

A phase II study of mitomycin-C and S-1 as third-line chemotherapy in patients with advanced colorectal cancer

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Abstract. This study was conducted to evaluate the efficacy and safety of the combination of mitomycin-C (MMC) and S-1 as third-line chemotherapy for patients with advanced colorectal cancer (CRC) showing resistance to irinotecan- and oxaliplatin-containing regimens. Patients were recruited into the study from January 2009 and 10 patients were enrolled for 10 months. However, since no patients had shown a response by 10 months, the study was terminated early according to the protocol. MMC 7 mg/m² was administered intravenously on day 1 every 6 weeks in the first 4 cycles. S-1 was administered twice daily at 35 mg/m², within 1 h of meals on days 1-14. Following a rest for 7 days, S-1 was administered again on days 22-35, followed by a 7-day rest. A total of 14 cycles were delivered for 10 patients. All 10 patients were assessable for response. A total of 3 patients (30%) had stable disease and the remaining 7 showed disease progression. With a median follow-up of 7 months, the median overall survival was 10.5 months. Grade 3-4 myelotoxicities included neutropenia in two patients, anemia in two and thrombocytopenia in one. Grade 1-2 nausea and vomiting developed in 5 patients. One patient experienced grade 3 diarrhea. Grade 1-2 hand-foot syndrome occurred in 4 patients. In conclusion, the combination of MMC and S-1 as third-line chemotherapy in patients with advanced CRC appears to be well tolerated but has poor activity.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality in Western countries. In South Korea, CRC is the fourth most commonly occurring malignancy, accounting for approximately 10% of newly diagnosed cancer

cases (1). Approximately 30% of CRC patients present with advanced disease at first diagnosis, and 50% of patients who have received surgery eventually develop metastases during the course of their disease.

5-Fluorouracil (5-FU) combined with leucovorin (LV) had been widely used in the treatment of metastatic CRC, showing an overall response rate (RR) of 20-30%. Since the 1990s, the introduction of irinotecan or oxaliplatin has extended the spectrum of therapeutic options. The addition of irinotecan or oxaliplatin to infused 5-FU and LV has shown a significant improvement in tumor response and patient survival (2-4). It is common practice to administer these two chemotherapeutic regimens sequentially for patients with metastatic CRC. However, no effective third-line chemotherapy exists currently for patients who are resistant to irinotecan or oxaliplatin combined with 5-FU/LV.

S-1 is an oral fluoropyrimidine, in which tegafur has been combined with gimeracil and potassium oxonate. S-1 has shown promising efficacy in untreated CRC. Moreover, in a phase II trial with metastatic CRC patients showing failure of irinotecan- and oxaliplatin-containing regimens, the overall RR obtained with S-1 monotherapy was 14.3% (5). Mitomycin-C (MMC) is an alkylating agent with an activity against adenocarcinoma of the stomach, pancreas, breast and colon. In a number of studies, MMC has shown a RR of 10-15% in advanced CRC (6,7). MMC has a mild hematologic toxicity and is not associated with stomatitis or diarrhea. Since MMC has demonstrated synergistic activity with 5-FU (8), it is usually combined with 5-FU for clinical use. The MMC/5-FU combination was considered to be one of the most essential regimens for gastrointestinal types of cancer (9,10); therefore, its role in combination with an oral fluoropyrimidine, such as S-1, should be investigated.

This study was conducted to evaluate the efficacy and safety of the combination of MMC and S-1 as third-line chemotherapy for patients with advanced CRC showing resistance during treatment with irinotecan- and oxaliplatin-containing regimens.

Materials and methods

Study design. This trial was a phase II study of the MMC and S-1 combination in metastatic CRC patients showing

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resistance during treatment with irinotecan- and oxaliplatin-containing regimens. The primary end-points were overall RR and safety, and the secondary end-points were time to progression (TTP) and overall survival (OS).

According to Simon's two-stage optimal design, 29 patients were required for a statistical power of 80% and a false positive rate of 5%, with a lower activity level of 10% and a higher activity level of 30%. At the first stage, if none out of the initial 10 patients showed a response, the study was due to be terminated. Assuming a 10% drop-out rate, 32 patients were planned to be enrolled for this study. The study was approved by the institutional review board, and all patients gave written informed consent prior to recruitment into the study.

Patients. Patients were recruited into the study from January 2009 and 10 patients were enrolled for 10 months. The patients included 7 males and 3 females, with a median age of 62 years (range 42-76). The eligibility criteria for the study were: histologically confirmed colorectal adenocarcinoma with bidimensionally measurable metastatic disease, age over 18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of <2, adequate bone marrow function (absolute neutrophil count $\geq 1.5 \times 10^9/l$, platelet $\geq 100 \times 10^9/l$ and hemoglobin ≥ 10 g/dl), adequate renal and hepatic function (serum creatinine ≤ 1.25 x upper normal limit, hepatic enzymes and bilirubin ≤ 1.25 x upper normal limit, prothrombin time ≤ 1.5 x control) and documented disease progression during treatment with irinotecan- and oxaliplatin-containing regimens. Patients were ineligible if they had other malignancies, brain metastases or active infection.

Treatment schedule. MMC 7 mg/m² was administered intravenously on day 1 every 6 weeks in the first 4 cycles. To prevent hemolytic uremic syndrome (HUS), MMC was restricted to a cumulative dose of 28 mg/m². MMC dose was reduced by 25% if grade 3 or 4 hematologic toxicity occurred. MMC administration was terminated if there was hemolytic anemia, severe and prolonged thrombocytopenia or fragmented red cells on the peripheral blood smear.

The starting dose of S-1 was twice daily at 35 mg/m². S-1 was administered within 1 h of meals on days 1-14. Following a rest for 7 days, S-1 was administered again on days 22-35, followed by a 7-day rest. S-1 dose was reduced by 10 mg/m² a day if grade 3 or 4 hematologic or non-hematologic toxicity developed. Treatment courses were repeated every 6 weeks unless there was evidence of disease progression, unacceptable toxicity or the patient refused to continue treatment.

Response and toxicity evaluation. Baseline evaluation included physical examination, complete blood counts (CBC), peripheral blood smear, blood chemistries and radiological examinations. Physical examination, CBC and blood chemistry were performed every 3 weeks. Tumor assessment by CT scan was performed every 6 weeks. Patients were evaluated for response if they received more than one cycle of treatment. Response to therapy was assessed according to the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. Toxicity was recorded according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC, version 3.0). For toxicity analysis,

Table I. Patient characteristics.

	No. of patients
Age, years	
Median	62
Range	42-76
Gender	
Male	7 (70%)
Female	3 (30%)
Performance status (ECOG)	
0-1	7 (70%)
2	3 (30%)
Primary site	
Colon	6 (60%)
Rectum	4 (40%)
Site of metastases	
Liver	5 (50%)
Lymph node	4 (40%)
Lung	3 (30%)
Peritoneum	2 (20%)
Bone	2 (20%)
Histology	
Well, moderate	6 (60%)
Poor	4 (40%)

the worst data for each patient in all cycles of chemotherapy were used.

Statistical analysis. Response and toxicity data were analyzed using simple descriptive statistics. TTP was determined from the first day of chemotherapy until tumor progression or mortality. OS was calculated from the first day of treatment until the date of mortality. Survival curves were established by using the Kaplan-Meier method.

Results

Patient characteristics. According to the study design, at least one out of the 10 patients were required to show a response to continue the study. However, since no patients had shown a response by 10 months, the study was terminated early. Baseline characteristics of the enrolled patients are shown in Table I. A total of 7 patients (70%) had an ECOG PS of 0 to 1 and 3 patients had an ECOG PS of 2. All 10 patients had multiple sites of metastases. The most common metastatic site was the liver, followed by the intra-abdominal lymph node, lung and peritoneum. A total of 4 patients had a poorly differentiated adenocarcinoma.

Treatment outcomes. A total of 14 cycles were delivered to the 10 patients. A total of 7 patients received 1 cycle and 2 patients received 2 cycles, and the remaining patient received 3 cycles. Chemotherapy was stopped due to disease progression in 9 patients and poor PS in one patient. A total of 9 patients were

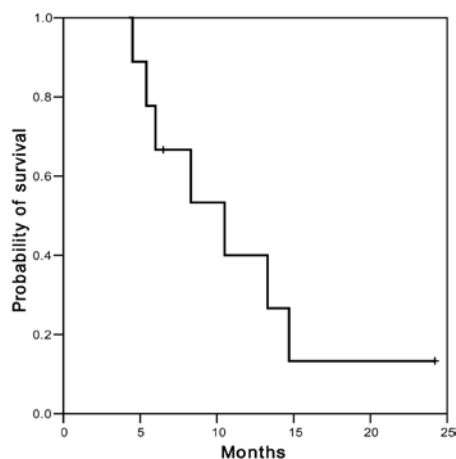


Figure 1. Overall survival.

not switched over to the following chemotherapy following disease progression. One patient received cetuximab plus irinotecan and experienced a partial response for 4 months.

All 10 patients were assessable for response. A total of 3 patients (30%) had stable disease and the remaining seven showed disease progression. The duration of stable disease was 6 weeks in two patients and 3 months in one patient. With a median follow-up of 7 months, the median overall survival was 10.5 months (range 3.7-24.2). One patient remains alive with a follow-up period of 24.2 months.

Toxicity. The patients were evaluable for toxicity. The toxicity profile is shown in Table II. NCI-CTC grade 3-4 myelotoxicities were as follows: neutropenia in two patients, anemia in two patients and thrombocytopenia in one patient. No febrile neutropenia occurred. Grade 1-2 nausea and vomiting developed in five patients. One patient experienced grade 3 diarrhea. Grade 1-2 hand-foot syndrome occurred in four patients. No patients developed hemolytic anemia or HUS.

Discussion

In this phase II study, the efficacy of MMC plus S-1 was evaluated as third-line chemotherapy for patients with advanced CRC showing resistance to irinotecan- and oxaliplatin-containing regimens. This study was terminated early as none of the initial 10 patients showed a response. Although this regimen failed to show activity for these patients, we believe the results are worth reporting.

Irinotecan and oxaliplatin are widely used in combination with 5-FU/LV as first- and second-line treatment for CRC (2-4). Targeted compounds including cetuximab and bevacizumab may also be introduced into the treatment of advanced CRC (11,12). However, few reports are currently available of salvage therapy for patients who are refractory to the first- and second-line chemotherapy (5,13). Although cetuximab with or without irinotecan is a potential option for patients without k-ras mutation (14), its use is limited due to the high cost involved. Therefore, new chemotherapeutic regimens remain to be determined.

The rationale for combining MMC with fluoropyrimidine was based on the different cytotoxic mechanism of the drugs

Table II. Toxicity profile by grade.

Toxicity	Grade 1-2 (%)	Grade 3-4 (%)
Hematologic toxicities		
Neutropenia	2 (20)	2 (20)
Anemia	3 (30)	2 (20)
Thrombocytopenia	2 (20)	1 (10)
Non-hematologic toxicities		
Nausea	5 (50)	0 (0)
Vomiting	5 (50)	0 (0)
Hand-foot syndrome	4 (40)	0 (0)
Diarrhea	1 (10)	1 (10)
Stomatitis	3 (30)	0 (0)

and their non-overlapping adverse effects. The combination chemotherapy of MMC and an oral fluoropyrimidine carbonate, capecitabine, has shown a synergistic effect in gastrointestinal tumors (15,16). In the present study, we combined MMC and S-1 to improve antitumor activity. In a phase II study in patients with advanced gastric cancer, MMC plus S-1 as second-line therapy has shown an objective RR of 21%, with a tolerable toxicity profile (17).

None of the 10 patients who were enrolled at the first stage of this study showed a response. Therefore, the study was terminated early according to the protocol. Three patients showed stable disease, which was maintained for 1.5 to 3 months. Jeung *et al* have reported a phase II trial of S-1 monotherapy in metastatic CRC patients showing failure of irinotecan- and oxaliplatin-containing regimens (5). Of 26 patients, the overall RR was 14.3% and the disease control rate was 42.9%. The difference in response between studies may be associated with a variety of patient characteristics and prognostic factors. The 10 enrolled patients in this study had shown disease progression during (not within 6 months after) treatment with irinotecan- and oxaliplatin-containing regimens. Four patients (40%) had a poorly differentiated adenocarcinoma, compared to 10.7% in the study by Jeung *et al*. Therefore, these differences may have an impact on the tumor response in this study. Additionally, in a phase II trial of a combination of MMC and another oral fluoropyrimidine, capecitabine, as third-line chemotherapy in patients with advanced CRC, only one out of 19 patients (4.8%) showed a partial response (13). These results suggest that the combination of MMC and an oral fluoropyrimidine, such as capecitabine or S-1, has poor activity in advanced CRC patients pretreated with irinotecan and oxaliplatin sequentially in combination with infused 5-FU/LV.

In terms of toxicity, the MMC and S-1 combination in this study showed favorable safety profiles. The most common toxicity was nausea and vomiting, followed by hand-foot syndrome. Hematologic toxicities were generally mild and manageable, and no febrile neutropenia developed. In association with MMC, none of the 10 patients developed hemolytic anemia or HUS.

In conclusion, the combination of MMC and S-1 in advanced CRC patients pretreated with irinotecan- and

oxaliplatin-containing regimens is well tolerated. However, the present result indicates that this regimen has poor activity for those patients. Therefore, attempts to develop other types of salvage therapy are required.

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