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ORIGINAL ARTICLE

Mitomycin-C in combination with fluoropyrimidines in the treatment of metastatic colorectal cancer after oxaliplatin and irinotecan failure

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Summary

Purpose: *To retrospectively evaluate the efficacy and tolerability of mitomycin-C (MMC) in combination with fluoropyrimidines as salvage 3rd -or 4th-line therapy in metastatic colorectal cancer (MCRC) patients.*

Methods: *All patients in this study had previously failed oxaliplatin and irinotecan-based chemotherapy. Patients were treated with MMC (6 mg/m^2 intravenously/i.v.) on day 1 in combination with either oral UFT (500 mg/m^2) and oral leucovorin (LV) (30 mg) on days 1-14 every 3 weeks (group A) or infusional 5-fluorouracil (5-FU) by deGramont regimen with i.v. LV (200 mg/m^2) on days 1 and 2, every 2 weeks (group B).*

Results: *Thirty-nine MCRC patients were analyzed. Twenty-two of them were in group A and 17 in group B. Thirty-three were evaluable for clinical efficacy. The clinical benefit in the intent-to-treat (ITT) population was 30.8%. Median progression free survival (PFS) was 6 months (95% confidence interval/CI 4-8) and median overall survival (OS) 9 months (95% CI 6.5-11.5). Median PFS was 3 months (95% CI 2.4-3.6) in group A and 7 months (95% CI 5.1-8.9) in group B (p=0.009). Median OS was 7 months (95% CI 4.3-9.7) in group A and 12 months (95% CI 5.4-18.6) in group B (p=0.422). The combination of MMC and fluoropyrimidines was generally well tolerated. The most common severe toxicities were nausea and vomiting, neutropenia, hepatotoxicity and diarrhea.*

Conclusion: *MMC in combination with fluoropyrimidines is safe and active in heavily-pretreated MCRC patients. This combination remains a viable option in these patients. However, better therapies are urgently needed.*

Key words: fluoropyrimidines, metastatic colorectal cancer, mitomycin-C, salvage therapy

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer [1]. Twenty percent of patients with CRC have metastatic disease at diagnosis and nearly half of them develop distant metastases at any time of the disease [2]. Prognosis of MCRC is poor with 4-6 months median OS with best supportive care alone [2] and 16-20 months with combinations of irinotecan or oxaliplatin plus fluoropyrimidines [3-5]. Targeted therapies using bevacizumab and cetuximab have become the standard of care in combination with irinotecan or oxaliplatin-based therapies in the treatment of MCRC [6].

Fluoropyrimidines (5-FU and oral 5-FU analogues such as capecitabine and UFT) have been the most widely used chemotherapeutic agents for MCRC. Oral fluoropyrimidine UFT is a prodrug of 5-FU, and a combination of tegafur and uracil in a molar ratio of 1:4 [7]. UFT has similar antitumor efficacy with less toxicity compared to i.v. 5-FU in the treatment of MCRC. MMC, a potent DNA cross-linker, is an alkylating antibiotic agent derived from *Streptomyces caespitosus* [8]. It has modest activity in MCRC, however the role of

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MMC has been diminished after the introduction of irinotecan and oxaliplatin in the last decade [9]. MMC and 5-FU combinations are used in the treatment of MCRC because of their synergistic effects [10,11].

After the failure of front-line combination chemotherapy with 5-FU, oxaliplatin and irinotecan, treatment options are limited in the 3rd-line setting and beyond. Herein, we retrospectively evaluated our experience with MMC in combination with fluoropyrimidines in the salvage treatment of heavily-pretreated MCRC.

Methods

Data were obtained from chart reviews of MCRC patients in 7 centers in Turkey. All patients had previously failed irinotecan and oxaliplatin-based regimens in combination with fluoropyrimidines. Most patients had also received targeted agents. A total of 39 patients treated with MMC and fluoropyrimidines were identified between April 2006 and August 2009. The patients had received MMC 6 mg/m^2 i.v. on day 1 in combination with either oral UFT 500 mg/m^2 and oral LV 30 mg on days 1-14 every 3 weeks (group A), or infusional 5-FU (deGramont regimen) (5-FU 400 mg/m^2 i.v. bolus on days 1 and 2, and 5-FU 600 mg/m^2 22 h infusion, and i.v. LV, 200 mg/m^2 on days 1 and 2) every 14 days (group B). Response evaluation was based on RECIST criteria every 2-3 cycles and at the end of treatment [12]. Treatment courses were repeated for at least 6 cycles or until progression. Toxicity was evaluated according to the National Cancer Institute (NCI) common toxicity criteria [13]. In case of grade 3/4 severe adverse event, a 25% dose reduction of all cytotoxic agents was done.

Statistical analysis

A preliminary statistical analysis revealed that the distribution of PFS and OS did not follow a normal distribution. Thus, the Mann-Whitney U test was used for statistical analysis. Data were presented as median and range. Statistically significant differences were defined as comparisons resulting in $p < 0.05$. To analyze the associations between variables, the Kruskal-Wallis and Spearman correlation coefficients were employed. Survival analysis was performed using the Kaplan-Meier method.

Results

Twenty-five males and 14 females patients were eligible for analysis. Their median age was 55 years (range 30-80). The site of the primary tumor was rectum in 10 patients (25.6%) and colon in 29 (74.4%). Only 2 patients had WHO performance status (PS) 2, all the others had PS 0 or 1. Patients were given a median of 5 cycles (range 1-12) of chemotherapy. The study regimen was used as 3rd-line (n=25) and 4th-line (n=14) therapy. Some patients were administered bevacizumab (n=34; 87.2%) and cetuximab (n=5; 12.8%) in the 1st- and 2nd-line setting. Patient characteristics are summarized in Table 1.

Twenty-two patients (56%) were in group A and 17 (44%) in group B. Thirty-three patients were evaluable for efficacy analysis. Clinical benefit in the ITT population was 30.8% (1 partial response/PR and 11 stable disease/SD). Median PFS was 6 months (95% CI 4-8) and median OS 9 months (95% CI 6.5-11.5) in the whole group. Median PFS was 3 months (95% CI 2.4-3.6) in group A vs. 7 months (95% CI 5.1-8.9) in group B (p=0.009) (Figure 1). Median OS was 7 months (95% CI 4.3-9.7) in group A vs. 12 months (95% CI 5.4-18.6) in group B (p=0.422) (Figure 2). In 6 patients, response

Table 1. Patient characteristics

Characteristics	*Patients, n*	*%*
Median age, years (range)	55 (30-80)	
Males/females	25/14	64.1/35.9
Treatment arm		
UFT	22	56.4
Infusional 5-FU	17	43.6
Location		
Colon	29	74.4
Rectum	10	25.6
Site of metastases		
Liver only	16	41
Lung only	5	12.8
Other	7	25.7
>2 sites	8	20.5

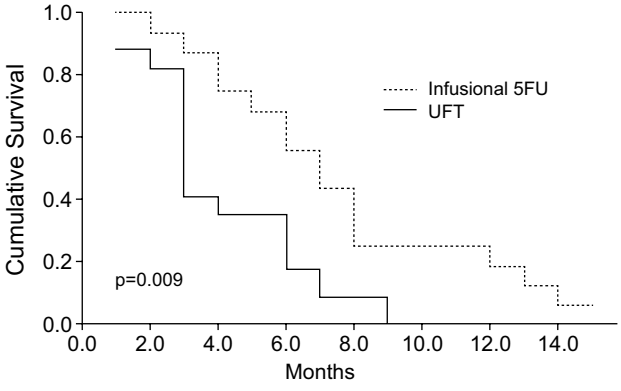

Figure 1. Progression free survival (PFS). Median PFS was 3 months (95% CI 2.4-3.6) in the UFT group vs. 7 months (95% CI 5.1-8.9) in the infusional 5-FU group B.

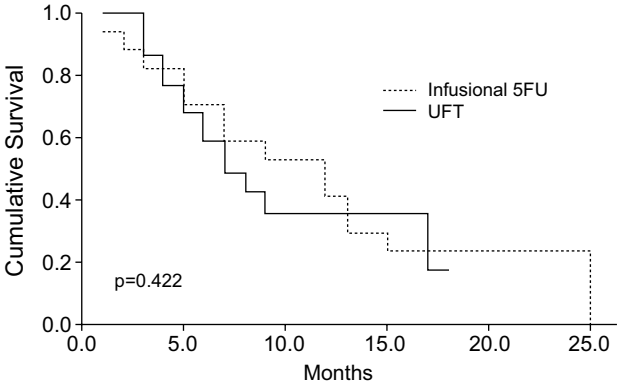

Figure 2. Overall survival (OS). Median OS was 7 months (95% CI 4.3-9.7) in the UFT group vs. 12 months (95% CI 5.4-18.6) in the infusional 5-FU group.

assessment was not carried out because of early termination after one cycle due to grade 2-4 toxicity (n=4: 3 gastrointestinal, 1 renal), and patient refusal (n=2).

All 39 patients were assessable for toxicity. The most common severe grade 3/4 toxicities were nausea and vomiting, neutropenia, hepatotoxicity and diarrhea (Table 2). Dose adjustment was required in 13 patients.

Table 2. Grade 3/4 toxicities

Toxicity	*NCI grade III/IV*	
	Patients, n	*%*
Nausea & vomiting	7	35
Neutropenia	2	10
Anemia	2	10
Hepatotoxicity	3	15
Diarrhea	2	10

Discussion

MCRC has become a chronic disease after the introduction of newer generation agents and targeted therapies. Chemotherapy is palliative, however, essential for quality of life (QoL) and survival. Treatment options after failure of irinotecan and oxaliplatin are limited and debated. MMC has become an option in the treatment of these patients in combination with fluoropyrimidines or as a single agent. We evaluated our experience with MMC and fluoropyrimidine combinations in the treatment of MCRC patients who failed irinotecan- and oxaliplatin-based therapy. MMC combinations showed reasonable activity in heavily-pretreated MCRC patients. Median PFS and OS were 6 months (95% 4-8) and 9 months (95% CI 6.5-11.5), respectively. While our results are in line with the literature, survival outcomes were better with infusional 5-FU schedules. This difference might be due in part to the difference in scheduling of the treatment regimens, i.e. 2 vs. 3 weeks intervals in between cycles. Moreover, there were more patients receiving MMC + UFT as 4th-line therapy in contrast to patients in the infusional 5-FU group who had 2 previous lines of therapy. In the present study, the most common severe toxicities were nausea and vomiting, neutropenia, hepatotoxicity and diarrhea. Toxicity profile was generally tolerable.

The role of MMC in the treatment of MCRC has markedly diminished after the widespread use of irinotecan and oxaliplatin [9]. This is partially due to the modest activity of MMC obtained in various studies. Response rates of 5-45% and median OS of 6-8 months have been reported in studies using MMC in combination with 5-FU in pretreated MCRC [14-20]. In the pre-oxaliplatin and pre-irinotecan era, Aphinives et al. treated 40 patients with liver metastatic CRC with MMC and 5-FU. Overall response rate (ORR) was 45% (CR in 3, PR in 15) and OS was 13.1 months. Grade 3-4 toxicities were experienced by nearly 12% of the patients [14]. Steitz et al. achieved an ORR of 30% leading to a median OS of 10 months and 1-year OS of 39.4% in the 2nd-line treatment of MCRC [15]. Conti et al. evaluated this combination in the same setting in 28 patients. They demonstrated 17% response rate and 11.5 months median OS in 24 evaluable patients [16]. Finally, a randomized study failed to reveal a survival advantage of MMC + 5-FU combination over 5-FU alone [17]. These results were not promising enough for further exploration.

Oral agents have the potential to enhance compliance and clinical response. Pharmacokinetic analyses of UFT showed an increased elimination half-life, higher plasma concentrations and similar area under the curve (AUC) compared with infusional 5-FU. In a combined phase I/II study of UFT and MMC, 24% clinical response rate was reported including 1 complete response (CR) and 4 PR in 21 patients [18]. Another phase II study showed 23% ORR leading to 5 months of PFS and 13 months OS in the 1st-line treatment of MCRC (19]. An interesting study from Austria presented results very similar to ours [20]. This Austrian retrospective study was performed in patients who had failed prior oxaliplatin- and irinotecan-based therapies. A total of 41 patients were treated with UFT + MMC combination resulting in 7% ORR, 2.5 months PFS and 6 months OS. These data are close to our results. Toxicity was tolerable. The convenience of oral fluoropyrimidines renders these agents attractive partners in combination regimens.

In conclusion, MMC and fluoropyrimidines combination is safe and active in MCRC patients. However, the infusional 5-FU-containing regimen was superior to MMC + UFT combination. Toxicity was tolerable.

MMC remains a viable option in these heavily-pretreated patients who might tolerate further treatment. Addition of new novel agents might help improve survival rates further.

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