Irinotecan/Thalidomide in Metastatic Colorectal Cancer

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The prognosis for patients with metastatic colorectal cancer is poor. Use of irinotecan (CPT-11, Camptosar) results in modest response rates of approximately 20% in refractory patients diagnosed with this advanced stage of disease and offers a side-effect profile that improves on that of previous standard treatments.

Patients with metastatic colorectal cancer have a poor prognosis—median survival time is described as being 12 to 18 months. The definitive therapy for colorectal cancer is surgery, which can be curative for disease stages I, II, and III. Chemotherapy or radiation therapy has a limited role, providing survival benefit in the adjuvant setting and palliation in the metastatic setting. For nearly 40 years, fluorouracil (5-FU) has been the only agent that has produced a response rate of approximately 20% in patients with metastatic colorectal cancer.[1] However, complete responses with 5-FU are rare.

5-FU is associated with a modest survival benefit in metastatic colorectal cancer patients in the adjuvant and metastatic settings. Various agents have been combined with 5-FU in attempts to improve response rates. Such agents include leucovorin, which binds to the ternary complex of 5-FU, and levamisole (Ergamisole), an anthelminthic with immunomodulatory properties. 5-FU can be administered in various ways—on a weekly schedule, via continuous infusion, on a high-dose weekly schedule, and as outlined by the popular Mayo Clinic regimen. Each regimen induces different response rates, but none has demonstrated a survival benefit over another.

Patients presenting with isolated hepatic metastases can be treated with surgery. Surgical resection is appropriate only in selected cases and improves 5-year survival from 10% to 35%. Recently, an improvement in hepatic disease-free survival and, possibly, overall survival time was demonstrated when Kemeny and colleagues administered hepatic arterial floxuridine (FUDR) with systemic 5-FU following resection of hepatic metastases.[2] Long-term benefits of this therapy are not known. Furthermore, while patients with hepatic metastases who are treated with chemotherapy consisting of hepatic arterial infusion of FUDR have higher response rates than do those receiving systemic 5-FU,[3] no survival advantage of hepatic arterial FUDR over 5-FU infusion has been demonstrated. Novel therapeutic approaches for unresectable hepatic metastases include radiofrequency ablation and cryotherapy.

Irinotecan in Metastatic Colorectal Cancer

Irinotecan, a semisynthetic derivative of camptothecin, is a topoisomerase I inhibitor associated with modest response rates of approximately 20% in refractory metastatic colorectal cancer and rare complete responses (Table 1 and Table 2).[4-11] Irinotecan is a prodrug that is converted to SN-38, the primary metabolite responsible for drug efficacy and toxicity. Irinotecan usually is administered in one of two schedules. According to the European schedule, the drug is given as 300 to 350 mg/m² every 3 weeks. The North American schedule is 125 mg/m² IV on a weekly basis × 4 followed by a 2-week rest. Response rates and toxicities are comparable for both schedules. Diarrhea can be the dose-limiting toxicity (Table 3).

Thalidomide as an Antiangiogenic Agent in Colorectal Cancer

Thalidomide is a glutamic acid derivative, which initially was sold in Germany as an over-the-counter sedative. The drug was withdrawn nearly half a century ago due to effects including teratogenicity and peripheral neuropathy. Subsequently, thalidomide was shown to be effective for the treatment of erythema nodosum leprosum and chronic graft-vs-host disease. Furthermore, based on its potent TNF-alpha inhibition, thalidomide has been useful in treating refractory Crohn’s disease.[12] More recently, the antiangiogenic properties of thalidomide were recognized initially by D’Amato and colleagues.[13] Angiogenesis plays a major role in malignant disorders, and the influence of
angiogenesis in colorectal cancer was demonstrated by Takahashi and colleagues.[14] Thalidomide was used successfully to treat patients with refractory multiple myeloma.[15] The mechanism of action of thalidomide in multiple myeloma is not understood, although it may be based on immunomodulatory rather than antiangiogenic properties.

**Combined Thalidomide/Irinotecan Therapy**

The efficacy of combined thalidomide and irinotecan therapy for metastatic colorectal cancer was demonstrated in a pilot study conducted at the University of Arkansas for Medical Sciences.[16] The data demonstrated good response rates with fewer gastrointestinal side effects than seen with use of irinotecan alone, which is associated with late-onset diarrhea as a dose-limiting toxicity. A phase II study combining thalidomide and irinotecan as second-line therapy for patients with metastatic colorectal cancer is being conducted at the same institution; a preliminary report follows.

**Phase II Study of Second-Line Thalidomide/Irinotecan in Metastatic Colorectal Cancer**

Patients with metastatic colorectal cancer with bidimensional measurable disease are being enrolled in a phase II study at the University of Arkansas for Medical Sciences.[17] All patients progressed on previous 5-FU-based therapy received in either the adjuvant or metastatic setting. The team is administering 350 mg/m² of irinotecan IV every 3 weeks (300 mg/m² for patients over 70 years of age); 400 mg of thalidomide is being given orally at bedtime. At the time of the interim analysis, 18 patients had received the thalidomide/irinotecan combination. Fourteen of the 18 patients were evaluable for response. The median patient age was 64 years (range: 29-76 years). A total of 77 irinotecan treatment cycles were delivered, with each patient given a median of three treatment cycles (range: 1-13 cycles). The median thalidomide dose was 400 mg/d (range: 100-400 mg/d), and the duration of thalidomide treatment ranged from 1 week to 40 weeks. Preliminary results showed that four patients responded (one complete response, three partial responses), six had stable disease, and four had progressive disease. Preliminary safety analysis in all 18 patients showed a marked decrease in gastrointestinal effects as compared with that expected with irinotecan monotherapy (Table 4). Final results of this ongoing phase II study are forthcoming.

**Conclusions**

Previous data from a pilot study of irinotecan and thalidomide in patients with refractory metastatic colorectal cancer have demonstrated a good response rate and acceptable tolerability regarding gastrointestinal effects. This combination now is being assessed as first- and second-line therapy in phase II trials, and preliminary results are encouraging.

**References:**


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