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[Articles]

Synergistic Activity of Oxaliplatin and 5-Fluorouracil in Patients With Metastatic Colorectal Cancer With Progressive Disease While on or After 5-Fluorouracil

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Abstract

From February 1995 through October 1996, 25 patients with metastatic colorectal cancer showing a clinical resistance to 5-fluorouracil (5-FU) entered this study. Thirteen received oxaliplatin alone and 12 received it in combination with 5-FU. Oxaliplatin was administered at 130 mg/m2 over a 2-hour infusion every 3 weeks, alone or added either to 5-FU as a continuous infusion at 200 mg/m2 to 300 mg/m2 (six patients) or to a 5-FU bolus, 375 mg/m2, plus leucovorin, 100 mg/m2, daily for 5 days every 3 weeks (6 patients).

Eighty-six of 98 administered cycles were evaluable for toxicity (47 for oxaliplatin plus 5-FU and 39 for oxaliplatin alone). Hematologic toxicity was mild, occurring as grade 2 leukopenia in 23% of the cycles of 5-FU and oxaliplatin and in 5% of the cycles of oxaliplatin alone. The most common toxicity was neurologic (grade 1 to 2 in 60%-6% of the cycles of the combination, respectively, and 68%-10% of oxaliplatin given alone) as hand-foot paresthesia or hypersensitivity to cold. No grade 4 toxicity was reported and only three patients in the 5-FU group developed grade 3 diarrhea. Grade 2 nausea and vomiting occurred in 33% of the cycles when both drugs were given and in 15% when oxaliplatin was administered alone.

The combination of oxaliplatin and 5-FU induced four partial remissions (33%; 95% confidence interval, 6%-60%), whereas eight patients of the whole group had stable disease. No response occurred when oxaliplatin was administered as a single agent. The results of this study confirm the antitumor activity of oxaliplatin when added to 5-FU in patients who have metastatic colorectal cancer previously refractory to 5-FU. The possible therapeutic synergy with 5-FU was not accompanied by increased toxicity.

In the past 30 years, the chemotherapeutic approach to advanced colorectal cancer has remained one of the major challenges for medical oncologists. Fluorinated pyrimidines, especially 5-fluorouracil (5-FU), have been the main active drugs.1 More recently, several randomized studies have provided the evidence that biochemical modulation of 5-FU with leucovorin confers a superior

response rate when compared with the administration of 5-FU alone.1,2 Conversely, the optimal dose, schedule, and route of administration of the combination have not been established. Complete response rates remain disappointingly low, and the improvement of the median survival appears to be small. Oxaliplatin is a new third-generation platinum complex that has no renal toxicity and minimal hematologic toxicity.3 The main site of action of oxaliplatin is DNA, producing adducts that block both replication and transcription. In contrast to cisplatin-for which the kinetics of binding with DNA are biphasic, with one rapid phase of approximately 15 minutes and a slower terminal phase lasting 4 to 8 hours-the DNA binding of oxaliplatin is complete after a maximum of 15 minutes. Preliminary studies suggest that the combination of 5-FU and oxaliplatin is synergistic against L1210 leukemia transplanted into mice.4,5

Phase I clinical trials recommended a dose of 130 mg/m2 given by 2-hour infusion and repeated every 3 weeks 6 for further phase II studies. Phase II-III trials demonstrated a certain degree of activity in advanced colorectal cancer. When oxaliplatin alone was given to patients refractory to 5-FU, the reported response rate was approximately 10%7; when given in combination with 5-FU and leucovorin, the response was 28% to 53%.8-10

These encouraging results prompted us to use oxaliplatin alone or in combination with 5-FU and leucovorin in advanced colorectal cancer patients who had disease refractory to 5-FU-based chemotherapy.

PATIENTS AND METHODS

Patients

From February 1995 through October 1996, 25 patients who had advanced colorectal cancer were treated in an outpatient setting at the Division of Medical Oncology, European Institute of Oncology, Milan, Italy. Twenty-three patients were pretreated and progressing while on or within 6 months of the last 5-FU-containing chemotherapy; two patients progressed more than 6 months after the last 5-FU regimen. Criteria for inclusion also required adequate bone marrow and renal function, age younger than 75 years, performance status higher or equal to 2 according to the Eastern Cooperative Oncology Group scale, and measurable disease according to the World Health Organization criteria. Patient characteristics are shown in Table 1.

All patients had undergone surgical resection of the primary lesion (7 rectal carcinoma, 18 colon), with histologic proof of cancer. Primary staging at surgical diagnosis was performed according to Dukes criteria, with 10 patients assigned to stage D, 10 to stage C, three to stage B, one to stage A, and one to unknown.

Metastatic sites of disease included liver in 20 patients, lung in 13 patients, soft tissues in five patients, and other sites in seven patients; patients who had single or multiple sites of metastatic disease were treated as detailed in Table 1.

Overall, 24 patients were evaluable for activity and for toxicity because one patient was lost to follow-up after one cycle.

Eligible patients underwent a complete staging of metastatic sites using radiographs, computed tomographic scanning or ultrasound as indicated, and physical examination. Weight, height, complete blood count, liver and renal function, carcinoembryonic antigen and CA19.9 were also determined.

Toxicity was assessed for each cycle, according to the World Health Organization scale. Informed written consent was obtained according to procedures set forth by the ethical committee of the institute.

Drug Administration

Oxaliplatin was supplied by Debiopharm (Lausanne, Switzerland) as a freeze-dried powder for infusion in vials containing 50 mg or 100 mg of the drug. Oxaliplatin was reconstituted in 5% glucose solution or water in the original vial for injection and diluted in 250 ml of 5% glucose solution for the infusion. The drug was administered at 130 mg/m2 as an intravenous infusion over 2 hours every 21 days. 5-fluorouracil was purchased from F. Hoffmann-La Roche Ltd. (Basel, Switzerland) as 5-ml vials containing 250 mg of the drug. It was administered as a bolus intravenously at 375 mg/m2 over 5 days with leucovorin 100 mg/m2 or by continuous intravenous infusion at 200 mg/m2/day up to 300 mg/m2/day through a central venous catheter with a Pharmacia CADD-Plus pump.

Oxaliplatin was added to 5-FU in those patients who were progressing while on 5-FU and were tolerating the treatment well.

Response Assessment

Responses were assessed according to World Health Organization criteria every two or three cycles. Patients who had stable disease continued oxaliplatin until tumor progression or until a maximum of nine cycles. Patients who achieved a partial response continued for at least two cycles after response stabilization. Similarly, in cases of complete response, patients were to receive at least two additional cycles of oxaliplatin. In contrast, patients who had progressive disease were immediately taken off study. All responses were reassessed after two or three additional cycles of therapy.

Statistical Analysis

The duration of response and the time to progression were both calculated from the first drug administration to disease progression. The comparison of toxicity results between different groups was performed using the chi-square test. The t test for paired data was used for different group comparisons of continuous measurements performed at different intervals before, during, and after therapy. The reported values are for two-tailed tests.

RESULTS

Thirteen patients were treated with oxaliplatin as a single agent; in the other 12 patients, it was added in combination to the ongoing 5-FU regimen. Among these 12 patients, six received 5-FU as a continuous infusion and six as a intravenous bolus plus leucovorin.

Globally, 98 cycles have been administered. To date, 86 are evaluable for toxicity: 39 cycles of oxaliplatin alone and 47 of the combination (29 with bolus 5-FU and 22 with 5-FU continuous infusion). Patients received a median of three cycles (range, 1-9 cycles): three for the oxaliplatin alone and four for the combination. The dose of oxaliplatin was reduced by 25% in four cycles (three patients), and the median interval between cycles was 21 days (range, 21-71 days).

Toxicities

The most common toxicities for oxaliplatin and 5-FU are shown in Table 2.

Leukopenia was mild, occurring in 23% of the cycles as grade 2; no grade 3 or 4 leukopenia was observed. Grade 2 neutropenia also was reported in 21% of the cycles. Grade 1 thrombocytopenia occurred in 9% of the cycles and grade 2 in 6%. Only two patients experienced grade 2 mucositis (4% of the cycles) and grade 3 diarrhea was present in three patients (6% of the cycles). Typical oxaliplatin neurologic toxicity, characterized by peripheral or pharyngolaryngeal dysesthesia caused and aggravated by cold and distal paresthesia, are reported as grade I (mild) in 60% of the cycles and grade 2 (intermediate) in 6% of the cycles. Only one patient had grade 2 renal toxicity in one cycle (2%). Nausea and vomiting occurred as grade 2 in 33% of the cycles. Alopecia was uncommon.

Considering the two different schedules of administration of 5-FU, the toxicities are similar in both schedules and without significant difference (Table 3).

The most common toxicities for oxaliplatin alone are shown in Table 4. Leukopenia occurred rarely-only in seven cycles (8%)-and the worst was grade 3 in one cycle (3%). In only six cycles (15%) did we observed grade 1 neutropenia. Grade 1 thrombocytopenia occurred in 13% of the cycles and grade 2 in 3% (1 cycle). Mucositis was mild also, occurring as grade 1 in only two cycles (5%), whereas grade 2 diarrhea was present in 10% of the cycles. Neurologic toxicity was reported as grade 1 (mild) in 68% of the cycles and as grade 2 (intermediate) in 10% of the cycles. Renal toxicity was absent. Nausea and vomiting occurred as grade 2 in 15% of the cycles. Alopecia was uncommon.

Antitumor Activity

The combination of oxaliplatin and 5-FU induced four partial remissions (33%; 95% confidence interval, 6%-60%) lasting, respectively, 6.9, 4.4, 7.9, and 6.9 months. No complete responses were observed and four (33%) of the patients had stable disease, with a median duration of 4 months (range, 3.2-4.5 months; see Table 4). Responding patients had visceral disease involving liver and lung in three patients and pelvis and lung in one patient. Of the responding patients, two were treated with 5-FU continuous infusion and two with 5-FU bolus plus leucovorin over 5 days. All were progressing while on 5-FU or within 6 months,

and they all received bolus 5-FU as a pretreatment. Two of these patients were progressing while on 5-FU continuous infusion-given as a second-line treatment-when oxaliplatin was added (Table 5). The response to previous bolus 5-FU plus leucovorin was not assessable for the four responding patients because they received the treatment in an adjuvant setting (n = 2) or after liver metastases resection (n = 2). See Table 6 for charactertistics of responding patients.

When oxaliplatin was administered as a single agent, no response was observed and four instances of stable disease were reported (33%); the median duration was 7.8 months (range, 3.3-11.3 months). The median time on study was 3 months (range, 1-8 months) and it was significantly lower (p = 0.07; t test) when oxaliplatin was given alone (2 months) and compared with the combination (4 months). The median time to response was 3.6 months (range, 2-4.6 months) and the median time to progression was 3 months (range, 1-11 months). Patients treated with the combination had a median time to progression of 4 months, compared with oxaliplatin alone, for which the time to progression was 2 months, but this difference is not significant.

DISCUSSION

No treatment can be considered to be standard for metastatic colorectal cancer because cures are rarely expected. Despite the many new promising compounds for cancer treatment that are available, only a few of them have some activity in this disease.

Metaanalysis reveals a better response rate for the combination of 5-FU plus leucovorin, compared with 5-FU alone, with no difference on survival.[11,12] In the last few years, low-dose 5-FU as a continuous infusion for many weeks has been described as a more rational, effective, and less toxic schedule for this drug.[13]

Actually, it is a common practice to treat patients who have metastatic disease with 5-FU plus leucovorin as first-line therapy and to consider 5-FU continuous infusion as a second-line regimen for patients who have progressive disease after an initial response. The role of second-line therapy in colorectal cancer

is doubtful, however, and patients progressing while on treatment are those less likely to benefit from further chemotherapy.

In our study of pretreated metastatic colon cancer patients, 33% benefited from treatment with oxaliplatin and 5-FU plus or minus leucovorin without showing a significant toxicity. We stress the fact that all the responding patients treated in our series were progressing while on 5-FU or within 6 months of 5-FU therapy. This may be clinical evidence of synergistic activity of oxaliplatin and 5-FU, as shown in in vitro studies.4 Similar results have been reported in a phase II study using the same combination of drugs, in which the response rate was 25%.4 The activity of this combination is even higher when oxaliplatin is chronomodulated with 5-FU and leucovorin, displaying a 58% response rate in pretreated metastatic colon cancer patients.8

Oxaliplatin has low toxicity; grade 2 emesis occurred in 33% of the cycles of the combination and in 15% when it was given as a single agent.

Our series is too small to show a significant advantage in terms of survival for the addition of oxaliplatin. In the literature, median overall survival of 14.9 months was reported in a subgroup of patients treated with 5-FU and leucovorin plus oxaliplatin 14 but results from randomized trials comparing standard 5-FU and leucovorin with the combination with oxaliplatin are not yet available.

The most frequent side effect that we observed was mild (grade 1 or 2) oxaliplatin neurotoxicity, characterized by peripheral paresthesia, hypersensitivity to cold, or pharyngolaryngeal dysesthesia in 21 patients. We did not see any grade 3-4 neurologic toxicities, which are reported in other series in which oxaliplatin alone induced 14% to 23% of grade 3 neurotoxicities and 4% to 8% of grade 4 neurotoxicities.7 The timing of the cycles has been always correct, with a median interval between cycles of 21 days (range, 21-71 days) because no significant hematologic toxicity was observed. Because quality of life is considered to be one of the most important targets of palliative chemotherapy for advanced cancer, oxaliplatin in combination with 5-FU may at least fulfill this important goal. In conclusion, oxaliplatin is a promising agent when given in combination with 5-FU or in a chronomodulated setting for treatment of advanced colorectal cancer.

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