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Report

Raltitrexed plus oxaliplatin as first-line chemotherapy in metastatic colorectal carcinoma: a multicentric phase II trial

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For advanced colorectal carcinoma, two new drugs, raltitrexed (TOM) and oxaliplatin (L-OHP), have recently shown interesting results. Preclinical and clinical studies suggest that this combination, because of its favorable toxicity profile, high response rate and convenient schedule of administration, can be administered successfully in this disease. In our phase II study, 37 non pre-treated patients with metastatic colorectal carcinoma were treated with TOM (3 mg/m^2) and L-OHP (130 mg/m^2) every 3 weeks. In total, 222 cycles were administered; all patients received at least 2 cycles (median 6, range 2–8). There were two complete and 14 partial responses for an overall response rate of 43% (95% CI 27–69%). The median time to response was 2.5 months (range 2–4) and the median duration was 10.3 months (range 5–18). Twelve of the 23 (52%) patients with symptomatic colorectal cancer were classified as clinical benefit responders for at least 4 weeks during the study period. Treatment was well tolerated, and both acute, essentially hematologic, and cumulative hepatic and neurologic toxicities were manageable and reversible. Response rate and toxic effects observed during this study warrant additional studies comparing this TOM–L-OHP regimen with CPT-11 and/or capacitebine-containing regimens in metastatic colorectal carcinoma. **[© 2002 Lippincott Williams & Wilkins.]**

Key words: Chemotherapy, metastatic colorectal carcinoma, oxaliplatin, raltitrexed.

Introduction

Colorectal cancer remains a leading malignancy, both in incidence and mortality,[1] and approximately 50% of all newly diagnosed patients develop metastatic disease either at the time of diagnosis or after surgery. The treatment of metastatic colorectal carcinoma presents a difficult challenge to the oncologist and although the overall mortality for colorectal cancer has decreased in recent years, patients with metastatic disease continue to face a grim prognosis.[2] Hepatic and lung metastases are the major cause of death and morbidity, and since 25% of these recurrences are eligible for resection, most patients with recurrent disease are suitable for systemic chemotherapeutic regimens. The standard chemotherapeutic agent for advanced colorectal cancer is 5-fluorouracil (5-FU), which generates a response rate of about 20% as a single agent when used intensively,[3,4] while prolonged continuous infusions of 5-FU have been shown to generate a higher response rate (30%) than an equitoxic bolus regimen.[5,6] Nevertheless, the median survival time of these patients does not exceed 12 months and the percentage of patients who really benefit from these treatments cannot be considered satisfactory.[7,8]

During the last few years, several new cytotoxic approaches have been tested. These include the development of several oral forms of 5-FU, and the introduction of three novel cytotoxic agents: irinotecan (CPT-11), raltitrexed [Tomudex (TOM)] and oxaliplatin (L-OHP). These agents are active in the management of colorectal cancer, in contrast to single-agent therapy as first-line treatment which has failed to demonstrate a substantial increase in survival. Preclinical studies have indicated that a combination treatment has the potential benefit of

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enhancing response rates. In particular, TOM is a folate-based quinazole-selective, specific thymidylate synthase inhibitor that undergoes extensive intracellular polyglutamation. Polyglutamation prolongs both the intracellular retention of TOM and the inhibition of thymidylate synthase, leading to high levels of cytotoxicity.[9] On the other hand, L-OHP is a new platinum derivative with an oxalatoligand and a 1,2-diminocyclohexane carrier that acts similarly to cisplatin by producing DNA adducts which block both replication and transcription.[10] The two drugs have different mechanisms of action and toxicity profiles, and have shown additive effects in experimental and preliminary clinical studies.[11–13] These data suggest that this combination, because of its favorable toxicity profile, may represent an useful regimen for the treatment of patients with metastatic colorectal cancer.[14,15] The specific objective of our phase II study was to obtain further data on the efficacy, safety and clinical benefit response of TOM–L-OHP combination in advanced colorectal cancer, and to evaluate it as an alternative to the active 5-FU–L-OHP regimen, with 5-FU replaced by TOM, another thymidylate synthetase inhibitor which is easier to handle.

Patients and methods

A total of 39 patients with metastatic colorectal carcinoma took part in this trial and all of them signed their informed consent. Before entering the study, all patients gave a full history, and underwent physical evaluation, complete blood count, routine blood chemistries, chest X-ray and abdominal computerized tomography (CT) scan. Baseline performance status, analgesic intake and pain intensity data were also collected. Eligibility criteria included: histologically proven metastatic adenocarcinoma with measurable or assessable disease as an indicator of response to treatment, patients aged $\leqslant 75$ years, life expectancy of $\geqslant 6$ months, Karnofsky performance status $\geqslant 40$,[16] no prior treatment for 6 months and adequate hematologic count (leukocyte $>4000/\mu$l, hemoglobin level >10 g/dl and platelet count $>150\,000/\mu$l), hepatic (serum bilirubin level <1.5 mg/dl) and renal function (serum creatinine level <1.5 mg/dl). Patients with ascites, pleural effusion, bone metastases as single lesion or active CNS disorder or known cerebral metastases were considered ineligible. The main clinical characteristics of the 39 patients enrolled are summarized in Table 1.

Table 1. Patient characteristics

Variable	No.
No. of patients	39
Gender	
male	25 (64%)
female	14 (36%)
Age (years) [median (range)]	63 (39–75)
Karnofsky PS	
$\geqslant 40$	3 (8%)
<60	8 (20%)
>80	28 (72%)
Location of primary tumor	
colon	3 (77%)
rectum	9 (23%)
Location of metastases	
liver	24
lung	11
abdominopelvic mass	13
peritoneum	7
local nodes	18
distant nodes	11
bone	5
No. of metastatic sites	
single	16 (41%)
multiple	23 (59%)

Treatment protocol

The treatment regimen was based on two previously published phase I–II studies, indicating that a dose intensity as high as the sum of the recommended doses of each agent given alone can be safely administered.[13–15] Chemotherapy consisted of TOM 3.0 mg/m^2 administered as a 15 min i.v. infusion, plus L-OHP 130 mg/m^2, diluted in 250 ml of 5% glucose, administered as a 2-h i.v. infusion. Treatment courses were repeated every 3 weeks; in responders and stable disease patients the treatment was extended for 8 courses. Concomitant medications routinely given before cytotoxic drug administration included 8 mg ondansetron and 8 mg dexamethasone.

Toxicity assessment and dose modification

Interval medical history and physical examination, including toxicity assessment, were performed at the initiation of each therapy cycle: serum chemistries, including electrolytes, creatinine, bilirubin and hepatic enzymes, were obtained on day 1 of each cycle. Complete blood counts were obtained on day 12–15 of each cycle.

Adverse reaction were evaluated according to WHO criteria.[17] In the event of grade $\geqslant 3$ organ

toxicity, the dose of TOM and L-OHP was reduced by 25% for subsequent courses or delayed up to 1–2 weeks. Administration of granulocyte colony stimulating factor was recommended in the event of grade $\geqslant 3$ hematological toxicity.

Evaluation of response and toxicity

The primary efficacy end-points were response rate and toxicity, which were evaluated according to WHO criteria[17] every two treatment cycles. Tumor measurements were based on the sum of the products of the bidimensional diameter of the lesions. To be classified as a complete responder (CR), a patient had to present complete regression of the disease and be free of symptoms related to the carcinoma for a minimum of 4 weeks. Patients with greater than a 50% reduction in lesion size and no new lesions were classified as partial responders (PR), while those presenting a lesion size less than 50% were considered minor responders. Patients were rated as having progressive disease (PD) if any new lesion appeared, if tumor size increased by 25% over pretreatment measurements or if their clinical status had worsened consistently with disease progression. Patients who failed to meet CR, PR or PD criteria and who remained on-study for at least 2 months were classified as having stable disease (SD). All tumor measurements in responders were reviewed and confirmed by a reference radiologist.

Secondary efficacy end-points included the evaluation of clinical benefit response obtained from measurement of three common debilitating signs or symptoms present in most patients with metastatic cancer, i.e. pain, functional impairment and weight loss. Consequently clinical benefit assessments included evaluations of pain intensity, analgesic intake, performance status and weight. To be considered clinical benefit responders, patients had to present more than one of the following symptoms: 50% decrease in pain intensity, 50% decrease in analgesic intake or sustained greater than 20-point increase in performance status for more than 4 weeks without deterioration in any of the other parameters. Patients who were stable in pain intensity, analgesic intake and performance status were required a 7% increase in dry body weight to be classified 'responders'. During the study, pain intensity was measured directly by the patients using a 10-cm linear analog scale and analgesic intake was calculated on the basis of a diary kept by patients. Performance status and weight were measured every 3 weeks by a nurse. Each patient was classified as positive, stable or negative for each of the clinical benefit measures. In all cases, 'positive' indicated a sustained (greater than 4 weeks) improvement with respect to baseline status in at least one variable, without a negative result in any other variable.

Statistical methods

An optimal two-stage design was employed in the protocol[18] using standard statistical methods. If no CR or PR were noted in the first cohort of 14 patients, a response rate of more than 15% could be excluded with 95% confidence interval (CI), causing the accrual would stop. If at least one CR or PR was observed, more than 30 patients were entered in the study to determine the response rate more accurately.

Results

Tumor response and toxicity

Thirty-seven of the 39 patients who entered this study had an adequate trial, and were assessable for both response and toxicity evaluation. One patient refused to continue the therapy after the second cycle and another died of cerebral hemorrhage during the second month of treatment. The 37 evaluable patients underwent a total of 222 courses, and the median number of treatment cycles was 6 (range 1–8). The median duration of follow-up at the time of analysis was 12 months (range 6–18). The best responses to treatment were two CR (5%) in patients with a single metastatic site (liver and distal node) and 14 PR (38%) for an overall response rate (CR + PR) of 43% (95% CI 27–69%). No evidence was found as to a preferential site of response. The median time to response was 2.5 months (range 2–4 months) and their median duration was 10.3 months (range 5–18). Fifteen patients (41%) showed SD and six showed PD (16%). The median survival duration of responders was 14.5 months (range 6–18), which was significantly longer ($p < 0.01$) than the 8 months (2–12) of non-responders.

Clinical benefit response

A total of 12 of the 23 (52%) patients with symptomatic colorectal cancer were classified as clinical benefit responders while five patients (22%)

experienced worsening of at least one variable (pain intensity, performance status or body weight). Ten patients (43%) experienced sustained improvement in performance status for at least 4 weeks during the study period. Seven patients (30%) suffering from pain at study entry, experienced a reduction of pain intensity and/or analgesic intake. With regard to weight gain, nine patients (39%) had a positive response.

Toxicity

Thirty-seven of the 39 patients who received the TOM–L-OHP regimen were assessable for toxicity. Treatment was well tolerated, and both the acute and cumulative side effects were within acceptable limits and completely reversible. Toxicities are summarized in Table 2.

We observed three groups of toxic effects: hematological, gastrointestinal and neurosensory toxicity. Hematological toxic effects occurred most often. As expected, leukocyte and granulocyte count nadir were the most common hematologic findings, but no patients required hospitalization due to severe myelosuppression. Infections (mainly pulmonary) experienced by six patients were all manageable on an outpatient basis. Regarding platelet nadir, there were no bleeding episodes and only one of the patients experienced grade 3 thrombocytopenia with 32 000/μl platelets. No patients required packed red blood cell transfusion. Seven patients (19%) had at least one treatment delay at some time during therapy.

Nausea and emesis were not major problems, and grade 3 emesis and diarrhea occurred in only two patients. Peripheral sensory neuropathy and asthenia were frequent but reversible and only one patient (3%) had severe paresthesia that interfered with function, while three patients (8%) occasionally reported pharyngeal constriction while drinking cold beverages. An acute episode of laryngeal spasm occurred in a patient during L-OHP infusion that required the discontinuation of treatment after 5 cycles. Reversible liver enzyme increase was occasionally found in four cases (11%). The reasons for delayed courses were hematologic in five patients (leukocytopenia and /or granulocytopenia) and non-hematologic in two patients (diarrhea and higher rates of liver functional parameters). No renal or cardiac toxicity was recorded.

Discussion

A number of recently published studies have investigated the role of new agents and new combinations in the treatment of advanced colorectal cancer. In the past 2 years, thymidylate synthase inhibitor (TOM), topoisomerase I inhibitors (CPT-11), the oral 5-FU prodrugs (capecitabine), ethynyluracil and L-OHP have been approved in most countries as therapy agents in advanced colorectal cancer, with response rates as single-agent of only 15–25%.[19–21] Greater interest has arisen in the activity observed when these agents are administered in combination and/or with 5-FU and leucovorin (LV) with significant improvement in objective response rate (35–50%) and median survival.[22–24] Despite these interesting results, however, additional investigational efforts will be necessary to further improvements not only in antitumor activity, but also in treatment tolerance and ease of administration schedule. The present

Table 2. Highest grade of treatment-related toxicity

Toxicity	No. of patients at toxicity grade[a]			
	1	2	3	4
Leukopenia	13 (35)	9 (24)	3 (8)	–
Granulocytopenia	12 (32)	9 (24)	5 (14)	1 (3)
Thrombocytopenia	7 (19)	5 (14)	1 (3)	–
Anemia	12 (32)	7 (19)	–	–
Nausea/emesis	8 (22)	7 (19)	1 (3)	–
Stomatitis	3 (8)	2 (5)	–	–
Diarrhea	7 (19)	6 (16)	1 (3)	–
Liver function	10 (27)	7 (19)	2 (6)	–
Alopecia	4 (11)	3 (8)	–	–
Asthenia	8 (22)	6 (16)	–	–
Peripheral neuropathy	12 (32)	13 (36)	1 (3)	–

[a]According to WHO criteria. Percentages in parentheses.

phase II study was initiated as in patients with metastatic colorectal cancer, based on TOM and L-OHP documented activity in preclinical and clinical studies,[12–15,24] once on the basis of their different mechanism of action, their favorable toxic profile, as well as preliminary evidence of addictive effects of the two drugs.

In our study TOM was combined with L-OHP as first-line therapy in patients with metastatic colorectal cancer, and the recommended doses for TOM and L-OHP are the same in combination as in single-agent use. Compared to other studies using the same regimen,[27] we observed less hematological toxicity and less non-hematological adverse reaction including diarrhea and vomiting when compared to CPT-11 or continuous infusion regimen.[25,26] There was no death due to toxicity. L-OHP-induced neurotoxicity and TOM-related worsening in liver functional parameters were always reversible.

In this study, a significant 43% overall response rate was achieved with 5% CR, 38% PR and an high percentage of SD, 43%. In 12 of 23 (52%) patients with symptomatic colorectal cancer, a significant palliative benefit was also noted in terms of reduction of pain, improvement of performance status and increase of body weight.

In conclusion, our data indicate that TOM and L-OHP can be administered in convenient 3-weekly schedules on an ambulatory basis, at active doses without severe toxicity. The promising results of this study, although from a small number of patients, indicate that additional studies are warranted comparing this regimen with randomized CPT-11 and/or capacitebine-containing regimens in metastatic colorectal carcinoma.

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