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Salvage chemotherapy in metastatic colorectal cancer with the combination of capecitabine and mitomycin C

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A significant proportion of heavily pretreated patients with metastatic colorectal cancer maintain good performance status (PS) and are eligible for further systemic treatment. Mitomycin C (MMC) combined with capecitabine can be considered as salvage treatment in this group of patients. To evaluate the efficacy and toxicity of mitomycin C and capecitabine as at least third-line systemic therapy (after failure of 5Fu, irinotecan, oxaliplatin-based chemotherapy regimens and targeted therapies) in patients with metastatic colorectal cancer. A total of 31 patients with a median age of 55.2 years with metastatic colorectal cancer received salvage chemotherapy at the Oncological Department of University Hospital in Krakow, Poland, between July 2011 and July 2014. Chemotherapy consisted of intravenous MMC 6 mg/m2 on day 1 and oral capecitabine 1000 mg/m2 twice daily on days 1-14 followed by a 7-day treatment-free interval. Each cycle was repeated every 3 weeks unless there was evidence of disease progression or unacceptable toxicity. All the31 patients were evaluable for response and toxicity. A total of 113 cycles were administered. Five of the 31 (16.1%) patients had stable disease after three cycles of chemotherapy, 24 (77.4%) patients progressed and 1 (3.2%) patient is still undergoing treatment. One patient (3.2%) died due to cardiac infarct 5 days after starting treatment. Median progression free survival (PFS) was 2.5 months. Median overall survival (OS) was 4.9 months. Toxicity was mild and easily manageable. Mitomycin C and capecitabine can be considered as salvage therapy in heavily pretreated patients with metastatic colorectal cancer and with good performance status. Toxicity of these drugs combination is moderate and easily manageable.

Key words: mitomycin C, capecitabine, metastatic colorectal cancer

Mitomycin C is an antitumor antibiotic with modest single-agent activity against metastatic colorectal cancer. Mitomycin C induces up-regulation of intratumoral thymidine phosphorylase – the pivotal enzyme for the convertion of capecitabine to 5Fu [1]. This mechanism can possibly be responsible for clinically significant synergy with capecitabine. A significant proportion of heavily pretreated patients with metastatic colorectal cancer present good performance status and are eligible for further systemic treatment. MMC and capecitabine can be considered as a salvage chemotherapy in this group of patients. The aim of this prospective study is to evaluate the efficacy and tolerability of MMC combined with capecitabine in patients with metastatic colorectal cancer pretreated at least three lines of systemic treatment.

Patients and methods

Thirty one patients (19 males and 12 females) with metastatic colorectal cancer were treated at the Oncological Department of University Hospital in Krakow, Poland, between July 2011 and July 2014. Patients with histologically confirmed metastatic colorectal cancer were enrolled in this study. All patients signed informed consent. Patients were pretreated with a minimum of three lines systemic treatment with progression, after failure of 5Fu, irinotecan, oxaliplatin-based chemotherapy regimens and targeted therapies such as: panitumumab, cetuximab, bevacizumab.

The vast majority of patients had the ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1. Overall

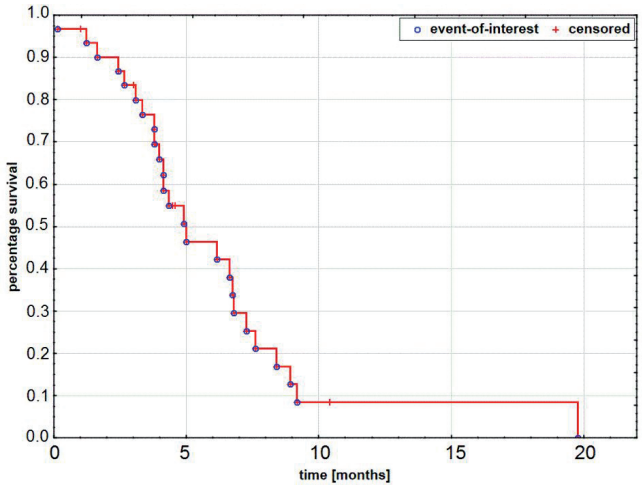

Figure 1. The Kaplan-Meier survival curve – the overall survival.

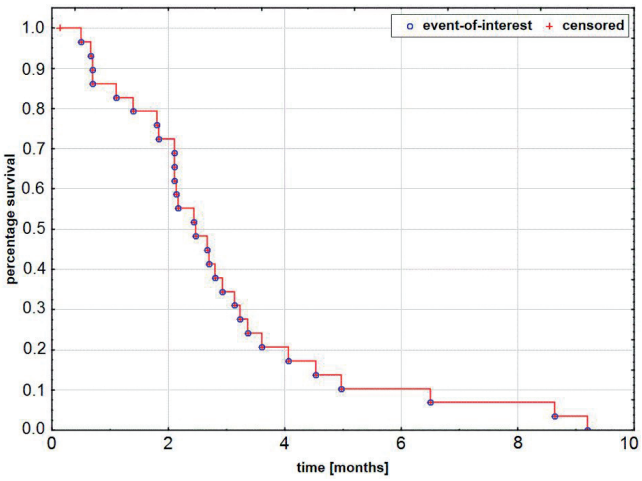

Figure 2. The Kaplan-Meier survival curve – the progression-free survival.

survivall was a minimum of 3 months. Patients had adequate bone marrow, renal and hepatic functions.

Table 1. Patient characteristics.

patient characteristics	number (n=31)
sex	M:F = 19 (61.3%) : 12 (38.7%)
median age (range)	55.2 years (34-74 years)
primary site	colon -18 (58.1%) rectum -13 (41.9%)
sites of metastases	liver – 15 (48.5%) liver and lungs – 10 (32.3%) peritoneum and local recurrence – 2 (6.4%) liver and bones – 1 (3.2%) liver and local recurrence – 1 (3.2%) liver, lungs and lymph nodes – 1 (3.2%) liver and lymph nodes – 1 (3.2%)
performance status	PS 0 – 10 (32.3%) PS 1 – 17 (54.8%) PS 2 – 4 (12.9%)
previous surgical treatment	YES – 29 (93.5%) NO – 2 (6.5%)
previous radiotherapy	YES – 4 (12.9%) NO- 27 (87.1%)
line of systemic treatment	third line – 13 (41.9%) fourth line – 12 (38.7%) fifth line – 6 (19.4%)
number of cycles (range: 1-13 cycles)	1 cycle – 5 patients (16.2%) 2 cycles – 5 patients (16.2%) 3 cycles – 7 patients (22.6%) 4 cycles – 9 patients (29.0%) 5 cycles – 1 patient (3.2%) 6 cycles – 1 patient (3.2%) 8 cycles – 1 patient (3.2%) 9 cycles – 1 patient (3.2%) 13 cycles – 1 patient (3.2%)

Adverse events were evaluated every three weeks according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.1). Treatment efficacy was evaluated according to the WHO criteria. Overall survival was calculated from the start of chemotherapy to the patient's death. Progression free survival was defined as time from the start of chemotherapy to the patient's deterioration or progression, evaluated on the basis of the abdomen and chest CT scans.

Chemotherapy regimen consisted of intravenous mitomycin C 6 mg/m2 on day 1 and oral capecitabine 1000 mg/m2 twice daily on days 1-14 followed by a 7-day rest treatment-free interval. Each cycle was repeated every 3 weeks till disease progression or unacceptable toxicity.

Patient characteristics are shown in Table 1.

Kaplan-Meier survival analysis was performed to assess overall survival and progression free survival. All survival times were calculated from the date of the first treatment. All calculations were performed using STATISTCA version 10.

Results

All 31 patients were evaluable for response and toxicity. A total of 113 cycles were administered (median 3.6; range:1-13 cycles). Five of the 31 (16,1%) patients had stable disease after three cycles of chemotherapy. Finally, 28 patients (90.3%) progressed (18/28 – radiologically confirmed progression – and 10/28 – deterioration in performance status within chemotherapy). One patient died due to cardiac infarct 5 days after starting treatment. The autopsy was not performed. The relation between the death cause and chemotherapy was probable but not certain that patient had cardiologic history. Reasons for treatment completion are shown in Table 2. One patient (3.2%) is still undergoing treatment. Twenty-five of the 31 patients (80.6%) died. One patient (3.2%) was lost to follow-up. The patient was 8.4 months in follow-up.

Five patients (16.1%) are still alive. In the group of all patients treated at the Department of Clinical Oncology mean observation time was 5.3 ± 3.7 months. Overall survival (OS, median, the survival time at which the cumulative survival function is equal to 0.5 calculated from Kaplan-Meier curve) for this group of patients was 4.9 months (the first quartile 3.5 months, the third quartile 7.3 months). Overall survival after treatment is shown in Figure 1. The mean time to progression was 2.9 ± 2.2 months. Progression-free survival (PFS) for this group of patients was 2.5 months (the first quartile 1.8 months, the third quartile 3.3 months). PFS after the treatment is shown in Figure 2. Toxicity was mild and easily manageable. Toxicity (G3) included thrombocytopenia 6.5%, diarrhea 3.2% and fatigue 3.2%. The whole spectrum of toxicity is shown in Table 3.

Disscusion

Mitomycin C is an old generation of anticancer drug that acts synergistically with capecitabine and irinotecan. It has been used in combination with modern compounds in various settings of metastatic colorectal cancer. The phase II study of capecitabine and mitomycin C was evaluated as first-line treatment in patients with advanced colorectal cancer. The overall response rate was 38%. One third of the patients achieved stable disease for over 12 weeks [2]. Mitomycin C combinations are less efficacious than those of modern drugs in first-line treatment of colorectal cancer according to available data from the last forty years (Corchane database, PubMed, etc.) [3].

There were studies evaluating the efficacy and safety of continuous infusion of single -agent mitomycin C in patients with metastatic colorectal cancer progression after first- , second- or further line 5-fluorouracil-based chemotherapy. The median survival time ranged from 3.6 to 4.7 months [4, 5]. Six month survival rate was 36% [4]. Continuous infusion of mitomycin C had good toxicity profile, but no satisfactory activity [4, 5, 6].

The efficacy and safety of mitomycin C in combination with oral uracil/tegafur (UFT) and leucovorin were estimated as third-line treatment for patients with metastatic colorectal cancer. All patients had failed prior treatment with fluoropyrimidine, irinotecan, oxaliplatin and targeted therapies. The median time to progression ranged from 2.5 months to 5 months and median overall survival ranged from 6 months to 7.5 months [7, 8, 9]. The combination mitomycin C with UFT was an efficacious therapeutic option in about 30% heavily pretreated colorectal cancer patients [7, 9]. Tolerance of the regimen was good [7, 8, 9]. In Alkis et al. study, mitomycin C in combination with fluoropyrimidines (oral UFT or infusional 5-Fu by de Gramont regimen) as third or fourth line in metastatic colorectal cancer patients resulted in 6 months progression free survival and in 9 months overall survival. Median progression free survival was 3 months in oral UFT group and 7 months in infusional 5Fu group. Median overal survivall was 7 months and 12 months, respectively [10].

The median time to treatment failure was 1.7 months and median survival was only 4.5 months in the largest published study of unselected refractory metastatic colorectal patients treated with mitomycin C alone or with capecitabine. Survival was comparable to that expected for the best supportive care. Generally, the results were disappointing [11]. As opposed to Ferrarotto' s study, promising results in patients previously treated with at least one chemotherapy regimen were reported in a study from Croatia. The objective response rate was 15.2%. Median failure-free survival was 5.4 months. The median time to tumor progression was 4.5 months, while median overall survival was13 months [12]. Similarly, in Chong et al. study, mitomycin C and capecitabine had comparable response rate(15.2%) to monotherapy cetuximab in patients pretreated with 5Fu followed by irinotecan. Capecitabine and mitomycin C may be alternative if targeted therapies are contraindicated [13]. In other published series [14.15], the median time to progression ranged between 2 and 3 months while overall survival ranged between 6 –6.8 months were reported. According to the literature data, clinical benefit, defined as stable disease, partial and minor remission, was observed in 23% to 48.5% of the patients treated with mitomycin C and capecitabine [14, 15, 16, 17].

The above data are related to the Caucasian patients. Only one study evaluating the efficacy and toxicity of Asian patients treated with mitomycin C and capecitabine has been published so far. Mitomycin C and capecitabine were given as third line systemic treatment. Overall response was in 33.3% of the patients. Median overall survival was 6.8 months. Tolerance of this regimen was good [18]. Kang et al. presented results of study regarding Asian patients treated with mitomycin C in combination with 5Fu as third line of systemic treatment. Stable disease was observed in 41.3%. Median progression-free survival was 10 weeks and median overall survival was 38 weeks. Toxicity profile was moderate [19].

Toxicity was moderate and generally acceptable in this group of patients. Hematological toxicity G3 occurred in 2

Table 2. Reason of the treatment completion

Reason	number (n= 29)
radiologically confirmed progression	18 (60%)
deterioration of performance status	10 (36.7%)
cardiac infarct	1 (3.3%)

Table 3. Toxicity of capecitabine and mitomycin C regimen.

toxicity	number	all the grades
palmar-plantar erythema	2 (6.5%)	G1/G2
nausea	1 (3.2%)	G1
diarrhae	1 (3.2%)	G3
thrombocytopenia	2 (6.5%)	G3
fatigue	1 (3.2%)	G3

Table 4. Combination of mitomycin C and capecitabine in the patients with metastatic colorectal cancer.

author/year of publication	number of subjects	line of treatment	overall response [%]	median PFS [months]	median OS [months]
Rao S/ 2004	92	I	38	7.1	14.3
Chong G/2005	36	III	15.2	5.4	9.3
Lim DH/2005	21	III	33.3	2.6	6.8
Rimassa L/ 2006	28	III	47	2.0	6.0
Scartozzi M/ 2006	61	III	48	3.0	6.0
Vdorljak E/ 2008	36	II, III or IV	55.6	4.5	13.0
Ferarotto/2012	109*	II-11%, III- 38%, IV and further- 51%	-	1.7	4.5
Saif MW/2013	15	IV and further	50	-	-

* part of the patients received mitomycin C as a single agent

patients only. Non-hematological toxicity was described in 2 patients. According to other studies the regimen was also very well tolerated without significant hematological toxicity [14, 16]. Rarely were single cases of hematological toxicity G3 and G4 observed [2, 11, 13, 15, 17, 19]. Therefore, the regimen may be an attractive option for patients with cumulative toxicities after previous systemic treatment [13].

In summary, overall survival lasting 4.9 months is disappointing, but other anticancer drugs such as gemcitabine or capecitabine have also very limited or hardly any efficacy in patients pretreated with 5 Fu, oxaliplatin and irinotecan [20]. It is important to emphasise that one fifth of the patients enrolled in this study had previously four lines osystemic treatment. Fifty percent of the patients had multiple sites of metastases. Patients may continue systemic treatment due to their good performance status and organ function reserves. This prospective study demonstrated a modest activity of mitomycin C and capecitabine in heavily pretreated patients with acceptable safety profile and low cost. Our results are consistent with the published data, especially with MIXE (mitomycin C-capecitabine) [16]. The significance and strength of this study lies in the fact that the regiment of mitomycin C and capecitabine can be an acceptable alternative for the best supportive care in the selected Caucasian and Asian patients with metastatic colorectal cancer. List of published studies with capecitabine and mitomycin C in colorectal cancer patients is shown in Table 4.

Conclusions

1. Mitomycin C and capecitabine can be considered as a salvage therapy in heavily pretreated patients with metastatic colorectal cancer and with good performance status. 2. Toxicity of these drugs combination is moderate and easily manageable.

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