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High-dose mitomycin C: activity in hepatocellular carcinoma

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Summary. Hepatocellular carcinoma is the most common cause of cancer death in Thai males. It is usually found to be inoperable, and the reported median survival for Thai patients is only 4.3 months. From October 1984 to December 1986, 30 cases of nonresectable hepatocellular carcinoma were treated at the National Cancer Institute, Bangkok, Thailand, with high-dose mitomycin C. Patients were given 20–25 m/m^2 (median, 40 mg) by i.v. injection, followed by 10–12.5 mg/m^2 (median, 20 mg) at 6-week intervals in responding patients until the disease progressed or toxicity was detected. In all, 23 patients were evaluable by WHO criteria. A partial response was achieved in 11 of 23 cases (48%); the median duration of this response was 7 months (range, 3–11 months). The median cumulative dose of mitomycin C was 80 mg (range, 40–120 mg). Toxicity was relatively well tolerated; only one patient developed an unusual erythematous, reticular skin rash that spontaneously disappeared within 1 month of injection of the drug. The median survival of responders was 12 months, and the longest survival was 18+ months. We conclude that high-dose mitomycin C given according to the present dose and schedule has antitumor activity in hepatocellular carcinoma in Thai patients. Although its response rate is as high as that produced by doxorubicin, with less toxicity, no complete response was achieved in this study.

Introduction

Hepatocellular carcinoma is the most common cancer in Thai males [1]; the previously reported median survival was 4.3 months [16]. Most cases are inoperable at presentation; radiotherapy has been shown to be ineffective, and various chemotherapeutic agents have been used with no major impact on survival. Systemic chemotherapy in the treatment of hepatocellular carcinoma showed only marginal, if any, benefit until it was recognized that single-agent doxorubicin had antitumor activity, with high response rates of up to 44% [8, 11]; however, this high response frequency has not been duplicated [15].

Recent reevaluation of mitomycin C [7, 9] has demonstrated its activity in cancers of the breast, bladder, lung, some gynecologic malignancies, and gastrointestinal carcinomas including pancreatic and liver carcinoma. Mitomycin C is considered to be the most active single agent in the treatment of biliary tract carcinoma [12]. Mathew [13] has reported good responses induced by high-dose mitomycin C in locally advanced cervical carcinoma, with minimal myelotoxicity. Vutriprux [17] has reported that mitomycin C given at a dose of 15 mg/m^2 in a single bolus via the hepatic artery twice a week for 4 weeks produced some good responses in a small group of patients with inoperable cholangiocarcinoma. Results of combination chemotherapy in hepatocellular carcinoma have also been variable, proving to be no better than those obtained using single agents [10]. Due to its complications and the lack of evidence for its superiority to systemic treatment, regional therapy with hepatic arterial infusion of chemotherapeutic agents cannot at present be considered the standard treatment for hepatocellular carcinoma [5, 6, 10].

Nonresectable hepatocellular carcinoma is one of the most rapidly fatal tumors in man [3, 4]. Our previous experience [2] with doxorubicin was disappointing, failing to induce even a partial response (PR). From October 1984 to December 1986, 30 cases of nonresectable hepatocellular carcinoma were treated with high-dose mitomycin C at the National Cancer Institute, Bangkok, Thailand, in a nonrandomized phase II study. The aims of this study were to determine the response rate, duration of response, and toxicity observed in patients with hepatocellular carcinoma treated with high-dose single-agent mitomycin C.

Patients and methods

A total of 30 patients were entered in this study (see Table 2), but only 23 had histologically or cytologically confirmed hepatocellular carcinoma; of the latter, 21 were men and 2 were women, with a median age of 51 years (range, 26–74 years). According to staging criteria [14] (see Table 1), 1 patient had stage I disease, 17 had stage II disease, and 5, stage III disease. Using the Eastern Cooperative Oncology Group (ECOG) scale of performance status, patients were classified as follows: 4 (17.4%), grade 0; 15 (65.2%), grade 1; and 4 (17.4%), grade 2. In all, 15 patients (65%) were alpha-fetoprotein (AFP)-positive; 9 patients (39%) were carcinoembryonic antigen (CEA)-positive. Hepatitis B surface antigen (HBS) was positive in only 9 patients (39%), negative in 11 (48%), and unknown in 3 (13%).

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Table 1. Staging criteria for hepatocellular carcinoma patients [14]

Stage	Characteristics			
	Wasting	Jaundice	Venous colaterals	Ascites
I	–	–	–	–
II	–	–	–	+
III	+	+	+	+

Table 2. Patient characteristics

Total cases	30
Evaluable	23
Sex (M : F)	21 : 2
Median age, years (range)	51 (26–74)
Pathology HCC	23
Staging:	
I	1
II	17
III	5
ECOG performance status	
0	4
1	15
2	4
3	–
4	–
AFP +ve:−ve:unknown = 15: 7:1	
HBS +ve:−ve:unknown = 9:11:3	
CEA +ve:−ve:unknown = 9:12:2	
Previous treatment	6
Chemotherapy:	
ADM	1
5-FU	1
epirubicin	1
Hormone:	
MPA	1
Surgery:	
hepatectomy	1
hepatic arterial ligation	1
Dose of mitomycin C received:	
Range	40–120 mg
Median	80 mg

HCC, hepatocellular carcinoma; ADM, adriamycin; 5-FU, 5-fluorouracil; MPA, medroxyprogesterone acetate

Previous treatment. A total of 17 patients had had no previous chemotherapy, hormonal treatment, or surgical intervention. Of the remaining six patients, two had failed to respond to previous conventional chemotherapy (5-fluorouracil; epirubicin), one had failed to respond to medroxyprogesterone acetate, two had failed to respond to partial hepatectomy and hepatic arterial ligation, respectively, and one showed a minimal response to doxorubicin before developing progressive disease (see Table 2).

Dose and schedule. Patients were treated with an initial or starting dose (week 0, day 1) of 20–25 mg/m^2 (median, 40 mg) mitomycin C (Kaowa, Japan) by slow i.v. infusion over 30 min. Complete blood counts (CBCs) and urinary examinations for microscopic hematuria were done every week for 6 weeks after the initial dose. Patients were reassessed for response and toxicity at week 6 (day 42); responding patients who had normal CBCs, urinary examinations, and serum blood urea nitrogen (BUN) and creatinine levels were then given their second dose of mitomycin C at 50% of the starting dose, i.e., 10–12.5 mg/m^2 (median, 20 mg).

Because severe cumulative myelosuppression had been reported by investigators, chemotherapy was repeated every 6 weeks at the second dose level until there was either disease progression or evidence of mitomycin C toxicity. No further dose reduction was made, but treatment was delayed for 1–2 weeks if signs of bone marrow suppression or impaired renal function developed (WBC, $<2.5\times10^9$ cells/l; creatinine, >1.5 mg%; or BUN, >30 mg%); it was stopped altogether if toxicity was irreversible (see Table 3). Antiemetics were not routinely given; patients with nausea were given metoclopramide at the standard dose.

Investigation. Prior to treatment all patients underwent a complete clinical examination, peripheral CBC, urinary examination, and plasma urea, serum creatinine, and serum liver-function tests, measurements of serum alpha-fetoprotein (AFP), HBS Ag, and CEA, a liver scan or ultrasound or computerized axial tomographic (CAT) scan of the liver (optional), a chest X-ray, and an ECG. Patients were stratified according to three stages of disease (see Table 1).

To be eligible for this study patients were required to have an area of known malignant disease that could serve as an objective indicator of response to treatment. Hepa-

Table 3. Treatment scheme for high-dose mitomycin C

Mitomycin C	Weeks																			
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Initial dose of 20–25 mg/m^2	↑																				
Subsequent dose of 10–25 mg/m^2 (50% of initial dose)							↑						↑						↑		
							No further dose reduction, but chemotherapy will be delayed for 1–2 weeks if CBC is unsatisfactory														
																			Until PD or toxicity		

PD, progressive disease

tomegaly was considered to be a measurable lesion when it had been histologically proven to contain hepatocellular carcinoma and extended below the costal margin or xiphoid process. Patients were reassessed by CBCs and urinary examinations every week after the initial dose of mitomycin C, then every 6 weeks after each subsequent course of treatment. Blood was taken for AFP and liver-function tests wherever response was shown.

Response and toxicity. Tumor response was defined according to standard criteria: a complete response (CR) was defined as the disappearance of all clinical, radiologic, and biochemical evidence of disease for at least 2 months; a partial response (PR) was defined as a reduction in the product of two diameters of measurable disease by at least 50% for at least 1 month. Toxicity was graded according to standard WHO criteria [18].

Table 4. Response

CR	0
PR	11/23
NC	9/23
PD	3/23
Duration of response:	
Range	3–11 months
Median	7 months
Survival:	
Range	2–18 months
Median	12 months
(Historic control, 4.3 months)	

NC, no change; PD, progressive disease

Results

Response

The disease stage, performance status, and response for both previously treated and nontreated hepatocellular carcinoma patients are given in Tables 2 and 4. Of 23 patients, 11 achieved a PR (44%), 9 showed either no change or a minimal response (39%), and 3 developed progressive disease (17%); none achieved a CR. The responses occurred regardless of previous treatment.

The median duration of response was 7 months for both previously treated and nontreated patients, the longest response being 11 months. All responding patients showed some evidence of objective tumor regression and improvement of subjective feeling after the first course of chemotherapy (i.e., within 4–6 weeks). The median duration of survival for all 23 treated patients was 12 months (range, 2–18+ months) (Table 4).

Toxicity

The main dose-limiting toxicity in this study was myelosuppression (details are shown in Table 5). Five patients (22%) had leukopenia, with $<3\times10^9$ cells/l, and five (22%) had anemia (<9.5 g%); of the latter, one (4%) had grade IV anemia (<6.5 g%) and one (4%) had thrombocytopenia, with $<99\times10^9$ cells/l (Table 5). This myelosuppression was attributable to previous cytotoxic drug treatment after the second course of high-dose mitomycin C.

Other toxic effects are listed in Table 6. Nausea or vomiting occurred in all 23 patients (100%) but did not require any treatment, disappearing within 3–4 days. Renal impairment, as assessed by urinary examination for microscopic hematuria, serial serum creatinine, and plasma BUN, was not seen. All patients showed a mild degree of

Table 5. Peripheral blood count nadirs after high-dose mitomycin C in 23 patients[a]

	WHO toxicity grade			
	I	II	III	IV
Leukocyte count[b]	0 (3–3.9)	4 (2–2.9)	1 (1–1.9)	0 (≤1.0)
Platelet count[b]	1 (75–99)	0 (50–74)	0 (25–49)	0 (<25)
Hemoglobin[c]	0 (9.5–10.9)	4 (8.0–9.4)	0 (6.5–7.9)	1 (<6.5)

[a] Data represent the worst toxicity for each patient
[b] $\times10^9$ cells/l
[c] g%

Table 6. Nonhematologic toxicity of high-dose mitomycin C in 23 patients

	WHO grade				
	I	II	III	IV	Total (%)
Nausea/vomiting	23	–	–	–	23 (100)
Alopecia	23	–	–	–	23 (100)
Skin rash	–	1	–	–	1 (4)
Constipation	–	–	–	–	
Diarrhea	–	–	–	–	
Infection	–	–	–	–	
Renal impairment	–	–	–	–	

alopecia that was not severe enough to require then to wear a wig. One patient developed an unusual erythematous, reticular skin rash after 1 week of mitomycin C injections, but it disappeared spontaneously without any specific treatment within 1 month. No pulmonary toxicity was noted in this study.

Discussion

Chemotherapy for hepatocellular carcinoma remains a challenge; numerous agents have been used in phase II studies, with rare complete responses and few partial responses. Only doxorubicin has been reported to induce a high response rate of 44% (22/50) [8, 11], which could not be duplicated by us or by other investigators. A recent evaluation of mitomycin C [9] has classified it as the frontline chemotherapeutic agent for gastrointestinal and biliary tract malignancies. We therefore initiated a nonrandomized phase II trial by treating nonresectable hepatocellular carcinoma with high-dose mitomycin C as shown in Table 3.

From October 1984 to December 1986, 23 patients were eligible for evaluation. In all, 11 patients (48%) achieved PR regardless of the previous form of treatment or of alpha-fetoprotein, HBS Ag, or CEA test results, but they had stage I–II disease (see Tables 1 and 2). No CR was observed in this trial. The median duration of response was 7 months, the longest being 11 months. The median survival was 12 months (range, 2–18+ months), compared with only 4.3 months for the previously reported median survival in nontreated patients [16]. Cumulative myelotoxicity was not seen because the median cumulative dose was only 80 mg (range, 40–120 mg) and most of the patients had previously not been treated. One nontreated patient developed grade IV anemia, grade III leukopenia, and grade I thrombocytopenia after receiving a total dose of 120 mg mitomycin C. No pulmonary or renal toxicities were observed in our trial, but a peculiar skin rash was seen in one patient.

In conclusion, our results show that high-dose mitomycin C showed antitumor activity in nonresectable hepatocellular carcinoma in Thai patients, with a response rate of 48% (equivalent to that of doxorubicin) but no cardiac toxicity. However, this response requires confirmation by prospective, randomized clinical trials divided into three arms (high-dose mitomycin C vs doxorubicin vs control, then a cross-over between high-dose mitomycin C and doxorubicin).

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