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Clinical paper

Phase II study of continuous 120 h infusion of mitomycin C as salvage chemotherapy in patients with progressive or rapidly recurrent colorectal cancer

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We evaluated the therapeutic activity and safety of continuously infused mitomycin C in patients with metastatic colorectal cancer who had recurred (less than 3 months) or progressed following first- or second-line 5-fluorouracil-based chemotherapy. Treatment consisted of mitomycin C 20 mg/m^2 i.v. given over 120 h (5 days) followed by a 3 week rest period. Fifty-two consecutively enrolled patients were assessable for toxicity and 49 for response evaluation (three patients evaluable but not measurable), completing at least one full course of chemotherapy. Previous chemotherapy regimens consisted of bolus 5-fluorouracil/folinic acid (5-FU/FA) (Machover) *n*=26 (50%) or continuous (24 h) 5-FU ± FA ± interferon *n*=26 (50%). Forty-two percent of patients had received one previous chemotherapy regimen and 58% more than one. One partial remission (2%) lasting 7 months and 11 disease stabilizations (23%) with a median duration of 3.2 months (range 1–8) were achieved in 49 patients. Median survival time since start of mitomycin C was 4.7 months (1.2–28.1) resulting in a 6 month survival rate of 36%. The progression-free interval was 10 weeks (range 4–36). Delayed and cumulative thrombo- and leukocytopenia (WHO grade III/IV) were observed in 19 and 6%, and anemia in 2% of patients. WHO grade III/IV mucositis, diarrhea and fever/infection occurred each in 6% of patients. Treatment delays and dose reductions were necessary in 11 (21%) and 21 (40%) patients, respectively. In three cases treatment was stopped due to cumulative thrombocytopenia (6%). Continuous infusion of single-agent mitomycin C displays modest activity in heavily pretreated 5-FU refractory colorectal cancer patients combined with a low toxicity level. [© 1998 Lippincott-Raven Publishers.]

Key words: Advanced colorectal carcinoma, continuous infusion, mitomycin C, salvage chemotherapy.

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Introduction

Mitomycin C is a quinone-containing antitumor antibiotic that is reductively activated by a variety of enzymes to metabolites that alkylate and cross-link DNA.[1] Antitumor activity was found in pretreated and untreated colorectal cancer patients,[2] and objective remissions were reported in 5–15% of patients.[3] Mitomycin C has been for several years a standard component of first-line combination chemotherapy for gastric and colorectal cancer, but other regimens that do not contain mitomycin C have demonstrated similar activity.[4,5] In most studies mitomycin C was applied as a bolus injection in a dose range of 8–10 mg/m^2 repeated after 4–6 weeks. This application schedule was associated with low gastrointestinal toxicity, some cases of severe cumulative thromocytopenia, lung fibrosis, hemolytic anemia and hemolytic uremic syndrome.[6] One investigation using continuous infusion of mitomycin C reported less hematological toxicity and increased activity, demonstrating that mitomycin C can be safely infused over 120 h.[7] Based on these data we performed a phase II trial of 5 day continuous infusion of mitomycin C in patients with advanced colorectal carcinoma who had disease progression after 5-fluorouracil/folinic acid (5-FU/FA)-based regimens.

Material and methods

Patient selection

Patients eligible for this study had advanced, incurable and bidimensionaly measurable colorectal cancer.

Patients were allowed to have received prior 5-FU-based chemotherapy for advanced disease excluding the previous application of mitomycin C or other fluoropyrimidine anticancer drugs. All patients had a histologically confirmed adenocarcinoma of the colon or rectum. Objective evidence of tumor progression (by ultrasound examination and/or CT scan) must have occurred while the patient was receiving 5-FU-based chemotherapy or within 3 months of receiving the last dose of previous chemotherapy. Prior adjuvant chemotherapy was allowed. Patients must have been off prior chemotherapy for at least 28 days, have a Karnofsky performance status of at least 50%, a pretreatment neutrophil count $\geqslant 3000/\mu l$, platelet count $\geqslant 100\,000/\mu l$, serum creatinine concentration $\leqslant 2.0$ mg/dl and total bilirubin level $\leqslant 2.0$ mg/dl.

All patients were informed of the investigational nature of this study, and had to provide written informed consent in accordance with institutional and federal guidelines. The study was approved by the local institutional ethical commitees.

Treatment plan

Mitomycin C (Medac, Hamburg, Germany) was administrated over a period of 120 h (5 days) on an outpatient basis followed by a 3 week rest period. This 4 week period constituted one treatment course or cycle. The total dose of mitomycin C was 20 mg/m^2. Mitomycin C was mixed in 50 ml aqua destilled and infused i.v. via a s.c. port chamber using a portable infusion pump. All patients prophylactically received 50 mg of prednisolone and 40 mg famotidine per day orally from days 1 to 5 during treatment. Antiemetic premedication was left up to the decision of the treating physician. Patients were seen on a weekly basis for a brief physical examination, toxicity assessment and complete laboratory testing.

Tumor reassessment was performed after every cycle of therapy. Classification of tumor response followed WHO standard criteria. All responses had to be confirmed by a repeated evaluation at least 4 weeks later (tumor reduction that lasted less than 4 weeks was not considered to be a response).

Treatment was continued until one of the following criteria was met: (i) development of progressive disease, (ii) unacceptable toxicity, (iii) intercurrent, non-cancer-related illness that prevented continuation of therapy or regular follow-up evaluation, (iv) withdrawal of consent or (v) completion of four cycles of therapy after attainment of complete remission. Duration of response was defined as the interval from the onset of partial response until evidence of disease progression. Overall survival was defined as interval from date on study until death (or last contact if patient was still alive).

Dose modifications for the following treatment cycle were based on the worst toxicity observed during the previous cycle of chemotherapy. Treatment was delayed in case of leukocytes $<3000/\mu l$ or thrombocytes $<75\,000/\mu l$ to a maximum interval of 2 weeks. In case of protracted cytopenia, dose modifications were performed or the patient was excluded (for details see Table 1).

Statistical analysis

Exact 95% confidence intervalls (CI) around the observed response rate were calculated from the binominal distribution. Overall survival was estimated by the method of Kaplan and Meier.[8]

Table 1. Dose modifications for hematological toxicity according to platelet and leukocyte count prior to next treatment cycle of continuous infusion mitomycin C

Blood counts		Dose modification
Leukocytes (μl)	>3000	
Thrombocytes (μl)	>75 000	→*none*
or		
Leukocytes (μl)	<3000	
Thrombocytes (μl)	<75 000	→*maximal treatment delay of 2 weeks*
For protracted cytopenia (more than 2 weeks treatment delay):		
Leukocytes (μl)	2500–3000	
Thrombocytes (μl)	75 000–100 000	→*2 mg/m² dose reduction*
or		
Leukocytes (μl)	<2500	
Thrombocytes (μl)	<75 000	→*stop treatment*

Results

A summary of baseline patient characteristics is given in Table 2. Fifty-two patients (32 men and 20 women) were entered into study, and all were assessable for toxicity and for survival. Forty-nine patients had measurable disease and were assessable for response evaluation, completing at least one full course of chemotherapy. The majority of patients had disease-related symptoms and a median Karnofsky performance status of 80%. Forty-two percent of the patients had received one and 58% two different 5-FU-based chemotherapy regimens. The mean number of courses of mitomycin C therapy on this trial was 2.5 (range 1-9 cycles).

Response and survival

One single patient (2%) attained a partial objective response (PR) to mitomycin C continuous infusion lasting 7 months and 12 patients (23%) achieved disease stabilization with a median duration of 3.2 months (range 1-8 months). All patients responding to treatment or revealing disease stabilizations belonged to the subgroup of patients which had received only one treatment regimen. As expected median survival time was only 4.7 months (range 1.2-28.1) and the 6 month survival rate was 36.5% (95% CI: 23.3-49.9%) considering the extent of prior therapy. Overall survival from diagnosis of metastatic colorectal cancer was 18.6 months (range 3-70).

Table 2. Patient characteristics

	N (patients)
Included	52
Eligible for	
toxicity	52
response	49
survival	52
Sex	
male	32
female	20
Median age [years (range)]	55 (range 35–76)
Karnofsky scale (range)	80 (60–100)
Localisation of primary tumor	
colon	23 (44%)
rectum	15 (29%)
sigma	14 (27%)
Site of metastases	
liver	42 (34%)
peritoneal carcinosis	12 (10%)
lymph node	30 (25%)
lung	23 (19%)
locoregional	9 (7%)
bone	2 (1%)
other sites	4 (2%)
Prior chemotherapy regimens before mitomycin C	
bolus 5-FU/FA	26 (50%)
protracted 5-FU/FA	26 (50%)
No. of previous chemotherapy regimens	
n=1	22 (42%)
n=2	30 (58%)

Toxicity

Mitomycin C was tolerated without any severe adverse effects. No major renal dysfunction, pulmonary toxicity or evidence of hemalytic uremic syndrome was observed with prophylactic application of 50 mg prednisolone (p.o.) for the 5 days of chemotherapy. Mucosal toxicity was generally mild and only in 6% of patients was either mucositis/diarrhea or fever/infection noticed (WHO grade III). Delayed and cumulative thrombo- and leukocytopenia (WHO grade III/IV) occurred in 19 and 6% of patients, respectively. There were three episodes of neutropenic fever associated with leukocytopenia (WHO grade III) requiring antibiotics but no hospitalization. Anemia occurred only in 2% of patients. Treatment delays and dose reductions were necessary in 11 (21%) and 21 (40%) patients, respectively. Treatment was stopped in three patients due to cumulative thrombocytopenia (6%). In these patients thrombocyte counts reached the border of $<75\,000/\mu l$ with a 4-8 week delay. All severe side-effects of continuous mitomycin C infusion are listed in Table 3.

Table 3. Worst toxicity and frequency of dose modifications and treatment delays per patient during treatment with mitomycin C for advanced colorectal cancer (*n*=52 patients)

Toxicity	WHO grade III/IV	(%)
Leukopenia	3	6
Anemia	1	2
Thrombopenia	10	19
Infection/fever	3	6
Nausea/vomiting	–	–
Mucositis	3	6
Diarrhea	3	6
	N (patients)	(%)
Dose reductions	21	40
Treatment delay	11	21
Stop of treatment	3	6

Discussion

Mitomycin C is a chemotherapeutic agent that has been a component of therapy for gastrointestinal cancer for many years. Earlier studies revealed objective response rates to single-agent mitomycin C in 10-20% of patients with advanced gastrointestinal cancer including colorectal carcinoma, both as first-line and as subsequent therapy when given as a short i.v. bolus injection.[3,4,9] Nowadays, bolus 5-FU and FA is considered standard treatment in metastatic colorectal cancer, because remission duration and survival were considered to be longer compared to mitomycin C. Since virtually all patients with metastatic colorectal cancer will develop progressive disease after 5-FU-based chemotherapy, there is a need to identify agents or modified treatment schedules with activity in patients refractory to 5-FU and FA. Mitomycin C is currently under investigation in combination with continuously infused 5-FU/FA in pre- and untreated colorectal cancer patients and as part of a systemic adjuvant chemotherapy.[10,11]

Recently, Irinotecan (CPT-11) has shown substantial activity as salvage chemotherapy in colorectal cancer patients who have failed bolus 5-FU treatment. Three clinical trials indicate that irinotecan (CPT-11) may be effective as second-line chemotherapy in colorectal cancer patients.[12-14] Another new compound, oxaliplatin, has demonstrated single-agent activity (10% partial remissions) in patients with refractory colorectal carcinoma. However, a marked synergism between oxaliplatin and 5-FU has been observed[15] using a chronomodulated scheduling of oxaliplatin combined with 5-FU/FA. A progression-free interval of 10.3 months and a median overall survival of 16.9 months (ORR=40%) was reported in 37 pretreated patients.[16]

The aim of the present investigation was to evaluate the therapeutic activity, feasibility and safety of 120 h continuously infused mitomycin C in patients with metastatic colorectal cancer who had recurred or progressed following first- or second-line 5-FU-based chemotherapy including continuously infused 5-FU plus high-dose FA. In multiple trials between 1968 and 1976 it was demonstrated that mitomycin C displays some activity in previously treated and untreated patients with colorectal cancer. Only the study of Ansfield and colleagues did not reported any activity.[17]

In the current investigation 58% of the patients had received at least two previous 5-FU-based regimens including treatment with 24 h protracted infusion. In these heavily pretreated patients only one objective response rate was observable and only 22% of patients revealed disease stabilization for a median duration of 3.2 months. All patients responding to treatment or revealing disease stabilization belonged to the subgroup of patients which had received only one treatment regimen. The toxicity profile of mitomycin C was found to be mild and no adverse toxicity occurred, although the patients were heavily pretreated.

In conclusion, 120 h continuous infusion of single-agent mitomycin C is a feasible regimen which displays only modest activity in heavily pretreated colorectal cancer patients refractory to 5-FU. Toxicity was found to be acceptable for palliative treatment.

References

1. Dorr RT. New findings in the pharmacokinetic, metabolic and drug-resistance aspects of mitomycin C. *Semin Oncol* 1988; **15**: 32-41.
2. Pritsos CA, Sarotelli AC. Generation of reactive oxygen radicals through bioactivation of mitomycin C antibiotics. *Cancer Res* 1986; **46**: 3528-32.
3. Moertel CG. Clinical management of advanced gastrointestinal cancer. *Cancer* 1975; **36**: 675-82.
4. Reitemeier RJ, Moertel CG, Hahn RG. Combination chemotherapy in gastrointestinal cancer. *Cancer Res* 1970; **30**: 1425-8.
5. Machover D, Goldschmidt E, Chollet P. Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol* 1986; **4**: 685-96.
6. De Lena, Brandi M, Lorusso V, *et al.* Single agent activity of mitomycin C in breast cancer. In Ogawa M, Rosencweig M, Staquet MJ, eds. *Mitomycin C. Current impact on cancer chemotherapy*. Amsterdam: Excerpta Medica 1981: 89-105.
7. Löffler TM, Weber FW, Hausamen TU. Klinische Erfahrungen mit der ambulanten Dauerinfusion von Mitomycin C. *Tumordiagnostik & Therapie* 1992; **12**: 132-5.
8. Kaplan EL, Maier P. Non-parametric estimation from incomplete observations. *J Am Stat Ass* 1958; **53**: 457-81.
9. Moertel CG, Reitemeier RJ, Hahn RG. Mitomycin C in advanced gastrointestinal cancer. *J Am Med Ass* 1968; **204**: 1045-8.
10. Ross P, Norman A, Cunningham D, *et al.* A prospective randomized trial of protracted venous infusion (PVI) 5-FU with or without mitomycin C (MMC) in advanced colorectal cancer. *Proc Am Soc Clin Oncol* 1997; **16**: 271 (abstr 962).
11. Becker K, Rinas U, Weidmann B, *et al.* High-dose 5-fluorouracil/folinic acid plus mitomycin C (MMC) in patients with refractory colorectal cancer. *Proc Am Soc Clin Oncol* 1997; **16**: 283 (abstr 1004).
12/ Rothenberg ML, Eckardt JR, Kuhn JG, *et al.* Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. *J Clin Oncol* 1996; **14**: 1128-35.
13. Shimada Y, Yoshino M, Wakui A, *et al.* Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. CPT-11 Gastrointestinal Cancer Study Group. *J Clin Oncol* 1993; **11**: 909-13.

14. Rougier P, Bugat R, Douillard JY, *et al.* Efficiency of Irinotecan (CPT-11) in patients with metastatic colorectal cancer after progression while receiving a 5-FU-based chemotherapy. *J Clin Oncol* 1997; **15**: 251–60.
15. Moreau S, Machover D, de Gramont A, *et al.* Phase II trial of oxaliplatin: L-OHP® in patients with colorectal carcinoma (CRC) previously resistant to 5-fluorouracil (5-FU) and folinic acid (FA). *Proc Am Soc Clin Oncol* 1993; **12**: 214 (abstr 645).
16. Bertheault-Cvitkovic F, Jami A, Ithzaki M, *et al.* Biweekly intensified ambulatory chronomodulated chemotherapy with oxaliplatin, fluorouracil, and leucovorin in patients with metastatic colorectal cancer. *J Clin Oncol* 1996; **14**: 2950–8.
17. Ansfield F. Clinical study of mitomycin-C (NSC 26980) in colorectal cancer. *Cancer Chemother Rep* 1969; **53**: 287.

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