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ORIGINAL ARTICLE

Mitomycin C and UFT/leucovorin as salvage treatment in patients with advanced colorectal cancer

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Summary

Purpose: *The purpose of this study was to determine the efficacy and toxicity of uracil/tegafur (UFT) plus oral leucovorin (LV) and mitomycin C as salvage chemotherapy for heavily pretreated patients with metastatic colorectal cancer.*

Methods: *A total of 44 patients were treated with i.v. mitomycin C (6 mg/m^2 on day 1) and oral UFT (350 mg/m^2) plus LV (90 mg), both divided in 3 daily doses from day 1 to day 14 every 3 weeks. All patients had failed prior first-line and second-line treatment with oxaliplatin, bevacizumab, irinotecan, cetuximab and 5-fluorouracil (5-FU). Forty -three patients were evaluable for the response.*

Results: *The overall response rate (intent-to-treat) was 9.3% and disease stabilization was achieved in 25.7% of the patients. Median time to progression (TTP) was 5 months (range 2-13) and median overall survival (OS) 7.5 months (range 4-16). Fatigue and myelosuppression were the most frequent side effects. The most common nonhematological toxicities consisted of mild and reversible nausea and diarrhea. Severe symptoms were only occasionally seen.*

Conclusion: *These data show that the combination of mitomycin C/UFT/LV provides an acceptable and safe therapeutic option in extensively pretreated metastatic colorectal cancer.*

Key words: colorectal cancer, mitomycin C, salvage therapy, tegafur

Introduction

Despite the existence of excellent screening and preventive strategies, colorectal carcinoma remains a major public health problem in western countries. The development of chemotherapy for colorectal cancer has become a very active field. After decades of 5-FU-based treatment with little clinical gains, the arrival of new, effective agents has significantly changed the way this cancer is treated [1,2]. Although 5-FU remains the backbone of most regimens, the new agents irinotecan and oxaliplatin have rapidly become an important part of front-line treatment of this disease in the USA and elsewhere. The rapid development of newer agents, such as the molecular targeted agents, holds promise that progress will continue in chemotherapy for colorectal cancer. However, when patients relapse following irinotecan and oxaliplatin-containing regimens, there are few therapeutic options. Efficacious and well-tolerated agents are urgently needed for use in this setting [3]. UFT is a preparation composed of tegafur and uracil in a molar ratio of 1:4. Tegafur is a prodrug of FU and is mainly converted to FU in the liver [4].

In preclinical studies, the co-administration of uracil with tegafur enhanced the antitumor activity achieved with tegafur alone. Uracil strongly inhibits the degradation of FU to 2-fluoro-beta-alanine, thereby increasing the concentration of FU in plasma without increasing the toxicity resulting from 2-fluoro-beta-alanine.

LV is used to modulate FU biochemically, and has been widely adopted for the treatment of advanced colorectal cancer. Given the extensive use of LV with FU, the combination of UFT with oral LV was assessed for the treatment of colorectal cancer, and administration schedules of UFT and oral LV were developed in phase I and II studies [5]. Those studies showed that the combination was very effective against metastatic colorectal cancer and had an acceptable safety profile [6]. A randomized cross-over trial in advanced colorectal cancer showed that oral UFT/LV compared favor-

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ably with i.v. 5-FU/LV in terms of toxicity and patient's preference, and that it prolonged FU exposure to a level comparable to the exposure achieved with continuous i.v. 5-FU administration [7].

Mitomycin C, an antineoplastic antibiotic, demonstrates single-agent activity in metastatic colorectal cancer. A randomized study of 200 patients showed a 54 vs. 38% response rate in patients receiving mitomycin C and infusional 5-FU, compared with 5-FU alone ($p = 0.024$); however, overall survival was much the same [8].

The aim of this study was to assess the activity and tolerability of the combination of mitomycin C and oral UFT/LV in patients with metastatic colorectal cancer after failure of irinotecan and oxaliplatin-containing regimens.

Methods

Eligibility criteria

Patients entered the study if they fulfilled the following eligibility criteria: histologic confirmation of colorectal carcinoma, inoperable metastatic disease, measurable lesions, performance status (PS) < 2 on the Eastern Cooperative Oncology Group (ECOG) scale, failure to prior first-line and second-line treatment with oxaliplatin, bevacizumab, irinotecan, cetuximab and 5-FU, adequate bone marrow function (absolute granulocyte count ≥ 1,500/μL and platelet count ≥ 100,000/μL), adequate liver function (serum bilirubin level ≤ 1.5 mg/dL and serum transaminases levels ≤ 100 U/L), and adequate renal function (serum creatinine level ≤ 1.5 mg/dL).

Treatment

A total of 44 patients were treated with mitomycin C (6 mg/m^2 on day 1) and oral UFT (350 mg/m^2) plus LV (90 mg), both divided in 3 daily doses from day 1 to day 14. Patients consumed no food for an hour before and after taking the drugs. Treatment was repeated every 3 weeks until disease progression or unacceptable toxicity.

Evaluation of response and toxicity

Patients were evaluated with physical examination and computed tomographic scans of the abdomen and chest, before entry into the study to determine the extent of disease. A complete blood cell count, liver and renal function tests were performed at least once every 3 weeks during treatment. Disease response was evaluated according to RECIST criteria [9].

National Cancer Institute common toxicity criteria were applied to evaluate the toxicity of this regime. Treatment was interrupted in case of grade ≥3 granulocytopenia or thrombocytopenia, or grade 2-4 non-hematologic toxicity. If any diarrhea developed, patients were instructed to withhold treatment. Treatment with loperamide was initiated for diarrhea > grade 2.

If treatment was discontinued because of a grade 2 nonhematologic toxicity, UFT and LV were resumed at the same doses when the toxicity had completely resolved.

Statistical methods

The primary endpoint was TTP. Secondary endpoints were overall response rate, clinical benefit rate, and OS. Progression time was censored at the close out date if progressive disease was not observed. TTP and OS were estimated using the Kaplan-Meier product-limit method. All statistics were carried out using the SPSS version 12.0 (SPSS Inc, Chicago, IL). The sample size was calculated according to the Simon's two-step optimal design [10]. This trial was approved by the institutional review board of the hospital participating in this study.

Results

The characteristics of the 44 eligible patients for age, gender, PS, and prior therapy are listed in Table 1. Almost all patients had good performance status, had undergone surgery, and had received 5-FU- based adjuvant chemotherapy. All patients had failed prior first-line and second-line treatment with oxaliplatin, bevacizumab, irinotecan, cetuximab and 5-FU.

Table 1. Patient characteristics

Characteristics	*No. of patients*	*%*
Age, years		
Median	59	
Range	41-75	
Performance status		
0	26	59
1	18	41
Gender		
Male	28	63
Female	16	37
Prior therapy		
Adjuvant chemotherapy	39	88
Chemotherapy for advanced disease	44	100
Radiotherapy	15	34
Sites of metastases		
Liver	41	93
Lung	16	36
Bone	4	9

Response

All 44 patients had measurable lesions. One patient was not assessable because of early withdrawal due to severe myelotoxicity. A total of 496 mitomycin C infusions and oral UFT/LV were administered (median 6, range 2-10). Forty-three patients were evaluable for response. Four patients had a partial response (9.3%) and disease stabilization was achieved in 11 patients (25.7%; Table 2).

Median TTP was 5 months (range 2-13) and median OS 7.5 months (range 4-16).

Toxicity

In general, treatment was well tolerated. One out of 44 patients developed grade 4 thrombocytopenia during the first course and was not assessable because of early withdrawal. Only one patient (2.3%) developed neutropenic fever.

Table 3 shows the grades of toxicities during all treatment courses. Fatigue and myelosuppression were the most frequent side effects. The most common non-hematological toxicities consisted of mild and reversible nausea and diarrhea. Grade 2 diarrhea occurred in 23% of the patients. Hand-foot syndrome was rarely observed (grade 2 in 2 [4.5%] patients). There were no treatment-related deaths.

Table 2. Overall tumor response

Tumor response	*No of patients*	*%*
Partial response	4	9.3
Liver mets	3	
Lung mets	1	
Duration, months (range) 4 (2-8)	3	
Stabilization/no change (> 6 months)	11	25.7
Liver mets	4	
Lung mets	7	
Progressive disease	28	65
Overall clinical benefit	15	35

Table 3. Toxicities

Toxicity	*Grade 1/2*	*%*	*Grade 3/4*	*%*
Myelosuppression	12	28	1	2.3
Nausea/vomiting	13	30	0	–
Fatigue	15	35	0	–
Diarrhoea	10	23	0	–
Treatment - related deaths	0	–	0	–

Discussion

Owing to potential synergy based upon upregulation of thymidine phosphorylase by mitomycin C, the combination of UFT/LV and mitomycin C may improve outcomes in irinotecan/oxaliplatin -refractory metastatic colorectal cancer. Two large phase III studies were performed to compare an oral regimen of UFT and LV with conventional i.v. 5-FU/LV therapy in patients with previously untreated metastatic colorectal carcinoma [11, 12]. In both trials, oral UFT/LV provided a safer, more convenient alternative to the standard bolus i.v. 5-FU/LV regimen for metastatic colorectal cancer and resulted in similar survival. These response rates are also compatible with the results (response rate 18 - 43%) of other phase II studies of UFT/LV for colorectal cancer in Western countries [13, 14].

UFT administration is only rarely complicated by hand-foot syndrome, and similarly it was rare in our trial [13-15].

Oral fluoropyrimidines such as UFT offer similar efficacy to bolus 5-FU, with an improved safety profile [16]. In addition, oral administration offers the obvious advantage of convenience for patients and is likely to be associated with pharmacoeconomic benefits. Combining UFT with oral LV and i.v. mitomycin C is, therefore, an attractive option, which has the potential to minimize side effects and maximize patient convenience. The results of our study indicate that the combination of UFT and LV plus mitomycin C is an acceptable and safe therapeutic option, in accordance with similar trials [17]. However, doses, schedules, eligibility and response criteria among trials differ, rendering a direct comparison of efficacy difficult.

In conclusion, the relatively low toxicity experienced by patients receiving UFT/LV and mitomycin C offers an attractive option for patients with metastatic colorectal cancer eligible for salvage therapy. Patients often have substantial cumulative toxicities from previous chemotherapy, and may have poorer performance status than those eligible for first-line therapy. Therefore, this combination could represent an effective and manageable treatment option for colorectal cancer patients failing previous chemotherapy regimens.

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