FOLFIRI as a second-line therapy in patients with docetaxel-pretreated gastric cancer: a historical cohort

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Abstract

Background: The role of second-line therapy in gastric cancer patients mostly stemmed from clinical trials with monochemotherapy carried out in Asian countries. Nevertheless, these results cannot be broadly generalized as molecular studies suggested the existence of different sets of deregulated gene networks correlated with ethnicity. In the present study, we investigated the activity and safety of FOLFIRI given as a second-line therapy in metastatic gastric or gastro-esophageal junction cancer patients who experienced disease progression on or after first-line docetaxel-containing chemotherapy.

Methods: Patients with histologically confirmed metastatic gastric cancer who failed docetaxel-containing first-line therapy and who received FOLFIRI in second line were eligible for the study. Seventy patients treated at three Italian cancer centers between 2005 and 2012 entered the study. Patients received every 2 weeks irinotecan 180 mg/m² as 1 h infusion on day 1, folinic acid 100 mg/m² intravenously days 1–2, and fluorouracil as a 400 mg/m² bolus and then 600 mg/m² continuous infusion over 22 hours days 1–2.

Results: We observed 1(1.4%) complete response, 15 (21.4%) partial response, for an overall response rate of 22.8% (95% confidence interval (CI): 13.4-32.3). Stable disease was recorded in 21 (30%) patients. Median progression-free survival and overall survival were 3.8 months (95% CI: 3.3-4.4) and 6.2 months (95% CI: 5.3-7.1), respectively. The treatment was well tolerated, as the most common G3-4 toxicities were neutropenia (28.5%) and diarrhea (14.5%).

Conclusions: FOLFIRI appears an effective and safe treatment option for pretreated metastatic gastric cancer patients, and deserves further investigation in randomized clinical trials.

Keywords: FOLFIRI, Gastric cancer, Second-line chemotherapy

Background

Gastric cancer and cancer of the gastro-oesophageal junction (GEJ) are a significant global health problem, representing the fourth most common cancer diagnosed worldwide [1]. The prognosis for these patients remain poor, as the majority of them are diagnosed with locally advanced or metastatic disease with a median survival of 7–10 months [2].

Several randomized clinical trials demonstrated the role of chemotherapy in the first-line setting, as different regimens determined an improvement in survival and in quality of life (QoL) compared with best supportive care (BSC) alone [3-5]. More recently, a wave of randomized clinical trials with superiority design was successfully completed, and novel active drugs such as docetaxel [6], S1 [7] and trastuzumab [8] changed the landscape of the clinical management of gastric cancer. Other agents including capectabine [9], oxaliplatin [10] and irinotecan [11] have proven antitumor activity, thus expanding the spectrum of therapeutic options available in the first-line setting. Even though novel active drugs and combinations entered the therapeutic scenario, second-line treatment...
has been historically considered largely empirical. Furthermore, geographic distributions exist in chemotherapy administration beyond first-line, being prevalently adopted in Asian countries. Indeed, the rates of administration of subsequent chemotherapy significantly differed among phase III studies conducted in front-line, spanning from 14% in the UK REAL 2 study [9] to 75% in the Japanese SPIRITS trial [7].

The clinical proof-of-concept for second-line chemotherapy stemmed from two recent randomized phase III trials, demonstrating the superiority of second-line monotherapy (docetaxel or irinotecan) over BSC [12,13]. Nevertheless, it is foreseeable that a widespread adoption of second-line chemotherapy will further be limited by multiple factors. Firstly, the non-Asian study was prematurely closed when only one-third of the preplanned 120 patients were enrolled [12]. As a result, evidence supporting second-line chemotherapy in non-Asian patients are still scattered being mostly extrapolated from the Korean study. Secondly, the different biological background of gastric cancer arising in Asian and Western patients must be taken into account as a potential confounding factor [14]. Finally, single-agent therapy may result suboptimal, at least for patients with good performance status.

On this basis, we conducted a retrospective study in order to evaluate the activity and safety of FOLFIRI given as a second-line therapy in a cohort of docetaxel-pretreated metastatic gastric cancer patients.

Methods
The study population was composed by patients with metastatic gastric or GEJ cancer who experienced disease progression on or after first-line docetaxel-containing chemotherapy. Patients were treated at three Italian cancer centers between 2005 and 2012. The majority of patients was selected from the “Regina Elena” National Cancer Institute, Rome. Medical records were reviewed in order to obtain information on demography, treatment received, safety and outcomes.

Patients with histologically confirmed, docetaxel-pretreated metastatic gastric cancer who received FOLFIRI in second line were eligible for the study. Other eligibility criteria included Eastern Cooperative Oncology Group performance status ≤2 (ECOG PS), aged between 18 and 75 years, adequate bone marrow (absolute neutrophil count ≥1500/μl, platelet count ≥100,000/μl), renal (serum creatinine ≤1.5 mg/dl) and liver (serum bilirubin ≤2 mg/dl) functions, normal cardiac function, absence of second primary tumor other than non-melanoma skin cancer or in situ cervical carcinoma, no central nervous system involvement, no prior radiotherapy in target lesions, and no concurrent uncontrolled medical illness.

Patients received every 2 weeks irinotecan 180 mg/m² as 1 h infusion on day 1, folinic acid 100 mg/m² intravenously days 1–2, and fluorouracil as a 400 mg/m² bolus and then 600 mg/m² continuous infusion over 22 hours days 1–2. The dose of irinotecan was reduced to 150 mg/m² in patients older than 70 years. Chemotherapy was generally administered on an outpatient basis for a maximum of 12 cycles. Treatment was continued until disease progression or unacceptable toxicity.

Toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria version 4.0 (NCI-CTC v. 4.0). Tumor response was evaluated according to the response evaluation criteria for solid tumors (RECIST 1.1). Progression-free survival (PFS) and overall survival (OS) were calculated from the date of therapy initiation to the date of disease progression, death from any cause or last follow-up evaluation, respectively. PFS and OS were analyzed according to the Kaplan-Meier method. The Cox proportional hazards regression model was used for univariate analysis of prognostic factors for survival. All statistical analyses were performed using SPSS statistical software version 20 (SPSS inc.,Chicago IL, USA). The study was approved by the coordinating centre’s Ethics Committee at the “Regina Elena” National Cancer Institute, Rome, and was carried out according to the principles of the Declaration of Helsinki. A written informed consent was obtained from all patients.

Results
Patients characteristics
Seventy patients with a median age of 65 years (range, 32–75) were included in this study. Patients’ characteristics are illustrated in Table 1. The primary tumor site was stomach in 54 patients (77%) and the GEJ in 16 patients (23%). The histology subtype was diffuse, intestinal and unknown in 33 (47%), 29 (41.5%), and 8 (11.5) patients, respectively. Primary tumor resection was carried out in twenty-five patients (36%). The ECOG PS was 0, 1 and 2 in 10 (14.5%), 40 (57%) and 20 (28.5%) patients, respectively. Fifty-three patients (76%) had two or more metastatic sites. PFS during first-line chemotherapy was ≥ 6 months in 42 patients (60%), and the chemotherapy-free interval was > 3 months in 38 patients (54%). Among regimens administered in the first-line setting, 25 patients (36%) received docetaxel, oxaliplatin and capecitabine [15], 20 patients (28.5%) received epirubicin, cisplatin and docetaxel [16], 19 patients (27%) were treated with epirubicin, oxaliplatin and docetaxel [17], and 6 patients (8.5%) received cisplatin and docetaxel [18].

Efficacy
Response to treatment is illustrated in Table 2. Among 70 assessable patients, we observed 1(1.4%) complete response (CR), 15 (21.4%) partial responses (PR), for an
overall response rate (ORR) of 22.8% (95% confidence interval (CI): 13.4–32.3). Stable disease (SD) was recorded in 21 (30%) patients, translating into a disease control rate (DCR) of 52.8%. Median PFS was 3.8 months (95% CI: 3.3–4.4), and median OS was 6.2 months (95% CI: 5.3–7.1) (Figure 1). In univariate analysis, the only significant predictors of OS were ECOG PS (0–1 vs 2: 7.0 months [95% CI: 5.7–8.3] vs 5.0 months [95% CI: 4.4–7.6], P = 0.01; HR 1.94 [95% CI: 1.13–3.33]) and PFS under first-line chemotherapy (≥ 6 months vs < 6 months: 7.1 months [95% CI: 6.2–8.0] vs 4.0 months [95% CI: 2.7–5.3], P = 0.04; HR 1.67 [95% CI: 1.02–2.34]). We did not observe any significant difference in efficacy nor in PFS and OS between patients who received fluoropyrimidine in the first-line compared with patients who did not (ORR: 24.4% vs 20%; PFS 3.8 vs 4.0 months, P = 0.79; OS 6.2 vs 6.5 months, P = 0.61).

Toxicity
Toxicities are listed in Table 3. A total of 352 cycles of FOLFIRI were analyzed in 70 patients, with a median of 6 cycles administered per patient (range, 2–12). The most common G3–4 toxicities were neutropenia (28.5%) and diarrhea (14.5%). Treatment discontinuation was necessary in 4 patients (5.7%). A 50% dose reduction was required in 2 patients (2.8%) for recurrent G3 diarrhea, whereas a 25% dose reduction was needed in 11 patients (21.2%), mostly correlated with G3 diarrhea (7 patients). Five patients required granulocyte colony-stimulating factor (G-CSF) for G4 neutropenia.

Discussion
In the present study, we reported that the use of FOLFIRI in the second-line setting in docetaxel-pretreated metastatic gastric cancer is associated with an ORR of 22.8% and a DCR of 52.8%. Median PFS and OS were 3.8 months and 6.2 months, respectively. To our knowledge, this is one of the largest series presented so far with second-line chemotherapy combination in non-Asian patients.

In the second-line setting, only two recent studies exploring the benefit of palliative chemotherapy were presented in full text. The Arbeitsgemeinschaft Internistische Onkologie (AIO) conducted in Germany analyzed single agent irinotecan (250 mg/m² every 3 weeks, increased to 350 mg/m² after the first cycle depending on toxicity) versus BSC [12]. Primary endpoint was OS. Even though the hazard ratio for death was 0.48 (95% CI 0.25–0.92), results must be interpreted with caution. Only 40 patients of the preplanned 120 entered the study, which closed prematurely due to poor accrual. Regarding efficacy, no objective tumor responses were documented, and disease stabilization for at least 6 weeks was reported in 53% of patients.
Figure 1 Kaplan–Meier curves. (A) progression-free survival. (B) overall survival.
Table 3 Main toxicity in 70 patients

| Toxicity            | Grade 3 (%) | Grade 4 (%) |
|---------------------|-------------|-------------|
| Neutropenia*        | 21.5        | 7           |
| Anemia              | 7           | -           |
| Thrombocytopenia    | 3           | -           |
| Diarrhea            | 13          | 1.4         |
| Nausea/vomiting     | 6           | -           |
| Mucositis           | 6           | -           |
| Fatigue             | 6           | -           |
| Hepatotoxicity      | 3           | -           |

*Four episodes of febrile neutropenia in 3 patients (4%).

We are aware of the intrinsic limitations of both retrospective studies and indirect comparisons. In our study, patient characteristics were similar, with the exception that in the AIO study none of the patients allocated in the irinotecan arm received docetaxel in first-line. However, even though the DCR was similar (52.8% vs 53%), we reported an ORR of 22.8%. Apparently, FOLFIRI compares favorably when considering PFS (3.8 months vs 2.5 months) and OS (6.2 months vs 4.0 months). Surprisingly, FOLFIRI seemed to be better tolerated than irinotecan monotherapy (G3-4 diarrhea 14.4% vs 26%, neutropenic fever 4% vs 16%), probably because of the lower irinotecan cumulative dose and the different schedule.

In the second phase III trial, 202 Korean patients were randomized in a 2:1 fashion to receive either chemotherapy, consisting in biweekly irinotecan 150 mg/m² or docetaxel 60 mg/m² every 3 weeks at the physician’s discretion, or BSC [13]. Docetaxel-containing chemotherapy was administered only in the 3% of patients. The intention to treat analysis showed an increase in OS with chemotherapy (5.3 months vs 3.8 months) with a HR of 0.657 (95% CI: 0.485-0.891, \( P = 0.007 \)). No differences were seen in correlation with the type of chemotherapeutic agent, thus complementing the results from the Japanese phase III WJOG4007 study (reported only in abstract form) and from an European, randomized, three-arm phase II study which also evaluated a liposomal nanocarrier formulation of irinotecan [19,20]. Even though these results have to be considered as a major step forward in the management of gastric cancer, we believe they cannot be broadly generalized. It is known that the topographic distribution (distal vs proximal), pathological features (intestinal vs diffuse) and, even more importantly, survival outcome differ between Asian and Western patients [14,21,22]. Treatment pattern is one of the factors proposed to explain such discrepancies, as extensive D2 resection in early stage gastric cancer is routinely used in Asian countries. Nevertheless, a comparison of surgical outcomes between patients treated at the Memorial Sloan Kettering Cancer Center, where D2 resection is extensively carried out, and patients treated in Korea revealed better disease-specific survival for the latter group [23]. Therefore, it is foreseeable that underlying biological differences play a crucial role, and growing evidence indicate that the molecular taxonomy of gastric cancer is influenced by ethnic factors. MicroRNA expression profiling, which is emerging as an excellent classifier in oncology, and next-generation sequencing studies are beginning to unveil the existence of different sets of deregulated gene networks potentially correlated with ethnicity [24-26]. Furthermore, the molecular analysis of the ToGA trial revealed that HER2 positivity is associated with the intestinal-type gastric cancer (32.5% intestinal vs 6.0% diffuse), the most common histology in Asia [8]. Overall, the different ethnicity-related molecular landscape of gastric cancer might reflect a different expression of therapeutic targets and, in turn, sensitivity to anticancer agents. Beyond tumor biology, also pharmacogenomic differences should be taken into account. For instance, while S1 is extensively used in front-line in Asia, its use in the Western hemisphere was initially constrained by evidence of more severe toxicity in Caucasian patients [27]. The different magnitude of toxic effects is thought to be correlated with CYP2A6 gene polymorphisms, affecting the conversion of S1 to fluorouracil. Indeed, in the phase III FLAG study conducted in non-Asian countries S1 was used at a lower dose compared to Japanese studies [28], despite the higher body surface of Western patients.

Next, in the European FFCD-GERCOR-FNCLCC trial 416 patients were randomized to receive two different sequential strategies in first- and second-line: epirubicin, cisplatin and capecitabine in first-line and FOLFIRI in second-line vs the reverse sequence [29]. The sequence with FOLFIRI in first-line resulted superior for the primary endpoint (time to treatment failure), a benefit deriving from the better tolerance and the correlated lower rate of treatment discontinuation. However, no firm conclusions can be drawn from this trial having been only presented in abstract form to date.

Finally, a recent retrospective Turkish study reported data from 97 docetaxel-pretreated patients who received FOLFIRI in the second-line setting [30]. Investigators reported an ORR of 26.8% and a DCR of 58.8%. However, it is worth considering that 19 patients (19.5%) had locally recurrent gastric cancer and 47 patients (48.5%) had only one metastatic site. In our opinion, the rather heterogeneous study cohort along with the inclusion of a consistent fraction of patients with lower tumor burden compared to those examined in our study led to an overestimation of the results, as investigators reported a median OS of 10.5 months.

Conclusions

FOLFIRI appears an effective and safe treatment option for pretreated metastatic gastric cancer patients. However, second-line chemotherapy comparative trials are needed to better define the role of FOLFIRI in gastric cancer (e.g. versus monochemotherapy).
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