–37].

In conclusion, the triplet of oxaliplatin, irinotecan, and fluorouracil/folinic acid represents a tolerated and active treatment for advanced/metastatic gastric cancer patients, and it deserves comparison with other standard triplets. Moreover, it could be taken as a backbone on which to add molecularly target agents to be explored in this disease.

Conflict of interest statement No financial disclosures from any authors.

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