Original article

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Raltitrexed plus oxaliplatin (TOMOX) as first-line chemotherapy for metastatic colorectal cancer. A phase II study of the Italian Group for the Study of Gastrointestinal Tract Carcinomas (GISCAD)

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Background: To evaluate the safety and efficacy of the novel raltitrexed/oxaliplatin combination (TOMOX) as first-line chemotherapy for patients with advanced colorectal cancer.

Materials and methods: Previously untreated patients with metastatic colorectal cancer received raltitrexed 3 mg/m^2 plus oxaliplatin 100 mg/m^2, both intravenously, on day 1 every 3 weeks. Patients were re-evaluated after every third cycle and chemotherapy was continued up to tolerance or disease progression.

Results: Fifty-eight patients from 13 Italian Group for the Study of Gastrointestinal Tract Carcinomas (GISCAD) centers were accrued from September 1999 to November 2000. According to the intention-to-treat analysis from 58 patients, the overall response rate was 50% [95% confidence interval (CI) 38% to 62%], with three complete responses and 26 partial responses. The median overall survival (44 patients currently alive) was >9 months and the median time to disease progression was 6.5 months (range 1–15 months). The main hematological toxicity was grade III/IV neutropenia, which occurred in 17% of patients, while anemia and thrombocytopenia were uncommon. Grade III/IV non-hematological toxicities were transient transaminitis (17% of patients); asthenia (16% of patients); neurotoxicity (10% of patients) and diarrhea (7% of patients). No toxic death was observed, one patient with grade IV asthenia after the first cycle refused chemotherapy.

Conclusions: The results of this study suggest that the TOMOX combination is an effective and well tolerated regimen for the treatment of advanced colorectal cancer. Its ease of administration and patient tolerance warrant further investigation as an alternative to fluoropyrimidine-based regimens with repeated and prolonged fluorouracil infusions.

Key words: chemotherapy, colorectal cancer, oxaliplatin, raltitrexed

Introduction

Over the last few decades, major improvements have been achieved in the treatment of metastatic colorectal cancer; new effective compounds and fluorouracil schedules have produced better results than conventional fluorouracil-based regimens [1]. The bimonthly combination of bolus plus continuous infusion of fluorouracil and folinic acid, known as the 'de Gramont' regimen, showed a higher response rate and longer progression-free survival than the combination of the same drugs in the monthly 5-days bolus North Central Cancer Treatment Group/Mayo clinic regimen [2]. New cytotoxic agents, such as the topoisomerase I inhibitor irinotecan [3], the

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platinum derivative oxaliplatin [4] or the novel thymidylate synthase inhibitor raltitrexed [5, 6] demonstrated significant single-agent activity in the setting of first- and second-line chemotherapy. At present, the de Gramont regimen coupled with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) can be considered as two of the most effective combinations for the treatment of advanced colorectal cancer [7, 8].

Ongoing clinical trials are investigating innovative chemotherapeutic strategies and combinations of new drugs. Chemotherapy with raltitrexed and oxaliplatin has the advantage of a short infusion every 3 weeks, with potentially higher levels of acceptability among patients than schedules with repeated and prolonged fluorouracil infusions [4, 6]. Raltitrexed and oxaliplatin have different mechanisms of action, different toxicity profiles and an additive effect in experimental studies. In two randomized phase III studies, patients who received the combination of oxalipatin, fluorouracil and leucovorin achieved higher response rates and longer progression-free survival than patients treated with fluorouracil/leucovorin [1, 8]. Raltitrexed was investigated in four randomized trials and compared with fluorouracil-based chemotherapy [9–12]. Response rates were similar between treatment arms, but one of these studies showed a survival advantage in favor of patients treated with conventional fluorouracil/leucovorin [9].

The raltitrexed–oxaliplatin combination has been explored in phase I studies, both drugs were administered as short intravenous infusions every 3 weeks and recommended doses for phase II studies resulted in the same doses as for single agent use [13, 14]. In early phase II studies [14, 15], the combination of raltitrexed 3 mg/m^2 with oxaliplatin 130 mg/m^2 showed promising results, although oxalipaltin-related neurotoxicity was one of the most common side effects, with an incidence in patients ranging from 67% [14] to 97% [15].

We performed a multi-institutional phase II study of a raltitrexed/oxaliplatin combination (TOMOX) as first-line chemotherapy for patients with metastatic colorectal cancer. Given the relationship between incidence of neurotoxicity and cumulative oxaliplatin dose [4], we assessed the safety and efficacy of a TOMOX combination with oxaliplatin 100 mg/m^2 every 3 weeks.

Materials and methods

Patient selection

Chemotherapy-naïve patients with pathologically confirmed, relapsed or metastatic colorectal cancer were considered eligible for the study. Other eligibility criteria were bidimensionally measurable metastatic lesions, Eastern Cooperative Oncology Group (ECOG) performance status 0–2; age <75 years, and normal liver, renal and bone marrow functions. Careful evaluation of renal function was performed before starting chemotherapy; patients were excluded in the case of serum creatinine concentrations >1.5 mg/dl and creatinine clearance <50 ml/min. If prior adjuvant chemotherapy had been given, it had to have been completed for at least 6 months. The protocol was approved by each local ethics committee and all patients gave written informed consent. The primary endpoints were the analysis of tumor response and toxicity. Secondary endpoints were time to disease progression (TTP) and overall survival.

Treatment plan

Chemotherapy consisted of a 1 day every 3 weeks intravenous administration of raltitrexed 3 mg/m^2 (15-min infusion) followed by a 2-h infusion of oxaliplatin 100 mg/m^2. Full doses of both drugs were given if the neutrophil count was $\geq 1.5 \times 10^9$/l and the platelet count $\geq 100 \times 10^9$/l. In the case of grade III toxicity, dose reductions were not recommended and patients necessitated a 7-day treatment delay. Patients were taken off study if there was no complete recovery from toxicity within 3 weeks after the last course. The doses of both drugs were reduced by 25% in the case of grade IV toxicity. Patients with complete response (CR) or disease progression did not receive further chemotherapy. Patients with partial response (PR) or stable disease continued chemotherapy until progression, toxicity or refusal.

Evaluation procedures

Pretreatment evaluation consisted of baseline studies including medical history, physical examination, blood chemistries, urinoanalysis, ECG and carcinoembryonic antigen (CEA) serum levels. Also, chest X-rays, abdominal computed tomography or magnetic resonance scan, bone scan and any other test to identify the extent of disease were performed within 1 month before the onset of chemotherapy. Patients were re-evaluated after every third treatment course and every 2 months after treatment withdrawal. Complete blood cell counts and serum chemistries for monitoring liver and renal functions were performed weekly during treatment and before every course. The study was monitored by the GISCAD Data and Safety Monitoring Committee and an internal panel evaluated tumor response according to World Health Organization criteria [16]. The National Cancer Institute/Common Toxicity Criteria (NCI/CTC) version 2.0 [17] were used to evaluate treatment-related side effects.

Statistical plan

A two-staged Simon accrual design was adopted for this phase II trial. The minimum target activity level was 20% and early discontinuation of the study was planned in the case of no response in the first 12 assessable patients. Alternatively, a planned sample size of 55 evaluable patients was chosen to better estimate efficacy; 25% maximum width of the 95% confidence interval (CI) for an expected 40% overall response rate. TTP was measured from the date of registration to the date of documented progressive disease or death. Overall survival was measured from the time of registration to the date of death resulting from any cause.

Results

The study population consisted of 58 patients enrolled from September 1999 to November 2000 from 13 participating GISCAD centers. Synchronous metastatic disease was observed in 27 patients. In 31 patients, metastatic colorectal cancer was diagnosed during follow-up and the median time to relapse from surgery was 13 months (range 2–96 months). The clinico-pathological features of the enrolled patients are summarized in Table 1. On the whole, 288 courses of chemotherapy were administered; five patients received less than three cycles, 23 patients three to four cycles, 24 patients six

Table 1. Characteristics of the 58 patients enrolled in the study

No. of patients	58
Sex ratio	
Male	31
Female	27
Median age (range)	61 years (45–70)
ECOG performance status	
0	31
1	26
2	1
Prior adjuvant therapy	
None	27
FU/LV	31
Number of organs involved	
1	33
2	13
>3	12
Sites of metastases	
Liver	45
Lung	30
Other	23
CEA level	
<10 ng/ml	20
≥10 ng/ml	38
Alkaline phosphatases >UNL	22
Lactate dehydrogenase >UNL	30

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; FU/LV, fluorouracil/leucovorin; UNL, upper normal limit.

to seven cycles and six patients nine to 10 cycles. For the intention-to-treat analysis, all 58 patients were evaluated for efficacy and toxicity.

Efficacy

Early discontinuation of treatment before the first evaluation was caused by early progression (two patients), refusal for personal reasons (two patients) and refusal due to grade IV asthenia (one patient). Objective responses were achieved as follows: 20 patients with PR after three cycles; six patients with PR and two patients with CR after six cycles; one patient with CR after nine cycles (previous stable disease). The median time to response was 1.9 months (range 1.5–6 months). According to the intention-to-treat analysis in the 58 patients, the best overall response rate was 50% (95% CI 38% to 62%), with three CRs, 26 PRs, 13 stable diseases and 16 failures.

Of the three patients who achieved CR, two had multiple liver metastases and one patient had bilateral lung metastases.

Follow-up and survival

At the time of the last analysis (May 2001), the median follow-up duration was 12 months (range 6–18 months), 44 patients were alive (75%) and 14 patients had died due to progressive disease. The median survival duration had not yet been reached [>9 months (range 2–22+)], and the median time to disease progression was 6.5 months (range 1–15 months). Second-line chemotherapy was administered to 30 patients; this consisted of CPT-11 plus fluorouracil in 28 patients and prolonged infusional fluorouracil in two patients. Two patients with PR and metastatic disease confined to the liver underwent thermoablative treatment or chemo-embolization for residual disease.

Toxicity

Toxicity data for the 58 patients are summarized in Table 2. Neutropenia was the most common hematological toxicity to occur: grade I/II in 52% of patients and grade III in 10% of patients. No episodes of grade IV neutropenia were reported and the median nadir of neutrophil counts was 1890/mm^3 (range 550–5400/mm^3). Transient transaminitis, nausea/vomiting, asthenia and neurotoxicity were the most common non-hematological side effects. Transient grade I–II transaminitis was observed in 61% of patients and grade III/IV in 17% of patients. The elevation of liver enzymes was asymptomatic and it resolved after 1- or 2-week treatment delays. Grade III/IV asthenia, diarrhea and nausea/vomiting were observed in 16%, 7% and 5% of patients, respectively. One patient, who experienced grade IV asthenia, refused further chemotherapy. Neurotoxicity was observed in 53% of patients and achieved grade III after 12 cycles delivered to six patients (10%). Minor toxicities were grade I alopecia in eight patients, grade I myalgia in four patients, grade I dermatitis in two patients and grade I renal toxicity in one patient.

According to the treatment plan, chemotherapy was delayed at least once for 20 of the patients for a maximum of 14 days. Treatment delays occurred more frequently after the third cycle of chemotherapy because of grade III neutropenia, transaminitis or asthenia. Three patients had a 25% dose reduction of both cytotoxic because of severe (grade IV) transaminitis or diarrhea. Neither allergic reactions nor drug-related toxic death were observed.

Discussion

Over recent decades, the results of fluorouracil-based chemotherapy for metastatic colorectal cancer have slowly improved, but the pace has quickened in recent years. Innovative fluorouracil schedules and new active compounds have allowed medical oncologists to offer patients first- and second-line treatments giving a higher chance of objective response and longer survival times than in the past [1].

Table 2. Side effects reported in the 58 enrolled patients (National Cancer Institute/Common Toxicity Criteria)

Toxicity	Number of patients with toxicity (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Transaminitis	20 (34)	16 (27)	9 (15)	1 (2)	46 (78)
Neutropenia	19 (32)	12 (20)	6 (10)	0	37 (62)
Nausea/vomiting	21 (36)	10 (17)	4 (5)	0	35 (58)
Asthenia	13 (22)	9 (15)	8 (14)	1 (2)	31 (53)
Neuropathy	17 (29)	8 (14)	6 (10)	0	31 (53)
Diarrhea	16 (27)	2 (3)	3 (4)	2 (3)	23 (37)
Anemia	17 (29)	4 (5)	1 (2)	0	22 (36)
Mucositis	5 (8)	6 (10)	1 (2)	0	12 (20)
Thrombocytopenia	8 (14)	2 (3)	0	0	10 (17)

In the present study, the combination of raltitrexed and oxaliplatin showed activity with good patient tolerance. So far, two previous studies have analyzed the toxicity and efficacy of this regimen. Scheithauer et al. [14] treated 42 patients in the phase II portion of their study, employing raltitrexed 3 mg/m^2 (15 min infusion) followed by a 2-h infusion of oxaliplatin 130 mg/m^2, both intravenously every 3 weeks. The intention-to-treat overall response rate was 47% (95% CI 32% to 63%), the median progression-free survival was 9 months and the median overall survival was >14.5 months (67% of patients still alive at the time of analysis). Grade III–IV neutropenia was the most common hematological toxicity (21% of patients); transient transaminitis, peripheral neuropathy and diarrhea were the most frequent non-hematological side effects. The same treatment schedule was used by Douillard et al. [15], who found in 63 patients an intention-to-treat overall response rate of 57% (95% CI 46% to 69%) and a median time to progression of 6.3 months. Safety data in 277 cycles (66 patients) confirmed neutropenia (grade III–IV in 16% of patients) and neurotoxicity (grade I–II in 97% of patients) as two of the most common side effects of the raltitrexed/oxaliplatin combination; two treatment-related deaths were observed.

Comparison of results between phase II trials is unfeasible; however, it seems that the TOMOX combination with oxaliplatin 100 mg/m^2 has a similar efficacy to that observed in patients treated with oxaliplatin 130 mg/m^2 [14, 15]. No unexpected severe adverse effects were observed in this trial and the toxicity profile of the TOMOX regimen parallels the clinical experiences with single-agent raltitrexed [18] and oxaliplatin [4]. Most likely, the strict inclusion criteria, the careful baseline evaluation of patients and their characteristics, and the appropriate treatment delays and/or dose reductions avoided life-threatening toxicities [18]. Also, the oxaliplatin 100 mg/m^2 dose may explain the low incidence of neurotoxicity. In the present study, 24 patients received six to seven TOMOX cycles and six patients received nine to 10 cycles. It was found that the risk of neurotoxicity increases with cumulative oxaliplatin dose [19]; for instance, oxaliplatin cumulative doses of 780 mg/m^2 and 1170 mg/m^2 correlated with an incidence of neurotoxicity of 10% and 50%, respectively. Combination chemotherapy with oxaliplatin at the maximum tolerated dose may not offer higher efficacy, and conversely, it may increase the incidence of neurotoxicity, which is reversible but dependent on the cumulative dose [19].

There is an increasing need to assess the impact of colorectal cancer therapies on the patients' quality of life [20–22]. Based on administration and/or side-effect attributes, Young et al. [20] compared raltitrexed and bolus or infusional 5-fluorouracil regimens in advanced colorectal cancer. On the basis of similar palliative effects, patients preferred raltitrexed over other regimens, and they ranked it more acceptable than the Mayo, de Gramont or Lokich regimens. These results are in contrast to that reported by Maughan et al. [12], who found an unexpectedly high incidence of treatment-related deaths (4% of patients) and a worse quality of life in patients treated with raltitrexed than patients treated with the de Gramont or Lokich regimens. Raltitrexed-based chemotherapy may represent a valid treatment option that offers the opportunity of improving acceptability of chemotherapy to patients; however, these data suggest the necessity of performing further assessments of toxicity and quality-of-life issues.

The TOMOX combination warrants evaluation of costs in comparison with other chemotherapeutic regimens. In two retrospective economic analyses, raltitrexed showed substantial equivalence of cost with the Mayo regimen [23], while it was less expensive than the de Gramont regimen [24]. Future clinical trials should consider economic evaluations and should clarify whether the high cost of chemotherapy drugs with the raltitrexed/oxaliplatin combination may be counterbalanced by lower demands on clinic and pharmacy resources.

In conclusion, the results of the present study and data from ongoing investigations provide evidence that the TOMOX regimen has good efficacy and moderate toxicity as first-line

chemotherapy for metastatic colorectal cancer. Most probably, the favorable characteristics of the majority of enrolled patients (median age 61 years, ECOG performance status 0–1, one or two organs involved, normal alkaline phosphatase and LDH values) contributed to the positive treatment results and avoided significant toxicity. For this reason, the results of this early phase II study should be looked at with caution and replicated in phase III trials. The TOMOX chemotherapy should be compared for efficacy, safety, quality of life and costs to the FOLFOX and FOLFIRI regimens in a prospective randomized trial.

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