Journal of BUON **13:** 513-518, 2008

ORIGINAL ARTICLE

Capecitabine and mitomycin-C in the therapy of pretreated patients with metastatic colorectal cancer: single center retrospective study with 36 patients

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Summary

Purpose: *To evaluate the therapeutic effectiveness and safety of treatment with capecitabine and mitomycin-C (MMC) in patients with metastatic colorectal cancer previously treated with at least one chemotherapy regimen for recurrent or metastatic disease.*

Patients and methods: *A total of 36 patients (male/female 21/15, median age 62.5 years) with metastatic colorectal cancer were treated with capecitabine and MMC as their second, third or fourth line chemotherapy regimen. Chemotherapy consisted of intravenous MMC 6 mg/m^2 on day 1 plus oral capecitabine 1000 mg/m^2 twice daily on days 1-15 followed by 7-day rest. Treatment courses were repeated every 3 weeks unless there was evidence of progressive disease or unacceptable toxicity.*

Results: *All 36 patients were evaluable for toxicity and response. A total of 175 cycles were administered (median 4.86, range 3-6). Two (5.6%) patients achieved complete response, 3 (8.3%) partial response, 14 (38.9%) had stable disease and 16 (44.4%) patients progressed. Median time to tumor progression (TTP) was 4.5 months and median overall survival (OS) 13 months. No toxic deaths occurred. Toxicity was mild and easily manageable.*

Conclusion: *This retrospective study demonstrated that the combination of capecitabine and MMC is an effective and well-tolerated regimen for patients previously treated for metastatic or recurrent colorectal cancer.*

Key words: capecitabine, metastatic colorectal cancer, mitomycin-C

Introduction

Colorectal cancer is the second most commonly diagnosed malignancy, accounting for about 15% of newly diagnosed cancer cases [1]. Surgery is the primary form of treatment and results in cure in approximately 50% of patients. Recurrence following surgery is a major problem and is often the ultimate cause of death [2].

Treatment of patients with recurrent or advanced colon cancer depends on the location of the disease. For patients with locally recurrent and/or liver-only and/or lung-only metastatic disease, surgical resection, if feasible, is the only potentially curative treatment [3]. Patients with unresectable disease are treated with systemic chemotherapy, immunotherapy or, ideally, their combination [4].

For many years, the only agent with significant activity in the therapy of advanced colorectal cancer was 5-fluorouracil (5-FU). Intravenous bolus administration of 5-FU yielded overall response rates of 10% and a median overall survival (OS) of 11 months [5]. Metabolic modulation of 5-FU by leucovorin (FA) and infusional 5-FU resulted in overall response rate of about 20-30% and median survival of 11-13 months [6].

Subsequent studies incorporated irinotecan and oxaliplatin in the treatment of patients with advanced colorectal cancer. These new regimens have improved the response rate, time-to-tumor progression, and median survival of patients with advanced disease, with

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Received 06-06-2008; Accepted 10-07-2008

tolerable side effects. The median survival of these patients has improved from approximately 12 months in the mid 1990s to more than 20 months in 2003 [7-11]. It is common practice to treat patients with metastatic colon cancer with these cytotoxic agents sequentially [12].

The results of recently published randomized trials have positioned bevacizumab and cetuximab in the combined, first-and second-line, chemo-immunotherapy of metastatic colorectal cancer [13-17]. Now, when all effective agents are used in the treatment of patients with metastatic disease a median survival of 24 months is expected [18].

Capecitabine is an oral tumor-selective fluoropyrimidine carbamate that was rationally designed to allow for selective 5-FU activation in tumor tissue. It is a pro-drug that is metabolized to 5-FU in a three-step process [19-21].

The final step of conversion of capecitabine to 5-FU depends on thymidine phosphorylase, which is more active in cancer cells than in normal tissues [20,22]. Capecitabine has been evaluated in two phase III studies, employing bolus 5-FU/FA as control arm. Equivalent times for disease progression and OS were observed in both arms. Thanks to greater patient convenience, capecitabine has been substituted for bolus or infusional 5-FU/FA in combined regimens with irinotecan and oxaliplatin [23,24].

MMC is an antitumor antibiotic with alkylating activity. MMC has shown activity in metastatic colorectal cancer with response rate of 10-15% [25,26]. MMC increases the level of thymidine phosphorylase, which is the critical enzyme for the conversion of capecitabine to 5-FU [27]. Therefore, MMC and capecitabine are potentially synergistic in combination.

The aim of this study was to register the therapeutic effectiveness and safety of the capecitabine and MMC combination in patients with metastatic colorectal cancer previously treated with regimens including 5-FU, irinotecan, oxaliplatin, high dose methotrexate (MTX) and capecitabine monotherapy.

Patients and methods

Patients

Between September 2004 and August 2006 36 metastatic colorectal cancer patients were treated with capecitabine and MMC as their second, third or fourth line chemotherapy regimen.

Pretreatment characteristics of the patients are presented in Table 1.

Table 1. Pretreatment patient characteristics

Characteristic	*Number*	*%*
Total number	36	100
Median age (years)	62.5	
range	39-78	
Gender		
Male	21	58
Female	15	42
ECOG PS		
0	21	58
1	14	39
2	1	3
Elevated CEA	23	64
Primary sites		
Colon	17	47
Rectosigmoid	5	14
Rectum	14	39
Metastatic sites		
Liver	28	84
Lung	9	25
Nodes	3	8
Bone	2	5
Adrenal gland	1	3
Locoregional	5	14
Previous therapy		
Resection of primary tumor	32	89
Metastasectomy	5	14
Adjuvant chemotherapy	11	31
Previous chemotherapy for metastatic disease		
FOLFIRI	28	78
Methotrexate + 5FU	8	20
Mayo regimen	4	10
Capecitabine	4	10
XELIRI	4	10
Methotrexate + capecitabine	3	8
FOLFOX 4	2	5
XELOX	1	3
Capecitabine and mitomycin-C given as:		
second line	21	58
third line	13	36
fourth line	2	6

Treatment schedule

The cytotoxic chemotherapy consisted of intravenous MMC 6 mg/m^2 on day 1 plus oral capecitabine 1000 mg/m^2 twice daily on days 1-15 followed by 7-day rest. Patients started with capecitabine at evening on day 1 and finished in the morning on day 15 (Table 2). Treatment courses were repeated every 3 weeks unless there was evidence of progressive disease or unacceptable toxicity.

Patient evaluation

Pretreatment evaluation included physical examination, complete blood cell (CBC) counts, serum biochemistry, CEA tumor marker level, and radio-

Table 2. Capecitabine and mitomycin C (MMC) combination

Days	*Drugs*
1	MMC 6 mg/m^2 intravenously over 2-5 min
1	Capecitabine 1000 mg/m^2 orally at evening
2-14	Capecitabine 1000 mg/m^2 orally twice daily
15	Capecitabine 1000 mg/m^2 orally in the morning
16-21	Rest period

logical examinations (CT scan). Tumor response was determined by the WHO criteria and chemotherapy-related toxicities were scored by the NCI/NIH common toxicity criteria. CBC counts were done on the day of treatment and in the mid-cycle to assess nadir; serum biochemistry including liver and renal function were performed every 3 weeks and tumor assessment by CT scan was performed every 3 cycles (9 weeks).

Statistical analysis

Descriptive statistics was performed using Excel software.

OS and progression-free survival were estimated according to the Kaplan-Meier method using SPSS 13.0 software.

TTP was measured from the date of start of the study treatment to the date of documented progression. OS was measured from the date of treatment initiation to the date of death from any cause.

Results

All 36 patients were evaluable for toxicity, response, TTP and OS.

There were 21 male and 15 female patients. Their median age was 62.5 years (range 39-78). Primary sites of disease were as follows: 17 colon, 5 rectosigmoid and 14 rectum. The most common metastatic site was liver (28 patients, 84%) followed by lung (9 patients, 25%), locoregional (5 patients, 14%), lymph node (3 patients, 8%), bone (2 patients, 5%) and adrenal gland (1 patient, 3%). 34% of patients had multiple sites of metastases. Pretreatment performance status range of the patients was ECOG 0-2: 21 (58%) patients with ECOG status 0, 14 (39%) patients with ECOG status 1, and 1 (3%) patient with ECOG status 2.

In 2 (6%) patients MMC/capecitabine combination was given as 4th line chemotherapy, in 13 (36%) patients as 3rd line chemotherapy and 21 (58%) patients received it as 2nd line chemotherapy.

A total of 175 cycles were administered with a median number of cycles 4.86, ranging from 3 to 6 (9 patients or 28% received 3 cycles, 5 patients or 17% received 4 cycles, 4 patients or 8% received 5 cycles and 18 patients or 47% received 6 cycles). The median cycle repetition was 22.8 days (range 21-49). Twenty-nine cycles (20.9%) were postponed for 3-28 days due to treatment toxicity.

Two (5.6%) patients achieved complete response, 3 (8.3%) partial response, 14 (38.9%) had stable disease and 16 (44.4%) progressed. The objective response rate was 13.9%. Median TTP was 4.5 months (range 2-8) (Figure 1). After a median follow-up time of 18 months, 78% of the patients had died at the time of analysis. The median OS was 13 months (range 3-21) (Figure 2).

According to NCI/NIH common toxicity criteria, grade I/II anemia, neutropenia and thrombocytopenia occurred in 103 (58.9%) cycles, while grade III/IV occurred in 6 (3.4%) cycles. Grade I/II nausea, vomiting and diarrhea developed in 47 (26.9%) cycles and 2 (1.1%) patients experienced grade III/IV gastrointestinal toxicity. Hand-foot syndrome was seen in 13

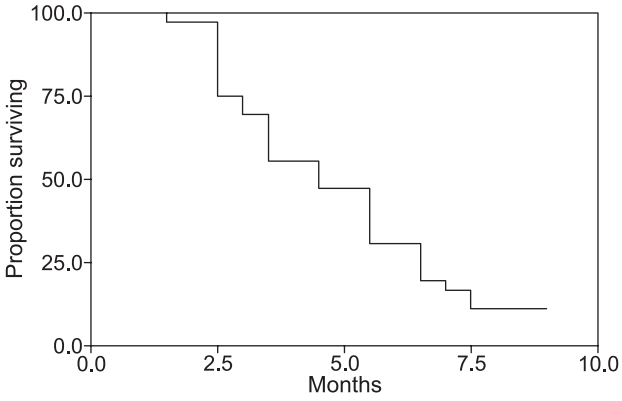

Figure 1. Time to progression.

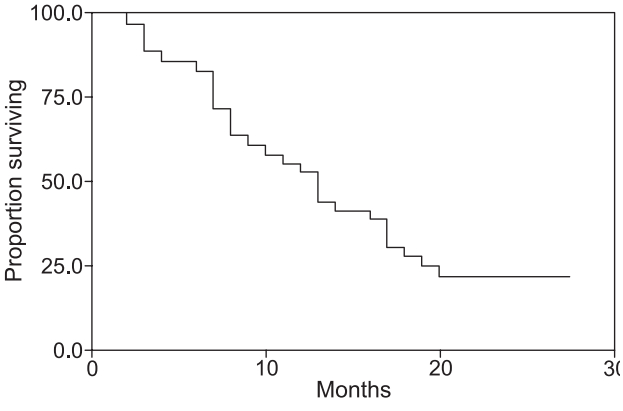

Figure 2. Overall survival.

(7.4%) cycles: 9 (5.2%) cycles with grade I/II and 4 (2.3%) cycles with grade III/IV. No cases of hemolytic uraemic syndrome were observed in our patient population. No toxic deaths occurred and no patient stopped therapy because of toxicity. Table 3 shows toxicities analytically.

Discussion

Chemotherapy in patients with locally advanced, unresectable, or metastatic colorectal cancer with 5-FU-based regimens produces partial responses and prolongation of the TTP, as well as improved OS and quality of life, compared to best supportive care [5-11].

When incorporated into 5-FU/FA-based regimens, both irinotecan and oxaliplatin improve response rate and survival over 5-FU/FA alone with tolerable side effects [7-11]. These combinations have set the new benchmark of survival for patients with metastatic colorectal cancer around 20 months [7-11]. Accepted first-line regimens are either irinotecan-based (FOLFIRI, IFL, AIO) or oxaliplatin-based (FOLFOX4, FOLFOX6, XELOX) [7-11]. Second-line regimens depend on which first-line regimens the patient has already received. Patients who were treated with irinotecan-based regimens are commonly treated with an oxaliplatin-based combination. Because of the lack of activity of single-agent oxaliplatin, use of this drug is recommended in combination with infusional 5-FU regardless of whether patients received infusional 5-FU as their first-line regimen [10-11]. Patients who had been treated with an oxaliplatin-based regimen as part of their first-line regimen should receive irinotecan-based chemotherapy for second-line treatment [9].

In addition, the newer colorectal cancer chemotherapy regimens are serving as the platform on which combined novel targeted agents such as inhibitors of the epidermal growth factor receptor i.e. cetuximab and vascular endothelial growth factor i.e. bevacizumab are tested [13-17]. Bevacizumab improves response rate and survival when used with 5-FU/FA, irinotecan or oxaliplatin-based regimens as initial or second-line therapy for metastatic colorectal cancer, and cetuximab doubles response rate and decreases the risk of cancer progression in irinotecan-refractory patients [13-17,28].

While effective cytotoxic agents are available for the first- and second-line therapy of advanced colorectal cancer, there are relatively few published results on third–line chemotherapy. Also, unfortunately, due to financial restrictions, many metastatic colorectal cancer patients are not able to afford novel targeted agents or relatively expensive cytotoxics. Therefore, low-cost and widely available therapeutic options are extremely desirable.

In two of three randomized trials of capecitabine compared with the Mayo Clinic regimen, response rate with capecitabine was superior, but with no benefit in time to progression or overall survival [29-31]. The toxicity profile for capecitabine was different with significantly less diarrhea, nausea, stomatitis, alopecia and neutropenia than bolus 5-FU/FA [32]. Following those results, 5-FU has been successfully substituted by capecitabine in many chemotherapy regimens [23,33,34].

It is also well known from *in vitro* studies that MMC results in an up-regulation of thymidine phosphorylase activity in tumor cells, which is the critical enzyme for the conversion of capecitabine to 5-FU [27, 35]. Besides this biological synergism, MMC and capecitabine do have compatible side effects: MMC mostly hematological and capecitabine dermatological and gastrointestinal [25,26,29,30]. Combination therapy with MMC and 5-FU/LV, bolus or infusional, has shown to be active and well-tolerated in several phase II and III studies in advanced gastric cancer (increased response rate, TTP and OS, no significant toxicity) [36,37]. Combined treatment of MMC and 5-FU/LV is also a valid option for patients with metastatic breast cancer patients [38-40].

Since capecitabine mimics 5-FU continuous infusion, we assume that combination of capecitabine and MMC will prove its clinical benefit in patients with metastatic colorectal cancer, similarly as it has been shown to be efficient and safe in the treatment of biliary tract and esophageal cancer [41,42].

Recently, several phase II studies were conducted to evaluate the efficacy of capecitabine plus MMC in patients who had previously received two lines of chemotherapy for metastatic colorectal cancer [43-45]. Two of those trials have shown that capecitabine

Table 3. Toxicities observed

Toxicity	*Grade, no. of cycles (%)*	
	I/II	*III/IV*
Hematological		
Neutropenia	28 (16)	2 (1.1)
Anemia	47 (26.9)	2 (1.1)
Thrombocytopenia	28 (16)	2 (1.1)
Non-hematological		
Nausea	25 (14.3)	1 (0.6)
Vomiting	10 (5.7)	0 (0.0)
Diarrhea	12 (6.9)	1 (0.6)
Hand-foot syndrome	9 (5.2)	4 (2.3)

plus MMC as third-line chemotherapy of patients with metastatic colorectal cancer could represent an effective and manageable treatment option for metastatic colorectal cancer patients failing previous chemotherapy regimens, with objective response rates of 15.2% and 8% and median TTP of 5.4 and 3 months, respectively [44,45].

In the absence of other chemotherapy options for our patients with metastatic colorectal cancer previously treated with at least one chemotherapy regimen for metastatic disease, it seemed logical to combine these two agents to achieve the best therapeutic gain.

During 2 years we have treated 36 metastatic colorectal cancer patients, who had previously received at least one chemotherapy regimen for metastatic disease, with capecitabine and MMC combination chemotherapy.

This combination produced in our patient population an objective response rate of 13.9% with median TTP of 4.5 months and median OS of 13 months. Two (5.6%) patients achieved complete response, 3 (8.3%) patients partial response, 14 (38.9%) stable disease and 16 (44.4%) patients progressed. These results are consistent with the observed efficacy of the same regimen when administered to patients as third-line chemotherapy in the previously mentioned trials [44,45].

The results of our study contrast the lack of response to capecitabine monotherapy seen in a phase II study by Hoff et al. in patients with 5-FU-refractory advanced colorectal cancer where no objective responses were observed [46].

The relatively low toxicity experienced by our patients receiving capecitabine and MMC is attractive for patients eligible for third-line chemotherapy for metastatic colorectal cancer despite substantial cumulative toxicities from previous chemotherapy.

In summary, this retrospective, single-center study has demonstrated that the combination of capecitabine and MMC is an effective and well-tolerated regimen for patients with previously treated metastatic or advanced colorectal cancer. In the era of targeted therapies, capecitabine/MMC combination may be an alternative therapy in case that cetuximab or bevacizumab are unavailable or contraindicated.

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