UFT/leucovorin and mitomycin C as salvage treatment in patients with advanced colorectal cancer – a retrospective analysis

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Active anticancer drugs and/or combination regimens for the treatment of patients failing oxaliplatin, irinotecan and 5-fluorouracil are desperately needed. In this analysis we describe the safety and efficacy of the combination of mitomycin C, UFT and leucovorin in such an extensively pretreated patient population. Between January 2002 and June 2004, a total of 41 patients were treated with mitomycin C (8 mg/m^2 on day 1) and UFT (350 mg/m^2) + leucovorin (90 mg) both divided into three daily doses from day 1 to day 14 every 4 weeks. All patients had failed prior first-line and second-line treatment with oxaliplatin, irinotecan and 5-fluorouracil. The aim of this retrospective analysis was to evaluate the efficacy and safety data of this potential salvage therapy regimen. Thirty-nine patients were evaluable for the response. The overall response rate (intent-to-treat) was 7.3% (95% confidence interval, 2.5–19.4%) and disease stabilization was achieved in 29.3%. Median time to progression was 2.5 months (range, 1.5–13.5) and median overall survival was 6 months (range, 1.5–26). Myelosuppression was the most frequent side effect. Grade 3 hematotoxicity, however, was observed in only three patients. The most common nonhematological toxicities consisted of mild and reversible nausea, emesis and diarrhea; again, severe symptoms were only occasionally seen. These data show that the combination of mitomycin C/UFT/leucovorin is safe and active in about one-third of patients in terms of abrogation of progression in extensively pretreated metastatic colorectal cancer. ***Anti-Cancer Drugs*** **18:709–712 © 2007 Lippincott Williams & Wilkins.**

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Introduction

After the failure of palliative first-line and second-line combination chemotherapy with fluoropyrimidines (FU), oxaliplatin and irinotecan in patients with metastatic colorectal cancer, there are only limited treatment options. Today, with the availability of targeted therapies our therapeutic armentarium has been improved [1]; even in the third-line setting antiepidermal growth factor receptor antibodies including cetuximab and panitumumab have shown antitumor efficacy. Objective response rates in the range of 5–15% and median survival times of 6–8 months have been reported in heavily pretreated patients [2–5]. The antiangiogenetic antibody, bevacizumab has shown no activity after failure of both oxaliplatin-based and irinotecan-based chemotherapy regimens [6], though it seems to enhance the antitumor potential of cetuximab when given in combination [7]; however, this experimental and rather cost-intensive treatment strategy warrants further clinical investigation.

As it concerns salvage chemotherapy with conventional anticancer agents, results have remained disappointing. Only a few mitomycin C (MMC) based phase II studies are available, which have shown modest to interesting activity [8–12].

We report here about the safety and efficacy of such a salvage combination regimen consisting of the antitumor antibiotic MMC and leucovorin-modulated UFT. The latter drug is an orally administered anticancer agent composed of the FU prodrug tegafur and uracil, which increases effective levels of 5-fluorouracil (5-FU). To further enhance the anticancer activity of the antimetabolite, coadministration of leucovorin (LV) was performed. We have retrospectively analyzed 41 consecutively treated patients with metastatic colorectal cancer who had failed previous chemotherapy with FU, oxaliplatin and irinotecan.

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Patients and methods

Patient population

We performed a retrospective analysis of the efficacy and safety data in 41 consecutive patients with histologically confirmed inoperable metastatic adenocarcinoma of the colon or rectum, who were treated with MMC/UFT/LV between January 2002 and June 2004. Data were obtained by chart review in the General Hospital of Vienna, the General Hospital of Neunkirchen and the General Hospital of Wiener Neustadt. All patients had radiologically documented progression of disease within 3 months after the last dose of oxaliplatin, irinotecan and FU-based first-line and second-line chemotherapy before salvage treatment with MMC/UFT/LV.

Treatment protocol

Chemotherapy consisted of MMC 8 mg/m^2 administered as intravenous bolus on day 1, combined with oral UFT 350 mg/m^2/day and oral LV 90 mg/day both given divided into three daily doses from day 1 to day 14 every 4 weeks. This dose regimen was based on the fairly good therapeutic index noted in a pilot patient series with advanced chemorefractory gastrointestinal cancers (data not published). 5-HT$_3$ receptor antagonists were routinely given as concomitant medication before MMC administration. Treatment courses were repeated every 4 weeks for a total of six cycles unless there was a previous evidence of progressive disease (PD). In case of World Health Organization (WHO) grade 4 hematotoxicity, repeated episodes of grade 3 thrombocytopenia and/or any other grade 3/4 severe adverse event (except alopecia), a 25% dose reduction of all cytotoxic agents was effected. Baseline investigations included physical examination, complete blood cell count, routine blood chemistry, and computed tomography scans of the thorax and abdomen. Evaluation of blood chemistry was performed before each cycle; complete blood cell counts on day 1 and day 10 of each cycle. Restaging computed tomography scans (which were analyzed according to WHO standard criteria) were performed after the third and the sixth cycle, and every 3 months thereafter.

Statistical analyses

All analyses were carried out using the statistical software package SAS (version 8.02; SAS Institute, Cary, North Carolina, USA). Differences between the two interesting groups [complete remission, partial remission and stable disease (SD) versus PD] in terms of response to previous therapies, performance status, number of metastatic sites and other potential prognostic relevant factors were examined with univariate and multiple logistic regression models. Survival analysis was performed using the Kaplan–Meier method.

Results

Patient characteristics

A total of 41 patients were eligible for this analysis. Twenty-six patients were men, 15 women and the median age was 63 years (range, 46–81). The site of the primary cancer was the rectum in 14 patients (34%) and colon in 27 (66%). Most patients (90%) had a WHO performance status of 0 or 1; only 10% had a WHO performance status of 2. The predominant sites of metastases were liver in 25 patients, lung in 21 and lymph nodes in 11. Other sites of metastases included abdominopelvic mass ± carcinosis peritonei in nine patients, soft tissue and bone in five patients each, and adrenal glands and spleen in one patient each. Previous palliative chemotherapies of the study population are summarized in Table 1. Median treatment-free interval before MMC/UFT/LV was 1.5 months (range, 1–26 months). Median time since initial diagnosis of metastatic colorectal cancer disease was 20 months (range, 4–72 months). After progression on MMC/UFT/LV, five patients received one additional line of treatment consisting of panitumumab, irinotecan rechallenge, cyclophosphamid and celecoxib or xelox rechallenge ($n = 2$). Two patients received two further lines of treatment, consisting of xeliri followed by cyclophosphamid and celecoxib in one case; in the other, case irinotecan was rechallenged followed by rechallenge of xelox.

Treatment response

The total number of MMC/UFT/LV treatment cycles was 142; at least two cycles were completed in 39/41 (95.1%) patients. Response was analyzed in an intent-to-treat population. No complete remission was achieved and 3/41 (7.3%; 95% confidence interval, 2.5–19.4%) patients had a partial response. In these three patients the time to response was 1.5, 2 and 3.5 months, and the duration of response was 3, 5 and 6 months, respectively. SD was observed in an additional 12 patients (29.3%) and PD occurred in 24 (58.5%). In two patients, response was not evaluable; one of these patients died of pulmonary embolism 3 weeks after the first treatment course,

Table 1 Previous chemotherapy regimens and treatment lines

Treatment regimen	First-line	Second-line	Third-line	Fourth-line	Fifth-line
UFT/LV/MMC	–	–	30	8	3
Oxaliplatin-based	29	5	4	–	–
Irinotecan-based	4	26	2	2	
Irox	3	3	–	–	–
Irinotecan/cetuximab	–	2	1	–	–
Capecitabine	1	1	2	–	–
5-FU/LV	1	–	–	–	–
Raltitrexed	3	4	–	–	–
Panitumumab	–	–	1	–	–
Tipifarnib	–	–	1	1	–

Irinotecan-based: capecitabine + irinotecan, raltitrexed + irinotecan, 5-FU/leucovorin + irinotecan; oxaliplatin-based: raltitrexed + oxaliplatin, capecitabine + oxaliplatin, 5-FU/leucovorin + oxaliplatin.
5-FU, 5-fluorouracil; Irox, irinotecan + oxaliplatin; LV, leucovorin; MMC, mitomycin C.

Table 2 Treatment-associated toxicities

Toxicity	World Health Organization grade			
	I	II	III	IV
Anemia	13	5	1	–
Thrombocytopenia	3	12	2	–
Neutropenia	8	4	2	1
Leucopenia	5	3	–	1
Fatigue	11	1	–	–
Diarrhoea	7	3	1	–
Nausea	5	3	1	–
Emesis	3	2	3	–
Liver	6	–	–	–
Constipation	5	–	–	–
Stomatitis	1	1	–	–
Infection	2	–	–	–
Fever	3	–	–	–

Table 3 Treatment delays

Reason	Patients [*n*(%)]	Weeks total
Thrombocytopenia	9 (23)	22
Leucopenia	3 (7.3)	4
Skin	1 (2.4)	1
Performance status	1 (2.4)	1
Dose adjustment	7 (17)	–
Thrombocytopenia	2 (4.8)	–
Neutropenia	1 (2.4)	–
Emesis	3 (7.3)	–
Diarrhea	1 (2.4)	–

the other was taken off the study owing to severe emesis before restaging was performed. Median duration of stabilization was 6.25 months (range, 3.5–13.5). Median time to progression was 2.5 months (range, 1.5–13.5). Response to MMC/UFT/LV and SD did not correlate with (1) response to first-line and/or second-line chemotherapy, and (2) treatment-free interval before initiation of salvage therapy (data not shown).

Survival

Median follow-up was 12 months; at the time of analysis 29 participants were dead. Median survival was 6 months (range, 1.5–26 months). Survival after MMC/UFT/LV salvage therapy did not correlate with (1) performance status, (2) number of metastatic sites or (3) pretreatment laboratory data including alkaline phosphatase and lactate dehydrogenase (data not shown).

Toxicity

All 41 patients were assessable for toxicity. As shown in Table 2, the most common hematological toxicities were grade 1/2 anemia (43.9%) and grade 1/2 thrombocytopenia (36.6%). Severe toxicities consisted of WHO grade 3/4 anemia, thrombocytopenia and neutropenia in a total of three patients.

The most frequent grade 1/2 nonhematological toxicity was fatigue in 12 patients (29.3%), followed by diarrhea in 10 patients (24.4%) and nausea, which occurred in eight patients (19.5%). Grade 3 emesis was noted in three patients; two more patients suffered from severe subjective symptoms, including one case of grade 3 nausea and one case of diarrhea. Other mild to moderate nonhematological toxicities included increase of liver functional parameters, constipation, stomatitis, infection and fever. The numbers of and reasons for treatment delays (nine patients) and/or dose adjustments (seven patients) are shown in Table 3.

Discussion

This analysis was conducted to evaluate the safety and efficacy of a combination of MMC/UFT/LV as salvage therapy in advanced colorectal cancer patients. With regard to safety, this regimen was fairly well tolerated in the large majority of our patients. The hematological toxicity, which had the greatest impact on the course of treatment was thrombocytopenia, leading to treatment delays in 23% of all patients. Grade 3/4 hematological toxicities were noted in only three cases, including two patients with bone metastases. Severe emesis occurred in three patients, but in two cases it seems that this could have been a symptom of advanced stage disease rather than drug-related toxicity, because partial mechanical ileus owing to peritoneal carcinomatosis and abdominal masses were present in both.

Analyzing the efficacy of this combination reveals that in three of our patients a partial response and in 12 disease stabilization was achieved, which adds up to disease control in 15 of 41 patients (36.6%). Comparing our results with those reported by Gyldenkerne *et al.* [11], who reported a response rate of 23% and disease stabilization in 41%, needs to account for the heavily pretreated nature of our patients.

Recently, two phase II studies have assessed the combination of MMC and capecitabine, another oral 5-FU prodrug, in the third-line treatment of metastatic colorectal cancer: Lim *et al.* [12] reported partial responses in 4.8% and disease stabilization in 19.0%. Chong *et al.* [9] who investigated the combination of MMC and capecitabine as third-line regimen found a response rate of 15.2% and disease stabilization in 48.5% of their patients. Regarding the latter promising data, however, it has to be taken into account that patients were included who had received 5-FU and irinotecan, but not oxaliplatin. The difference in response rates reported by Chong *et al.* [9] and those found by Lim *et al.* [12] may reflect the substantial difference between treating oxaliplatin-naive and oxaliplatin-refractory patients.

Today, the optimal therapeutic management for patients with disseminated colorectal cancer seems to depend less on the front-line treatment regimen, than on consequent

sequential use of active drugs and/or combinations during the course of the disease [13]. The therapeutic potential of conventional chemotherapeutic drug combinations and sequences has recently been expanded by novel therapeutics such as monoclonal antibodies against vascular endothelial growth factor and epidermal growth factor receptor [1].

In view of the exorbitant costs of the novel agents and limited financial resources of the health budget in many countries, we tend to believe that MMC/UFT/LV could serve as an additional salvage treatment option in patients having failed 5-FU, oxaliplatin and irinotecan. Prospective validation of this drug combination to better define response rates and survival outcomes is warranted.

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