Mitomycin C and High-Dose 5-Fluorouracil With Folinic Acid as a Therapeutic Option for Heavily Pretreated Patients With Metastatic Colorectal Cancer: Prospective Phase II Trial

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AUTHOR SUMMARY

ABSTRACT

Background. Standard treatment for patients with unresectable colorectal cancer metastases includes chemotherapy regimens based on irinotecan, oxaliplatin, fluoropyrimidines, anti-vascular endothelial growth factor therapy, and anti-EGFR. Additional therapeutic options are needed for patients with good performance status who have disease progression during or after standard therapies.

Methods. A nonrandomized phase II study was modeled as a two-stage Chen design. Eligible patients had a diagnosis of metastatic colorectal cancer (mCRC) with progression after prior cytotoxic regimens based on oxaliplatin and irinotecan. Treatment consisted of mitomycin C in combination with high-dose 5-fluorouracil (5-FU) and folinic acid (the MLF regimen; mitomycin C as an intravenous bolus of 6 mg/m² i.v. on days 1 and 22 every 7 weeks; folinic acid at 250 mg/m² in combination with 5-FU at 2,600 mg/m² as a continuous intravenous infusion (24 hours) weekly for 6 of every 7 weeks.

Results. The median age of the 74 eligible patients was 62 years (range: 47–79 years). In these heavily pretreated patients with mCRC, the MLF regimen was the fourth or fifth line in more than 60% of the patients. Two patients (3.2%) achieved a partial response, and 33 (53.2%) achieved a best response of stable disease, defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. Median progression-free survival was 4.9 months. The median overall survival was 9.7 months. The most common nonhematologic side effects included mucositis (24.4% for all grades, and 9.5% with grade 3/4), diarrhea (15.0% for all grades, 13.6% with grade 3/4), fatigue (44.7% for all grades, 13.6% with grade 3/4), nausea (12.3% for all grades, 6.8% with grade 3/4), and peripheral neuropathy (17.6% for all

Figure 1. Clinical benefit response (partial response and stable disease).

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

grades, 2.7% with grade 3/4). Among the most frequent hematological toxicities were neutropenia (27.1% for all grades, 14.9% with grade 3/4), thrombocytopenia (18.9% for all grades, 8.1% with grade 3/4), and anemia (13.6% for all grades, 4.1% with grade 3/4). Dose reductions due to adverse events were necessary in 29 of 74 patients (37.6%), and discontinuation of therapy due to toxicity was necessary for 14 of 74 patients (18.2%).

Conclusion. Our study shows the MLF regimen can be administered safely to patients with heavily pretreated mCRC. Median progression-free and overall survival compares favorably with other options used or approved in this setting. A randomized trial in this setting should be considered. *The Oncologist* 2014;19:356–357

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DISCUSSION

The prognosis of patients with recurrent, unresectable, heavily pretreated metastatic colorectal cancer (mCRC) remains poor, with a median survival of about 5 months without treatment. There has been no standard treatment for these patients to date beyond exclusively symptomatic treatment, despite the fact that the performance status of many patients is good to very good. Guidelines do not recommend the use of mitomycin C (MMC) in heavily pretreated patients with mCRC, but there are very limited data, especially with regard to prospective clinical studies, on the efficacy of chemotherapy consisting of MMC in combination with 5-fluorouracil (5-FU). The activity of an MMC chemotherapy regimen in combination with 5-FU has mainly been shown in clinical studies and retrospective analyses (Fig. 1). The aim of this study was to prospectively evaluate the efficacy and toxicity of MMC in combination with 5-FU and folinic acid—the MLF regimen—in heavily pretreated patients with mCRC (Fig 2). Previously, all patients had received oxaliplatin- and irinotecan-based regimens. This prospective study represents the largest reported series treated with an MLF regimen in the third and subsequent lines of chemotherapy.

Figure 2. Overall survival (Kaplan-Meier) for colorectal cancer patients treated with the MLF regimen.

Abbreviations: CI, confidence interval; MLF, mitomycin C in combination with high-dose 5-fluorouracil, and folinic acid; OS, overall survival.

Author disclosures available online.