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Clinical study

Mitomycin C continuous infusion as salvage chemotherapy in pretreated patients with advanced gastric cancer

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Our purpose was to evaluate the safety and therapeutic activity of continuously infused mitomycin C in patients with recurring or progressive metastatic gastric cancer following first-line chemotherapy. Patients were treated with mitomycin C 20 mg/m^2 i.v. over a time period of 120 h followed by a 3-week rest period. All patients received prednisone 50 mg p.o. prophylactically for 5 days to prevent hemolytic uremic syndrome and pulmonary side effects. Twenty-two consecutively enrolled patients were assessable for toxicity and 20 for response evaluation completing at least one full course of chemotherapy (two patients evaluable but not measurable). Patient characteristics: median age: 63 years (39–76); Sex (M/F): 13/9; median Karnofsky status: 70% (50–100%); resection of primary tumor *n* = 12 (55%); sites of metastases: liver *n* = 17 (77%), locally advanced *n* = 10 (45%), peritoneum *n* = 13 (59%), lungs *n* = 5 (23%), bone *n* = 3 (14%) and lymph nodes *n* = 14 (64%). Previous chemotherapy regimens: bolus 5-FU/folinic acid *n* = 6 (27%), ELF *n* = 4 (18%), EAP *n* = 3 (14%) and continuous 5-FU/folinic acid/cisplatin/paclitaxel *n* = 9 (41%). In 20 evaluable patients one complete and five partial remissions were observed; overall response rate 30.0% [95% confidence interval (CI): 9.1–50.9%] with a median response duration of 2.1 months (range: 2–6). The median survival was 3.6 months (95% CI: 2.1–6.0) resulting in a 6-month survival rate of 30% since start of mitomycin C. WHO grade III/IV mucositis, diarrhea and fever/infection occurred in 9% of patients each. Cumulative thrombo- and leukocytopenia (WHO grade III/IV) were observed in four and two patients, respectively. Treatment had to be stopped early in two patients. No severe renal dysfunction, pulmonary toxicity or evidence of hemolytic uremic syndrome was observed. Fatigue during the 120 h infusion of mitomycin C was common (11 of 22 patients). We conclude that continuous infusion of mitomycin C is feasible on an outpatient basis, revealing an acceptable toxicity. Mitomycin C demonstrates single-agent activity in pretreated gastric cancer, but has only limited efficacy following cisplatin/paclitaxel-based first-line chemotherapy. [© 1999 Lippincott Williams & Wilkins.]

Key words: Advanced gastric cancer, continuous infusion, mitomycin C, salvage chemotherapy.

Introduction

Mitomycin C is a quinone-containing anti-tumor antibiotic that is reductively activated by a variety of enzymatic systems to reactive oxygen metabolites with alkylating activity.[1–4] For several years mitomycin C has been part of combination chemotherapy regimens for gastric and colorectal cancer. Objective responses of approximately 30% in 211 patients with gastric cancer have been reported when given as a single agent.[5,6] In most studies mitomycin C was applied as a bolus injection at a dose of 8–10 mg/m^2 repeated every 4–6 weeks. This schedule was associated with low gastrointestinal toxicity but severe cumulative thrombocytopenia, and rarely with the development of major complications such as lung fibrosis and hemolytic uremic syndrome. The use of continuous infusion of mitomycin C appears to be less hematotoxic[7] and even may possibly be more active as observed in 29 patients with gastrointestinal adenocarcinomas demonstrating that mitomycin C could be safely infused over 120 h.[8] Regimens without mitomycin C are nowadays used as primary chemotherapy approach in patients with gastric cancer.[9] However, with the lack of effective salvage chemotherapy strategies, we conducted a phase II trial using continuously infused mitomycin C in patients with advanced gastric carcinoma with evidence of disease

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progression or recurrence after first-line chemotherapy.

Patients and methods

Eligibility

Patients eligible for the study had advanced, incurable gastric adenocarcinoma. All patients had received one prior chemotherapy regimen. Objective evidence of tumor progression (by ultrasound examination and/or computer tomographic scan) had to be demonstrated before study entry. Patients must have been off 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 a total bilirubin level $\leqslant 2.0$ mg/dl.

All patients were informed of the investigational nature of this study and had to provide informed consent. The study was approved by the local ethical committee.

Treatment protocol

Mitomycin C was administrated at a dose of 20 mg/m^2 over a period of 120 h (4 mg/m^2/day) followed by a 3-week rest period. Four weeks constituted one treatment course. Treatment was applied in an outpatient oncology unit. Mitomycin C was mixed in 50 ml aqua dest. and infused i.v. via a s.c. port chamber using a portable infusion pump (Logomed Pharma, Frankfurt, Germany). All patients prophylactically received 50 mg of prednisolone and 40 mg famotidine p.o. from day 1 to 5 during treatment. Antiemetic premedication was left up to the decision of the treating physician but usually metoclopramide was applied. Patients were seen on a biweekly basis for a brief physical examination, toxicity assessment and laboratory testing.

Tumor reassessment was performed after every cycle of therapy. Tumor response was graded according to WHO standard criteria. All responses had to be confirmed by repeat 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: development of progressive disease or of unacceptable toxicity; intercurrent, non-cancer-related illness that prevented continuation of therapy or regular follow-up evaluation; withdrawal of consent or 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 the 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 to a maximum of 2 weeks in case of leukocytes $<3000/\mu l$ or thrombocytes $<75\ 000/\mu l$. In case of prolonged cytopenia a dose reduction of 2 mg/m^2 was assigned for the next treatment cycle (see Table 1).

Statistical analysis

Exact 95% confidence intervals (CI) around the observed response rate were calculated from the binomial distribution. Overall survival was estimated by the method of Kaplan and Meier.[10] Univariate comparisons were made using the log-rank test or χ^2 test.[11]

Results

Patients

A summary of the baseline patient characteristics is listed in Table 2. Twenty-two patients, 13 men and nine women, were enrolled and all patients were assessable for survival analysis and toxicity. Twenty patients had measurable disease and were assessable for response evaluation completing at least one full course of chemotherapy. The majority of patients

Table 1. Dose modifications for hematological toxicity of continuous mitomycin C

Leukocytes (μl)	>3000		<3000	
Thrombocytes (μl)	>75000	→none	<75000	→maximal delay of 2 weeks
Next cycle:				
Leukocytes (μl)	2500–3000		<2500	
Thrombocytes (μl)	75–100000	→2 mg/m^2 dose reduction	<75000	→stop of treatment

Table 2. Patient characteristics

	N (patients)
Included	22
Eligible for	
toxicity	22
response	20
survival	22
Sex	
male	13 (59%)
female	9 (41%)
Median age, range (years)	63 (39–76)
Karnofsky scale, range (%)	70 (50–100)
Site of metastases	
liver	17 (77%)
locally advanced	10 (45%)
peritoneal carcinosis	13 (59%)
lung	5 (23%)
bone	3 (14%)
lymph nodes	14 (64%)
Prior chemotherapy regimens	
bolus 5-FU/folinic acid	6 (27%)
ELFregimen	4 (18%)
c.i. 5-FU/folinic acid/cisplatin/paclitaxel	9 (41%)
EAPregimen	3 (14%)

c.i., 24 h continuous infusion of 5-FU.

were symptomatic with a median Karnofsky performance status of 70%. The mean number of courses of mitomycin C therapy administrated on this trial was 2.4 (range: 1-6).

Response and survival

Six patients attained objective remissions to mitomycin C continuous infusion. One patient achieved a radiographic complete and five patients partial remissions lasting for 2 to 6 months (median response duration: 2.1 months). This represents a 30% response rate (95% CI: 9.1-50.9%) for the 20 assessable patients. Due to the short duration of responses and the extent of pretreatment, the median survival time was only 3.6 months (95% CI: 1.2-6.0). Responding patients had a longer progression-free and overall survival (1.2 versus 2.5 months, p=0.01, respectively, 3.1 versus 8.6 months, p=0.03). There was a trend of prolonged survival in patients who had not received aggressive first-line therapy (p=0.06), reflecting a lower probability to respond to mitomycin C following cisplatin/paclitaxel-containing pretreatment. In contrast to the activity of mitomycin C observed following 5-fluorouracil (5-FU)-based chemotherapy (5-FU/folinic acid/ELF) with five remissions in eight patients (56%), only one remission occurred in 12 patients (8%) who had received cisplatin/paclitaxel combinations.

Toxicity

Mitomycin C was tolerated without severe adverse effects (Table 3). No renal dysfunction, pulmonary toxicity (irreversible interstitial pneumonitis) or evidence of hemolytic uremic syndrome was observed with the prophylactic application of 50 mg prednisolone for the 5 days on chemotherapy. Mucosal toxicity was generally mild with only three and two patients developing WHO grade III mucositis and diarrhea, respectively. Thrombocytopenia occurred in four patients (18%) and appeared to be cumulative. There were two episodes of neutropenic fever associated

Table 3. Worst toxicity per patient during treatment with mitomycin C for advanced gastric cancer (n=22 patients)

Toxicity	WHO grade III/IV	Percent of patients
Leukopenia	2	9
Anemia	5	23
Thrombopenia	4	18
Infection/fever	2	9
Nausea/vomiting	3	14
Mucositis	2	9
Diarrhea	2	9
Alopecia	6	27
Constipation	0	
Skin toxicity	0	
Lung toxicity	0	
Neurotoxicity	0	
Pain	0	
Allergy	0	
Renal toxicity	0	
Vascular toxicity	0	
Fatigue	3	14

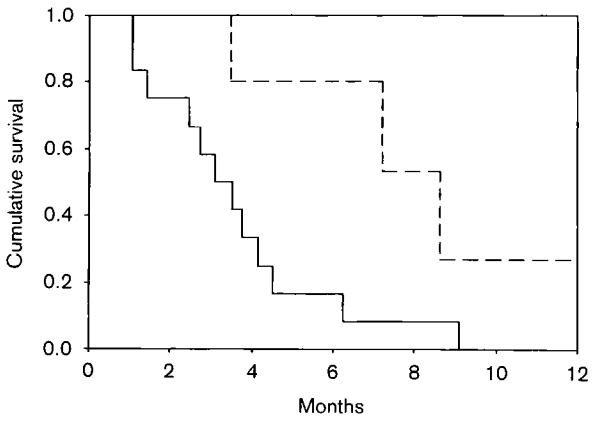

Figure 1. Overall survival depending on response status [complete/partial remission (dashed line) versus stable/progressive disease (solid line)] during continuous infusion of mitomycin C in gastric cancer patients.

with leukocytopenia (WHO grade III) requiring antibiotics. Severe nausea and vomiting was seen in 14% of patients. Treatment had to be stopped early in two patients because of cumulative thrombocytopenia (9%). In both patients thrombocyte counts recovered to $\geqslant 75\ 000/\mu l$ with a 4-6 weeks delay.

Discussion

Mitomycin C is a chemotherapeutic agent that had been incorporated in treatment regimens for gastrointestinal cancer for many years. Early studies revealed objective responses to single-agent mitomycin C in approximately 10-30% of patients with advanced gastric cancer, both as first-line and as salvage therapy.[5,6,12,13] In 1991 mitomycin C was replaced as part of the FAM regime by methotrexate (FAMTX protocol).[14] Newer treatment protocols are based on bolus (5-FU/FA or ELF) or continuously infused 5-fluorouracil/folinic acid combined with cisplatin or cisplatin/anthracyclines regimens (EAP) in combination with methotrexate (FAMTX/FEMTX/FEMTX-P). The role of new drugs such as paclitaxel or irinotecan are currently being investigated in the first-line setting.[15-21] Since virtually all patients diagnosed with metastatic gastric cancer will develop progressive disease at some point following first-line chemotherapy, there is a great need to identify agents with activity in the salvage setting.

Data concerning second-line treatment of relapsed or progressive gastric cancer are rare. Vanhoefer *et al.* reported a response rate of 18% (95% CI: 0-38%) in 17 patients using a schedule of weekly 24-h continuous 5-FU modulated by 500 mg/m^2 folinic acid. Fourteen patients had progressive disease or a relapse after initial bolus 5-FU combination chemotherapy. Median survival was 5 months (1.5-10). Diarrhea of WHO grade III/IV occurred in two patients (12%); no other severe toxicites were seen.[22] The activity of doxifluridine given orally in combination with leucovorin has been reported to be in the same range. Bartolomeo and colleagues achieved a response rate of 15% in 26 patients with pretreated gastric carcinoma (95% CI: 1-29).[23] All of the responses were seen in patients previously treated with 5-FU-containing regimens. The median survival in gastric cancer patients was 7 months. Toxicity was moderate with WHO grade III/IV diarrhea in 15%. Treatment with doxetaxel revealed a response rate of 18% in 11 evaluable pretreated patients. Considerable hematologic toxicity occurred (WHO grade IV neutropenia in 82% and neutropenic fever in 18% of patients).[24] Paclitaxel appeared to be effective in 36 pretreated patients treated with a dose of 225 mg/m^2 every 3 weeks. The objective response rate was 22% (95% CI: 9-35%) and the median survival was 8 months.[25] Other trials using the FEMTX regimen as salvage chemotherapy in gastric cancer or single-agent fotemustine did not reveal any activity.[26,27]

Few data are available regarding mitomycin C as second-line chemotherapy in patients with gastric cancer. In the current investigation, six of 20 evaluable patients with advanced gastric cancer achieved a radiologically documentated remission using a protracted infusion schedule over 5 days. With one exception, responses were observed in patients who had not received extensive first-line treatment including cisplatin or paclitaxel/cisplatin combination regimen. Considering the pretreatment the median survival was only 3.6 months but responding patients lived for almost half a year with symptomatic improvement. A continuous infusion schedule of mitomycin C with prophylactic application of prednisone orally was used because it appeared to be less toxic compared to bolus administration.[7,8] Treatment was easily applicable since most patients had implanted venous port chambers for the administration of first-line chemotherapy. Severe thrombocytopenia was seen in four of 22 pretreated patients, which appears to be lower than observed with i.v. bolus injection requiring a dose interval of at least 6 weeks. Thrombocytopenia was cumulative in two of 22 patients and therapy had to be stopped. No pulmonary toxicity, renal complications or hemolytic uremic syndrome occurred, which is associated with the use of bolus mitomycin C in 8.5%.[28] In conclusion, mitomycin C demonstrated single-agent activity in advanced pretreated gastric carcinoma patients using a 120 h continuous infusion.

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