FOLFIRI with or without celecoxib in advanced colorectal cancer: a randomized phase II study of the Gruppo Oncologico dell’Italia Meridionale (GOIM)

E. Maiello1,2*, F. Giuliani1, V. Gebbia3, N. Di Renzo4, G. Pezzella5, S. Romito6, R. Mallamaci1, M. Lopez7 & G. Colucci7

On behalf of GOIM (Gruppo Oncologico dell’Italia Meridionale)

1Oncology Institute, Bari; 2Casa Sollievo della Sofferenza Hospital, S. Giovanni Rotondo; 3University of Palermo; 4Oncologic Center, Rionero in Vulture; 5Ospedale Nord, Taranto, 6Cardarelli Hospital, Campobasso, 7Regina Elena Institute, Rome, Italy

Background: The aim of the study was to verify the efficacy and safety of the addition of celecoxib to FOLFIRI combination therapy in patients affected by advanced colorectal cancer.

Patients and methods: Eighty-one chemotherapy-naïve patients entered in this randomized phase II trial of the GOIM (protocol no. 2301). Patients were randomized to receive FOLFIRI regimen (arm A): irinotecan 180 mg/m² on day 1 with LV5FU2 regimen (LV at 100 mg/m² administered as a 2-h infusion before FU at 400 mg/m² as an intravenous bolus injection, and FU at 600 mg/m² as a 22-h infusion immediately after 5-FU bolus injection on day 1 and 2); or FOLFIRI plus celecoxib 400 mg twice daily for 14 days (arm B). Both treatments were repeated every 2 weeks.

Results: Seventy-seven patients (38 in arm A and 39 in arm B) were evaluable for response. The overall response rate was 41% in arm A (95% CI 27% to 57%) and 35% in arm B (95% CI 20% to 50%). When only assessable patients were analyzed, overall response rate was 45% in arm A (95% CI 29% to 61%) and 36% in arm B (95% CI 21% to 51%). Median time to progression, median duration of response and survival were, respectively, 8 months, 9 months and 16 months in arm A, and 7 months, 9 months and 19 months in arm B. All patients were evaluable for toxicity, which was globally mild in both arms; grade 3–4 toxicity was uncommon, and gastrointestinal disturbances were the most common.

Conclusions: FOLFIRI regimen is effective and well-tolerated as a first-line treatment in patients with advanced colorectal cancer. The addition of celecoxib to FOLFIRI regimen does not improve results.

Key words: colorectal cancer, folinic acid, fluorouracil, irinotecan, celecoxib

Introduction

Currently, the standard chemotherapy treatment for advanced colorectal cancer patients is the combination of 5-fluorouracil (5-FU) and leucovorin (LV) with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI). The efficacy of these regimens is well known [1, 2] and in order to establish the best treatment between FOLFOX4 or FOLFIRI regimen, the GOIM carried out in 1999 a randomized trial (GOIM protocol no. 9901) to compare the FOLFIRI and the FOLFOX4 combination therapies in patients with advanced colorectal cancer. The primary end point of this study was response rate and secondary end points were time to progression, overall survival and toxicity profile. Three-hundred and sixty consecutive, non-selected patients entered into this trial and no difference in response rate, time to progression and overall survival were observed between the two treatments. The difference between these two combination therapies remained mainly in the toxicity profile [3].

The cyclooxygenase enzymes are key enzymes of prostaglandin (PG) biosynthesis, responsible for the conversion of arachidonic acid into PG. Two isoforms of COXs are known: the constitutive COX-1 and the inducible COX-2, the latter preferentially expressed in inflammatory and neoplastic tissues [4].

Numerous studies have shown that cyclo-oxygenase-2 (COX-2) may be related to colorectal cancer development and propagation through multiple mechanisms, including stimulation of growth, migration and invasiveness, resistance to apoptosis and enhancement of angiogenesis [5]. Expression of COX-2 has been identified in 70%–90% of resected human colorectal cancers [6].

Several in vitro, in vivo and clinical studies previously showed that celecoxib, a specific COX-2 inhibitor, may prevent colorectal cancer [7, 8]. The specific mechanism of action of COX-2 inhibitors as anticancer agents has not yet to be established [9] and the addition of COX-2 specific inhibitors
not appear to be subject to investigator bias. Thus, the stratification factors were as follows: (a) size of disease, ‘limited’ or ‘extensive’ disease (less or more than 10 cm², respectively) and (b) patients with or without liver involvement (H+ and H-, respectively). Four patient categories were obtained: group 1: H+/>10 cm²; group 2: H+/<10 cm²; group 3: H-/>10 cm²; and group 4: H-/<10 cm².

Patients were randomized to receive FOLFIRI regimen (arm A) as follows: CPT-11 at 180 mg/m² only on day 1, together with LV at 100 mg/m² (l-isomer-form) administered as a 2-h infusion before 5-FU at 400 mg/m² as an intravenous bolus injection, and FU at 600 mg/m² given as a 22-h infusion immediately after 5-FU bolus injection; LV and FU were repeated on days 1 and 2. In arm B, patients received FOLFIRI regimen as previously reported plus celecoxib 400 mg/m² twice daily from day 1 to day 14. Both regimens were administered at 2-week intervals.

Prophylactic antiemetics were routinely given before each administration of CPT-11. Diarrhea or abdominal cramping or important symptoms of a cholinergic syndrome that occurred during or within 1 h after receiving CPT-11 were treated with atropine (0.25 mg s.c.). Routine use of a colony-stimulating factor was not utilized in this trial. For symptoms of diarrhea and/or abdominal cramping that occurred more than 12 h after receiving treatment, patients were instructed to begin taking loperamide as soon as the first liquid stool occurred (2 mg p.o. every 2 h for at least 12 h and up to 12 h after the last liquid stool without exceeding a total treatment duration of 48 h). Oral rehydration with large volumes of water and electrolytes was prescribed during the whole diarrhoeal episode. If diarrhea persisted for more than 24 h despite the recommended loperamide treatment, a 7-day treatment, patients were instructed to begin taking loperamide as soon as the first liquid stool occurred (2 mg p.o. every 2 h for at least 12 h and up to 12 h after the last liquid stool without exceeding a total treatment duration of 48 h). Oral rehydration with large volumes of water and electrolytes was prescribed during the whole diarrhoeal episode. If diarrhea persisted for more than 24 h despite the recommended loperamide treatment, a 7-day prophylactic oral, broad spectrum antibiotic therapy with fluoroquinolone was initiated.

patients and methods

patient selection

The eligibility criteria included the following: histologically confirmed locally advanced and/or metastatic colonic carcinoma with bidimensionally measurable disease, age ≥18 and ≤75 years, life expectancy of at least 3 months, performance status 0–2 according to the Eastern Cooperative Oncology Group (ECOG) scale, adequate bone marrow (platelets count ≥100 000/l, WBC count ≥40000/l, granulocyte count ≥1500/mm³, a hemoglobin level of ≥10.0 g/dl), renal (serum creatinine concentration ≤2.0 mg/dl) and hepatic functions (serum bilirubin level ≤2.0 mg/dl and AST three or less times the institutional normal level in the absence of liver involvement with cancer or up to five times the institutional normal level when cancer was present in the liver). No concurrent uncontrolled medical illness was allowed. Patients had to be previously untreated for advanced disease, but prior adjuvant chemotherapy was allowed if 6 months had elapsed since discontinuation of treatment.

Patients were excluded if any of these criteria was not met and also in the presence of active infections, cerebral metastases, evidence of congestive heart failure, serious cardiac arrhythmias, symptoms of coronary artery disease, history of thromboembolic disease or other malignancy (apart from adequately treated non-melanotic skin cancer and carcinoma in situ of the uterine cervix), or any psychological condition that precluded treatment or adequate follow-up. Radiotherapy was allowed only in sites other than those measurable for response evaluation.

Pretreatment evaluation included a complete medical and clinical–physical examination, baseline measurement of tumor size based on scans, X-ray examination or other radiographic means (comprising full assessment of all known metastatic disease), chest X-ray, electrocardiogram (ECG) and tumor markers.

Patients had to agree to, and sign, a statement of informed consent prior to entry in this study. Informed consent was previously approved by the Scientific Committee of the GOIM and ethic committees of each individual participating institutions.

treatment plan

According to our previous experience [3], the size and site of disease were considered as prognostic variables for the stratification of cases and therefore patients were stratified according to the presence or absence of hepatic disease, and by total tumor burden defined as ‘limited’ or ‘extensive’ disease using 10 cm² as the cut-off. The value of this cut-off was arbitrarily chosen. The estimation of tumor size (more or less than 10 cm²) was determined according to the sum of the products of the largest perpendicular diameters of all measurable disease. It was found that this stratification method could be easily reproduced in the various centers participating in the study and did enhanced the effects of cytotoxic agents [10]. In a recent study [11], celecoxib was combined with irinotecan to treat HT-29 colonic cancer xenograft tumors in nude mice: a reduction in tumor growth of 91.4% was observed with combined celecoxib plus irinotecan, compared with 28.7% with irinotecan or 72.3% with celecoxib alone. Furthermore, in this study a reduction in the occurrence of irinotecan-induced late diarrhea was also observed.

Taking into account the above studies, in 2003 the Gruppo Oncologico dell’Italia Meridionale (GOIM) initiated a phase II randomized trial (GOIM protocol no. 2301) to compare the FOLFIRI regimen, according to the schedule of Douillard et al. [1], and the same regimen plus celecoxib in patients with advanced colorectal cancer.

study design and statistics

The primary end point of this trial was objective response rate (ORR). Secondary end points included toxicity, time to progression and overall survival (OS). Patients were randomized to FOLFIRI versus FOLFIRI plus celecoxib with a random ratio of 1:1.

Simon’s optimal two-stage design was used for calculation of the sample size. With a 5% alpha risk and a power of 0.90, we determined a first-stage response probability of 20% (which, if true, implied discontinuing the trial) and a minimal rate of efficacy of 30% (which, if true, implied moving on to the second stage of the trial). Therefore, more than four responses in 17 evaluable patients were required to move on to the second phase of enrollment up to 37 patients.

evaluation of response and toxicity

Response was first evaluated after four cycles and then every 2 months, according to RECIST criteria [11]. Objective responses were reported as relative rates with their 95% confidence intervals (95% CI). Response rates were provided for all patients (intent to treat analysis) and for evaluable patients.

Survival, response duration and time to progression were determined from the date of first treatment until death or last follow-up, and progression.

All toxicities were graded according to the NCI Common Toxicity Criteria. If multiple toxicities were observed, the dose administered was based on the most severe toxicity experienced. The dose adjustment schedule was evaluated at the beginning of a new course (based upon laboratory analyses on the scheduled day of treatment and upon maximum toxicity encountered during the previous course). Dose reductions or treatment delays were calculated according to the non-hematological toxicity or myelosuppression recorded at the time of the planned recycling (day 14). The drug dose level was reduced in the case of severe or persistent toxicity; the LV dose remained fixed (100 mg/m²), while CPT-11 was reduced to...
150 mg/m², 5-FU bolus to 300 mg/m² and 5-FU c.i. to 500 mg/m². In the case of persistent grade 3 toxicity or whenever grade 4 toxicity was recorded, chemotherapy was definitively stopped. In the presence of grade 2–3 hematological toxicity, treatment was delayed for 1 week or until hematological recovery. If recovery was not reached, the dose level was reduced. For grade 0–2 gastrointestinal toxicity dose administration was 100%, and for grade 3 toxicity, after a 1-week delay, the dose level was reduced.

**results**

**patient and clinical characteristics**

From January 2003 to December 2004, 81 patients were admitted to this trial from the participating centers. The main characteristics of the entered patients are summarized in Table 1. The median age of all patients was 62 years. The majority of patients had a primary colon cancer and liver metastases. Multiple disease sites were found in 44% of patients in arm A and in 47% in arm B.

**therapeutic outcome**

A total of 77 (96%) patients were deemed assessable for response (38 in arm A, 39 in arm B). Overall, three patients in arm A and one in arm B were considered non-evaluable for the following reasons: three patients (arm A) refused to continue the treatment despite low toxicity and one patient (arm B) for early death unrelated to chemotherapy.

Main results are listed in Table 2. One complete response (CR) was observed in both arms, while 16 partial responses (PR) and 13 PR were obtained in arm A and in arm B, respectively. Globally, in the intent to treat (ITT) analysis objective response rate (ORR) in arm A and in arm B was 45% (95% CI 29% to 61%) and 36% (95% CI 21% to 51%), respectively. When only assessable patients were analyzed, ORR was 41% (95% CI 27% to 57%) with the FOLFIRI regimen and 35% (95% CI 20% to 50%) with the addition of celecoxib.

When considering stable disease (SD), the overall tumor growth control rate (CR+PR+SD) was 70% and 77% in the ITT analysis in arms A and B, respectively. Twenty-nine patients received a second-line therapy in both arms (all with oxaliplatin containing regimen). With a median follow-up of the study of 18 months (range 10–32 months), the median duration of response (arm A versus arm B) was 9 versus 9 months, while the median time to progression by ITT analysis was 8 versus 7 months. According to the ITT analysis, the median survival time was 16 months in arm A and 19 months in arm B.

**toxicity**

All patients were evaluable for toxicity. There were no therapy-related deaths in both arms. The percentages of the observed toxicities, according to the NCI criteria, are outlined in Table 3. Globally, toxicity was mild and grade 3–4 disturbances were uncommon. As expected, gastrointestinal toxicities (mainly grade 1–2) were the most frequent toxicities. Symptoms related to a cholinergic syndrome occurred in 13% of patients. All these events were manageable. No cardiac toxicity was observed.

**discussion**

In recent years, in the treatment of advanced colorectal cancer patients, a number of new treatment options have become available. New approaches were clearly needed to improve...
clinical results. In order to enhance the results and following progress on the knowledge of colon cancer biology, new strategies were developed. In this scenario, COX-2 inhibitors appeared interesting. Despite a lack of phase I data, a few phase II trials investigated the addition of COX-2 inhibitors to conventional chemotherapy.

In the Blanke et al. phase II study [12], combining celecoxib with the Saltz regimen (IFL) [13], a 28% objective response rate was observed in the 23 enrolled patients, with a possible trend towards a decrease in the rate of grade 3/4 febrile neutropenia. In another similar phase II trial of the Hoosier Oncology Group [14], patients received IFL regimen plus celecoxib, with the addition of glutamine to reduce diarrhea. In the 38 patients evaluable for toxicity, 32% of cases showed grade 3 diarrhea and 34% grade 3–4 neutropenia; no grade 4 diarrhea and neutropenic fever was observed. Two CR, 11 PR and nine SD were obtained in the 31 patients evaluable for response.

Recently, Lin et al. [15] reported the results of a retrospective study. Sixty-seven patients with advanced colorectal cancer received capecitabine for their disease (first or second-line therapy); 35 of these patients received capecitabine alone and 32 capecitabine plus celecoxib (200 mg p.o. b.i.d.) administered for pain management. Patients receiving both drugs showed a higher rate of stable disease than patients treated with the single drug (62.5% versus 22.8%; \( P = 0.001 \)), an increase in the median time to tumor progression (6 versus 3 months; \( P = 0.002 \)), and seemed to attenuate capecitabine-induced diarrhea (grade 2 diarrhea: 3.1% versus 28.6%; \( P = 0.005 \)). In addition, a marked reduction in the incidence of hand–foot syndrome was noted with the combination therapy (15.6% in the capecitabine plus celecoxib regimen versus 51.4% in the capecitabine alone group).

The addition of another COX-2 inhibitor (rofecoxib) to chemotherapy was investigated. In Becerra et al. [16], 10 patients with advanced colorectal cancer received 5-FU plus leucovorin (Mayo regimen) and rofecoxib. The addition of the COX-2 inhibitor in this study did not enhance the antitumor activity (no objective response was obtained), and resulted in increased gastrointestinal toxicity (four patients showed an upper gastrointestinal bleeding).

In a recently published phase I–II study [17], 48 patients were enrolled to receive weekly irinotecan, infusional 5-FU and rofecoxib as second-line treatment for advanced colorectal cancer. Sixteen patients achieved PR (48.5%) and 10 SD (30%), with a median time to progression of 7 months and a median overall survival of 18 months. Side-effects appeared moderate and the most common toxicity was diarrhea occurring in grade 3 in 36% of patients.

Our study confirmed the efficacy and safety of FOLFIRI regimen as previously reported in the GOIM experience [3, 18]. The addition of celecoxib to this combination therapy did not improve the results obtained with FOLFIRI alone: the ORR was lower in the arm with combined celecoxib, but more SD and a slight improvement in the overall tumor growth control rate was observed in the COX-2 inhibitor arm.

Toxicity was mild in both arms and the addition of celecoxib did not alter the toxicity profile of the FOLFIRI regimen. The reported cardiovascular toxicity associated with celecoxib in a clinical trial for colorectal carcinoma [19], was not observed in our study. A high percentage of patients (about 75%) received a second-line treatment with oxaliplatin containing regimens, resulting in a favorable median survival time of 16 and 19 months in arms A and B, respectively.

In conclusion, our experience confirmed the efficacy of the addition of CTP-11 to LV5FU2 schedule and the mild toxicity of this regimen. The FOLFIRI regimen together with FOLFOX combination therapy remains an efficacious first-line choice in the treatment of advanced colorectal cancer patients. Results of our study (GOIM protocol 2301) did not demonstrate the advantage of the addition of COX-2 inhibitor celecoxib to FOLFIRI combination treatment.

A definitive response on the role of COX-2 inhibitors in the treatment of colorectal cancer patients will be available with the results of the ongoing phase III trials.

### references


### Table 3. NCI Toxicities (percentages values)

<table>
<thead>
<tr>
<th></th>
<th>Arm A Total</th>
<th>Arm A Grade 3–4</th>
<th>Arm B Total</th>
<th>Arm B Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>17</td>
<td>2</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>2</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15</td>
<td>–</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>46</td>
<td>–</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>50</td>
<td>5</td>
<td>45</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>7</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Mucositis</td>
<td>17</td>
<td>2</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Fever</td>
<td>22</td>
<td>–</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Loss of hair</td>
<td>15</td>
<td>–</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Cholinergic syndrome</td>
<td>15</td>
<td>–</td>
<td>15</td>
<td>–</td>
</tr>
</tbody>
</table>


