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ORIGINAL ARTICLE

**Do Hyoung Lim · Young Suk Park · Byeong-Bae Park
Sang Hoon Ji · Jeeyun Lee · Keon Woo Park
Jung Hoon Kang · Se-Hoon Lee · Joon Oh Park
Kihyun Kim · Won Seog Kim · Chul Won Jung
Young-Hyuck Im · Won Ki Kang · Keunchil Park**

Mitomycin-C and capecitabine as third-line chemotherapy in patients with advanced colorectal cancer: a phase II study

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Abstract *Purpose*: The aim of this study was to investigate the therapeutic value and safety of third-line treatment with mitomycin-C (MMC) and capecitabine (Xeloda) in patients with advanced colorectal cancer pretreated with combination regimens including 5-fluorouracil (5-FU), folinic acid (FA) and irinotecan (CPT-11) or 5-FU, FA and oxaliplatin (L-OHP). *Patients and methods*: A total of 21 patients (M/F 16/5, median age 60.0 years) with advanced colorectal cancer, all of whom had developed progressive disease while receiving or within 6 months of discontinuing two sequential chemotherapy lines with 5-FU, FA and CPT-11 or 5-FU, FA and L-OHP, were accrued to this study. At the time of their relapse or progression, cytotoxic chemotherapy, consisting of intravenous MMC 7 mg/m^2 on therapeutic day 1 plus oral capecitabine 1000 mg/m^2 twice daily on days 1–14, was initiated. After rest for 7 days, capecitabine 1000 mg/m^2 twice daily was administered on days 22–35 followed by 7 days rest. Treatment courses were repeated every 6 weeks unless there was evidence of progressive disease, unacceptable toxicity or patient refusal of treatment. *Results*: All the patients were assessable for toxicity and 19 for response. The median number cycles of chemotherapy was two (range one to four). Only 1 patient (4.8%) had a partial response, 4 patients (19.0%) had stable disease, and 14 patients (66.7%) progressed. The median follow-up period was 7.3 months and median time to progression was 2.6 months. The median overall survival was 6.8 months. No toxic deaths occurred. Toxicities of third-line treatment were mild and manageable. As NCI/NIH common toxicity criteria, grade 3/4 anemia, neutropenia and thrombocytopenia occurred in two, one and one patients, respectively. *Conclusion*: Our findings suggest that the combination of MMC and capecitabine in patients with advanced colorectal cancer pretreated with combination regimens including 5-FU, FA and CPT-11 or 5-FU, FA and L-OHP is safe. However, this regimen had a poor response rate and no definitive contribution to increasing patients' overall survival time. Further evaluation of other salvage regimens seems to be warranted.

Keywords Capecitabine · Mitomycin-C · Advanced colorectal cancer · Third-line chemotherapy

D. H. Lim · Y. S. Park (✉) · B.-B. Park · S. H. Ji · J. Lee
K. W. Park · J. H. Kang · S.-H. Lee · J. O. Park · K. Kim
W. S. Kim · C. W. Jung · Y.-H. Im · W. K. Kang · K. Park
Division of Hematology/Oncology, Department of Medicine,
Samsung Medical Center, Sungkyunkwan University School
of Medicine, 50 Ilwon-Dong, Kangnam-Ku,
Seoul, 135-710, Korea
E-mail: pys27hmo@smc.samsung.co.kr
Tel.: +82-2-3410-3454
Fax: +82-2-3410-0041

Introduction

Colorectal cancer is the fourth most commonly diagnosed malignancy, accounting for about 11% of newly diagnosed cancer cases in Korea. Up to 30% of patients present with metastatic disease, and approximately 50–60% eventually develop metastatic or advanced disease. Until several years ago, the only agent with significant activity in advanced colorectal cancer was 5-fluorouracil (5-FU). Metabolic modulation of 5-FU by leucovorin (FA) and infusional 5-FU schedules have been used in a variety of regimens which have resulted in an overall response rate of about 20–30% and a median survival believed to be 11–13 months [1–2]. In the last 10 years, several new cytotoxic agents with activity as single agents have widened the spectrum of therapeutic options in advanced colorectal cancer [3]. In particular, chemotherapy protocols including irinotecan (CPT-11) and oxaliplatin (L-OHP) alone or combined with 5-FU/FA have been extensively studied, as both first- and

second-line therapies. Recent trials have demonstrated that addition of CPT-11 or L-OHP to the infused 5-FU/FA regimens as first-line treatment results in a significantly superior response rate, and time to progression and survival [4–6]. It is a common practice nowadays to treat metastatic colon cancer patients with these chemotherapeutic agents sequentially. There are no data suggesting that a third-line chemotherapy provides survival benefit in patients who are resistant to 5-FU/FA/CPT-11 or 5-FU/FA/L-OHP.

Mitomycin-C (MMC) is a natural product, isolated from *Streptomyces caespitosus*. It is an alkylating agent and active against adenocarcinoma of the stomach, pancreas, colon and breast. In some previous studies, MMC has shown marginal activity in advanced colorectal cancer (response 10–15%) [7–8]. Capecitabine (Xeloda; Roche), an oral fluoropyrimidine carbamate, was rationally designed to generate 5-FU predominantly within tumor cells [9–11]. The tumor selectivity of capecitabine has been confirmed in patients with colorectal cancer [12]. Sawada et al. [13] have demonstrated that MMC increases the levels of thymidine phosphorylase (dThdPase) significantly, which is an essential enzyme for the activation of capecitabine and its intermediate metabolite (5′-dFUrd) to 5-FU in tumors, and of tumor necrosis factor-α, which is an upregulator of dThdPase [13].

The aim of this study was to investigate the therapeutic value and safety of third-line treatment with MMC and capecitabine in patients with advanced colorectal cancer previously treated with regimens including L-OHP and CPT-11 combined with 5-FU and FA.

Patients and methods

Patients

Between March 2003 and March 2004, 21 patients with advanced colorectal cancer were enrolled. The eligibility criteria were as follows: histologically confirmed colorectal cancer (adenocarcinoma), bidimensionally measurable disease, no secondary malignancy, age over 18 years, ECOG performance status (PS) 0–2, adequate bone marrow function (WBC ≥3000 cells/μl, granulocytes ≥1500 cells/μl, platelet count ≥100,000 cells/μl), serum creatinine concentration ≤ 1.5 mg/dl and total bilirubin ≤ 1.5 mg/dl, pretreatment with two sequential chemotherapy lines based on L-OHP and CPT-11 combined with 5-FU and FA. The pretreatment characteristics of the patients are presented in Table 1. Written informed consent was required before chemotherapy.

Treatment

The cytotoxic chemotherapy initiated consisted of intravenous MMC 7 mg/m^2 on therapeutic day 1 plus oral capecitabine 1000 mg/m^2 twice daily on days 1–14.

Table 1 Pretreatment characteristics of patients

Sex	
Male	16
Female	5
Age (years)	
Median	60.0
Range	37–67
Primary site	
Colon	8
Rectosigmoid	2
Rectum	11
Site of metastasis	
Liver	14
Lung	10
Lymph node	12
Peritoneal carcinomatosis	6
Locoregional	8
Performance status (ECOG criteria)	
1	17
2	4
Previous regimen	
5-FU/FA/CPT-11 followed by 5-FU/FA/L-OHP	12
5-FU/FA/L-OHP followed by 5-FU/FA/CPT-11	9

After rest for 7 days, capecitabine 1000 mg/m^2 twice daily was administered on days 22–35 followed by 7 days rest. The infused dosage of MMC in our study was designed according to a previous trial by Ross et al. [14]. Treatment courses were repeated every 6 weeks (Table 2) unless there was evidence of progressive disease, unacceptable toxicity or patient refusal of treatment. If grade 3/4 toxicity occurred, the doses of both drugs were reduced by 25%.

Evaluation

Pretreatment evaluation included physical examination, complete blood cell counts, blood chemistries, tumor marker level (CEA), and radiological examinations (chest PA view radiograph, CT scan and other imaging techniques as clinically indicated) within 1 month of starting of chemotherapy. The tumor responses were determined by WHO criteria and chemotherapy-related toxicities were scored by NCI/NIH common toxicity criteria. Complete blood cell counts and serum chemistries including liver and renal function, chest PA radiograph were performed at least every 3 weeks and tumor assessment by CT scan was performed every two cycles (12 weeks).

Statistics

Statistics was performed using SPSS 11.5 software (SPSS Korea, data solution). The 95% confidence

Table 2 Chemotherapy regimen (every 6 weeks)

Day 1	MMC 7 mg/m^2 + normal saline 100 ml intravenously over 30 min
Days 1–14	Capecitabine 1000 mg/m^2 orally twice daily
Days 22–35	Capecitabine 1000 mg/m^2 orally twice daily

interval (CI) was calculated from the binominal distribution. Overall survival and time to progression were estimated according to the Kaplan-Meier method. Time to progression was measured from the date of registration to the date of documented progression. Overall survival was measured from the time of registration to the date of death from any cause.

Results

All 21 patients were evaluable for toxicity and survival, whereas 19 patients were assessable for response evaluation and for time to progression. Two patients died before cessation of one cycle of chemotherapy. There were 16 male patients and 5 female patients. The median age of the patients was 60.0 years (range 37–67 years). Primary sites of disease were as follows; 8 colon, 2 rectosigmoid, and 11 rectum. All of the 21 patients had multiple sites of metastases and the most common metastatic site was liver followed by lymph node, lung, locoregional and peritoneal carcinomatosis. Performance status of the patients was relatively good (17 patients PS 1; 4 patients PS 2).

All patients received third-line chemotherapy with MMC and capecitabine and the median number of cycles of chemotherapy was two, ranging from one to four. The chemotherapy was stopped due to disease progression in 19 patients, poor performance status in two patients. The median follow-up period was 7.3 months. Only one (4.8%) partial response was seen. The duration of response was 1.8 months. Four patients (19.0%) had stable disease and 14 patients (66.7%) progressed. The duration of stable disease was 2.0 months in one patient, 4.1 months in two patients and 4.7 months in the other patient. The median time to progression was 2.6 months (95% CI 2.5–2.7 months) and the median overall survival was 6.8 months (95% CI 0.9–12.7 months). Figures 1 and 2 show the time to progression and overall survival curves.

A total of 43 cycles were administered. The toxicities of third-line treatment with MMC and capecitabine were mild and manageable. The toxicities are outlined in Table 3. According to NCI/NIH common toxicity criteria, grade 3/4 anemia, neutropenia and thrombocytopenia occurred in two, one and one patients, respectively, and no febrile neutropenia occurred. Grade 1/2 nausea, vomiting, and diarrhea developed in some patients, but no patient experienced that of grade 3/4. Hand-foot syndrome was the most common toxicity. Grade 3/4 hand-foot syndrome developed in three patients (14.3%). No toxic deaths occurred.

Discussion

To the best of our knowledge, there are no reports of the positive effects of third-line chemotherapy in advanced colorectal cancer after sequential administration of 5-FU and FA, CPT-11 and L-OHP as first- and second-line therapy. Rosati et al. [15] reported negatively on raltitrexed, a specific thymidylate synthase inhibitor, and

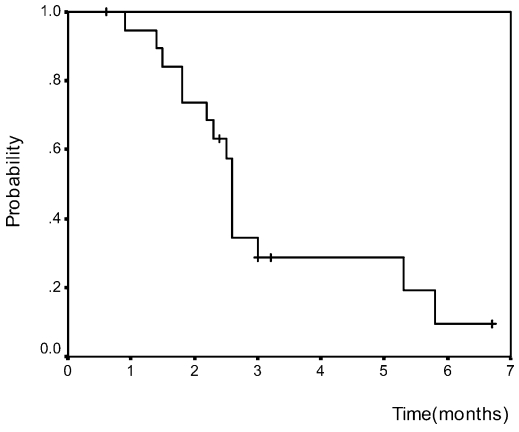

Fig. 1 Kaplan-Meier time to progression curve. The median time to progression was 2.6 months (95% CI 2.5–2.7 months)

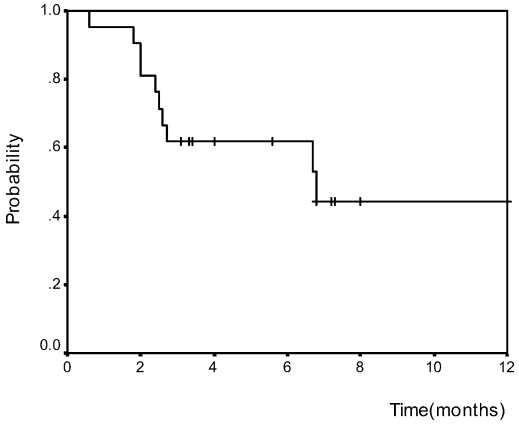

Fig. 2 Kaplan-Meier overall survival curve. The median survival was 6.8 months (95% CI 0.9–12.7 months)

Table 3 Toxicities per patient

Toxicity	Grade, *n* (%)	
	1/2	3/4
Hematologic		
Neutropenia	2 (9.5)	1 (4.8)
Anemia	2 (9.5)	2 (9.5)
Thrombocytopenia	8 (38.1)	1 (4.8)
Non-hematologic		
Diarrhea	2 (9.5)	0 (0)
Nausea	4 (19.0)	0 (0)
Vomiting	1 (4.8)	0 (0)
Stomatitis	6 (28.6)	0 (0)
Hand-foot syndrome	5 (23.8)	3 (14.3)

MMC as third-line chemotherapy for advanced colorectal cancer. There was no response group and the median time to progression and median survival time were 2.3 and 5 months, respectively. More recently, Hoff et al. [16] reported a phase II study of single-agent capecitabine in patients with 5-FU-resistant metastatic colorectal cancer. No objective responses were observed and the median time to progression and overall survival were 64 and 389 days. These findings are comparable to those of our study.

5-FU and FA, CPT-11 and L-OHP alone or combination have proven effects in the treatment of advanced colorectal cancer [17]. With CPT-11 and L-OHP beginning to be widely used clinically in the mid-1990s, many other chemotherapeutic agents, such as MMC, cisplatin, dacabazine, methyl-CCNU, methotrexate, cytarabine and etoposide, were investigated for their potential role in 5-FU-resistant colorectal cancer [18–21]. The reported overall response rate was 0–19% and median overall survival was 6–8 months. These drugs, compared with the currently used CPT-11 or O-LHP [17], have low effectiveness in 5-FU-resistant advanced colorectal cancer.

Most recently, Saltz et al. [22] have reported a phase II study of cetuximab in patients with refractory colorectal cancer. Cetuximab (C225, Erbitux) is an antibody directed against the ligand-binding site of epidermal growth factor receptor. This drug modulates tumor cell proliferation, disrupts the cell cycle phase, and modulates apoptosis and radiosensitivity. Cetuximab was administered to patients who were pretreated with irinotecan, either alone or combination, and showed a very limited activity with the response rate being 9%. Unlike this study, Cunningham et al. [23] reported salvage options with cetuximab, and in particular in combination with CPT-11 it showed significant activity. The response rate was 22.9% and time to progression and overall survival were 4.1 and 8.6 months, respectively.

Despite recent advances in the treatment of advanced colorectal cancer, the outcome in colorectal cancer patients who are refractory to 5-FU, FA and CPT-11 or 5-FU, FA and O-LHP, is not satisfactory and not fully investigated. The combination chemotherapy of MMC and capecitabine shows a synergistic effect in many gastrointestinal cancers [24–25] and a synergistic effect of this combination has even been shown in patients pretreated with 5-FU [26]. MMC is known to increase the levels of thymidine phosphorylase (dThdPase) and tumor necrosis factor-α, which is an upregulator of dThdPase, and also to enhance the metabolism of the intermediate metabolite (5′-dFUrd) to 5-FU in tumor tissues [13].

However, it was confirmed in our study that this regimen has a poor response rate and makes no definitive contribution to increasing patients' overall survival time. Therefore further investigation of other salvage regimens and the development of new molecular targeted agents seem to be warranted.

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