Irinotecan and Thalidomide in Metastatic Colorectal Cancer

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Fifteen patients with metastatic colorectal cancer were treated with irinotecan (CPT-11, Camptosar) at 300 to 350 mg/m² every 21 days and thalidomide (Thalomid) at 400 mg/d. Of the 15 patients, 11 were in a pilot study and 4

Introduction

Colorectal cancer is one of the major causes of morbidity and mortality in this country, with about 130,000 cases diagnosed per year and 50,000 to 55,000 deaths per year. It is the third leading cause of death in this country for both men and women.

No Effective Therapy

Fluorouracil (5-FU) has been the only chemotherapeutic agent available for the treatment of metastatic colorectal cancer over the past 40 years. Although 5-FU has been used in a number of different schedules, the response rate has been less than 25%, and complete responses have been extremely rare.[1,2] In 1996, the US Food and Drug Administration (FDA) approved irinotecan (CPT-11, Camptosar), a topoisomerase I inhibitor, as a second-line salvage regimen for patients with metastatic colorectal cancer.

In various trials conducted in Europe and North America, the response rate to irinotecan has been around 20%, complete responses being < 1%.[3-6] In three phase II and III trials, irinotecan was administered at 300 to 350 mg/m² every 21 days (Europe), and 125 mg/m² weekly (North America). In the two large, randomized, phase III trials, complete responses were either not seen or not cited.[3-6]

Initial Protocol Development

Two important features of thalidomide (Thalomid) are its antiangiogenic properties and its ability to inhibit tumor necrosis factor-alpha (TNF-alpha). This latter feature has made thalidomide especially useful in the treatment of patients with Crohn’s disease.[7,8] The control of diarrhea in these patients, mediated by suppression of TNF-alpha, may partially explain the antidiarrheal effect of thalidomide. The protocol for our study is based on this information and anecdotal experience with thalidomide in treating a patient with metastatic colorectal cancer.

Our initial patient was a 48-year-old man whose cancer progressed after he received the standard Mayo Clinic regimen (5-FU plus leucovorin) for stage III colon cancer. He had liver metastases, which were treated by local therapy with radiofrequency ablation and hepatic artery-directed chemotherapy. After three cycles, the patient developed pulmonary and multiple liver metastases. At that time, and at the patient’s request, we started him on 350 mg/m² of irinotecan IV for 90 minutes every 21 days and 400 mg/d of thalidomide. Six months after starting this regimen, there was no radiologic evidence of disease. The thalidomide dose of 400 mg/d was based on experience at our institution using thalidomide in combination with chemotherapy.

All patients received a baseline computed tomography (CT) scan or x-ray and measurement of carcinoembryonic antigen (CEA) level. Responses were assessed after three cycles by CT scans or x-rays. According to the protocol, those who responded and those with stable disease would proceed to receive further treatment and to be reassessed after three additional cycles. The plan is to continue two cycles of irinotecan after complete response or until disease progression. In all patients who have complete response, thalidomide will be continued for 1 year.
Eligibility and Response Criteria

Eligibility criteria are outlined in Table 1. The responses were defined as complete, partial, or minimal response, or as stable disease or progression according to the following criteria:

- Complete response: no evidence of disease
- Partial response: $\geq 50\%$ tumor reduction
- Minimal response: $< 50\%$ tumor reduction
- Stable disease: no change in measurable disease
- Progression: tumor size increased by $\geq 25\%$

Data Collection

Until the protocol was formally opened, we were treating patients on a compassionate basis. Data from the pilot study were therefore collected separately from the official protocol, though all the criteria were strictly followed. We treated 11 patients in the pilot study, 9 men and 2 women, ranging in age from 29 to 79 years, with stage IV colorectal cancer (see Table 2). All patients were treated with prior 5-FU with or without leucovorin. In addition, some patients received fluorodeoxyuridine (FUDR) and radiation therapy.

Of these 11 patients, 10 were evaluable (1 ineligible due to pretreatment with irinotecan), and responses were noted in 4. Two patients had complete responses to the irinotecan/thalidomide regimen after eight and six cycles of treatment, although one patient subsequently progressed; another two had partial responses after eight and three cycles of treatment.

The UARK 99-057 Protocol

The official protocol is called UARK (University of Arkansas) 99-057 and so far has accrued four patients (three men and one woman) between the ages of 51 and 58 with confirmed metastatic colorectal cancer. All patients had been treated previously with 5-FU. In addition, one patient had received FUDR and radiation therapy (Table 3).

Of these four patients, two experienced a decrease in CEA levels after two cycles of the irinotecan/thalidomide regimen. One patient showed a decrease in CEA level from 12 to 5.3 ng/mL, and a second a decrease from 239 to 130 ng/mL (with the 239 ng/mL representing a progression from an initial CEA level of 59 ng/mL). No response was noted in the two other patients, one of whom developed a grade 3 rash and was taken off the study. In this latter patient, he was hospitalized with grade 4 diarrhea 48 hours after thalidomide was discontinued. He remained in the hospital for 2 weeks.

Toxicity

Among all 15 patients—11 treated in the pilot and 4 treated in the UARK 99-057 study—the main side effects were constitutional (see Table 4). Three patients experienced grade 3/4 hematologic toxicity with febrile neutropenia. Six patients had grade 2 nausea/vomiting and constipation; in two of the six patients, constipation was severe (grade 2/3). In the patient removed from UARK 99-057 due to the
grade 3 rash, nausea worsened, becoming grade 3/4. One patient developed bradycardia and three patients developed skin rash. There was one death and one grade 1 neuropathy. One patient was hospitalized with diarrhea after stopping thalidomide for skin rash. One patient had constipation and, subsequently, blood in the stool.

**Discussion**

Diarrhea occurred in nearly 80% to 85% of patients in previous studies, especially in the North American ones, where grade 3/4 diarrhea occurred in approximately 34% of patients. Excluding the one patient who developed grade 3 diarrhea after discontinuation of thalidomide, none of the patients in this study required intravenous fluids due to diarrhea. This was a striking observation (Table 5).

**Case Histories**

UARK 99-057 was developed based on our experience with the first patient in the pilot study. He was a 48-year-old man with metastatic colon cancer who developed progressive pulmonary and hepatic metastases after treatment with 5-FU and FUDR. Complete response was achieved after 6 months on the irinotecan/thalidomide regimen.

In a second case, a 78-year-old woman with liver metastases was treated on a Southwest Oncology Group (SWOG) protocol with high-dose 5-FU and leucovorin. She did not respond and her liver metastases were treated with cryoablation. The patient again progressed and developed pulmonary metastases, at which time she was treated on our protocol. After six cycles of irinotecan/thalidomide, the pulmonary metastases had disappeared, and her liver metastases were almost gone. At this time, she has received eight cycles of chemotherapy and is due to be reassessed.

A 29-year-old man with rectal cancer had a tumor mass that extended all along the rectal wall. He was treated with standard preoperative radiation therapy, along with 5-FU. Exploratory surgery was performed, and the tumor was determined unresectable. The patient received a colostomy. He was started on the protocol with irinotecan and thalidomide. After three cycles of irinotecan/thalidomide, radiologic evaluation revealed that the tumor mass was no longer visible along the whole rectal wall, though there was some evidence of the tumor in the coronal sections of the MRI. The patient was classified as a partial response, and further assessment is needed.

**Summary**

To date, 15 patients with a median age of 56 years have been entered onto the irinotecan/thalidomide regimen in a pilot study and 4 in UARK 99-057. Of these, 10 are evaluable. A total of 53 irinotecan cycles have been administered, with a range of one to eight cycles per patient. None of those patients have stopped therapy due to side effects of irinotecan, even though in previous studies of irinotecan many patients stopped treatment within the first month due to side effects.

The median dose of thalidomide was 400 mg. In one patient, the dose was reduced because of somnolence. The current maximum duration of thalidomide therapy is 12 months. Of the 10 evaluable patients originally in the pilot study, disease has progressed in six. The median time to response is about 9 weeks from the first time we assessed the patient.

**Future Directions**

The optimal dose of thalidomide to be given in combination with irinotecan remains to be determined, as does the optimal dose of irinotecan to be given in combination with thalidomide. Further, the toxicities and responses of the combination need to be evaluated. The FDA has approved 5-FU/leucovorin and irinotecan as first-line chemotherapeutic agents. Our next aim is to study 5-FU/leucovorin in combination with irinotecan and thalidomide.
References:


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