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Phase II study of mitoxantrone in unresectable primary hepatocellular carcinoma following hepatitis B infection

Kwok-Hung Lai, Yang-Te Tsai, Shou-Dong Lee, Wai-Wah Ng, Ho-Chung Teng, Tseng-Nip Tam, Gin-Ho Lo, Han-Chieh Lin, Hwai-Jeng Lin, Jaw-Ching Wu, Chii-Shyan Lay, Sun-Sang Wang and Wing-Kai Chan[1]

Division of Gastroenterology, Departments of Medicine and [1]Cancer Therapy Center, Veterans General Hospital and National Yang-Ming Medical College, Taipei, Taiwan 11217, Republic of China

Summary. A total of 20 patients with histologically proven primary hepatocellular carcinoma (PHC) received mitoxantrone IV at a dose of 10–16 mg/m^2 every 3 weeks. All patients had previous hepatitis B infection. None underwent remission after treatment; 2 had stable disease and 18 progressive disease. The median overall survival was 13 weeks (range, 1–59 weeks). There was no evidence of significant antitumor activity for mitoxantrone in our patients with PHC. Hematotoxicity occurred in 100% of the patients with grades 2–4 leukopenia, 89% of those with grades 1–4 anemia, and 26% of those with grades 2–3 thrombocytopenia. Cardiotoxicity occurred in 20% of the patients after 14–30 mg/m^2 mitoxantrone; these included complete heart block with fatal outcome in one case, decreased ventricular ejection fraction in one, and sinus tachycardia in two. Nausea, vomiting, fever, diarrhea, and alopecia were mild and occurred in 15%–45% of the patients (Table 3). Therefore, patients with PHC following hepatitis B infection may be less tolerant to mitoxantrone, resulting in the apparent increase in toxicities.

Introduction

Surgical resection remains the only potentially curative treatment of primary hepatocellular carcinoma (PHC). Unfortunately, about 80% of the patients with PHC in Taiwan are multicentric, concomitant with liver cirrhosis and hepatitis B infection, and most of them are unsuitable for surgical resection at diagnosis [7]. Transcatheter arterial embolization provided limited benefit to a limited number of our patients because of frequent portal vein invasion, diffuse lesions of the liver, and other major organ involvement. Various kinds of single or combination chemotherapies given IV or IA have been tried in patients with PHC, but the results were poor [1, 5, 8, 9]. The identification of an effective antineoplastic agent for the treatment of PHC patients is urgently needed. We therefore conducted a phase II clinical trial with mitoxantrone (Novantrone, dihydroxyanthracenedione) in 20 patients with unresectable PHC and assessed the beneficial and adverse effects.

Offprint requests to: Kwok-Hung Lai, Division of Gastroenterology, Department of Medicine, Veterans General Hospital, Taipei, Taiwan 11217, Republic of China

Materials and methods

A total of 20 patients with histologically proven PHC were entered into this study, all of whom were unsuitable for surgery because of the multicentric origin of the tumor or main portal vein and other major organ involvement. The patients' characteristics are shown in Table 1: 18 were positive for hepatitis B surface antigen (HBsAg) and the remaining 2 were positive to antibody against HBsAg. None of our patients had received prior chemotherapy. Other eligible criteria included serum bilirubin <2 mg%, serum albumin >3 g%, granulocyte count >2000/mm^3, platelet count >100,000/mm^3, serum creatinine <2 mg%, no known heart disease, and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Informed consent was obtained from all patients.

Table 1. Patients' characteristics

Characteristics	No. of patients
Total	20
Age (years) median: 58, range 29–68	
Sex (M:F)	19:1
Performance status[a]	
1	19
2	1
Functional stage II[b]	20
HBsAg- anti-HBs-positive	18/2
Alpha-feto-protein level median: 1172 ng/ml, range: 10.95–273,190 ng/ml	
Concomitant liver cirrhosis[c]	15
Main portal vein involvement	12
Other organ involvement	10
Lung	8
Lymph node	1
Pancreas	1
Gallbladder	1

[a] Eastern Cooperative Oncology Group Criteria: 0, normal activity; 1, symptoms but ambulatory; 2, in bed <50% of time; 3, in bed >50% of time; 4, 100% bedridden

[b] Criteria of International Symposium of Liver Cancer held in Uganda, 1971

[c] 14 patients were positive to HBsAg and 1 was positive to antibody against HBsAg

Mitoxantrone was given by IV bolus every 3 weeks. The initial dose was 14 mg/m^2. The dose was increased or decreased at an increment of 2 mg/m^2, according to the hemogram (i.e., granulocyte nadir $>2000/mm^3$, platelet nadir $>100,000/mm^3$, increase the dose by 2 mg/m^2 in the next course; granulocyte nadir $<2000/mm^3$ and/or platelet nadir $<100,000/mm^3$ for more than 21 days, decrease the dose by 2 mg/m^2 in the next course). In patients with persistent granulocytopenia or thrombocytopenia just before chemotherapy, treatment was withheld until the granulocyte count rose to $>2000/mm^3$ and the platelet count to $>100,000/mm^3$. In patients with posttreatment hyperbilirubinemia, the modification of the mitoxantrone dose was as follows: 1.25–2.5 times the normal bilirubin values, 100% dose; 2.6–5 times the normal bilirubin value, 50% dose; >5 times the normal value, stop treatment.

A weekly hemogram, complete physical examination, blood chemistry, hepatitis B markers, alpha-fetoprotein, and electrocardiogram were carried out before each cycle of chemotherapy. A chest X-ray, computerized tomographic scans of the liver, and cardiac ejection fraction were done every 2–3 months to evaluate the responses and side effects.

The criteria of response were defined as follows: a complete response was defined as the disappearance of all symptoms and signs of clinically detectable tumor; a partial response was defined as a decrease in size of at least 50% of the sum of the products of the longest perpendicular diameters of the clearly measurable mass lesions, with no increase in any other indicator lesion and no new areas of malignant disease. If palpable hepatomegaly is the primary indicator, there must be at least a 30% reduction in the sum of the liver measurement below the costal margin at the midclavicular line and at the xiphoid process. The reduction in the volume of the liver must also be accompanied by a trend toward the normalization of all pretreatment abnormalities in liver function.

A stable disease was defined as insufficient regression of the measurable mass lesions to meet the above criteria, less than 25% increase in any measurable lesions, and no appearance of new areas of malignant disease. Toxicities were reported according to WHO recommendations.

The end points of this study were response rates and survival.

Results

A total of 20 patients were entered into this study and all were evaluable. The response results are shown in Table 2.

One female patient dropped out after the first course of treatment due to patient refusal and died 13 weeks later. No patient in this study underwent partial or complete remission. The median survival was 13 weeks (range, 1–59 weeks). The median number of treatments was two courses (range, 1–11) and the median dose given was 12 mg/m^2. Of the patients, 19 had grades 2–4 hematological toxicities (Table 3) usually occurring after the first injection. Nausea and vomiting occurred in 45%, alopecia in 15%, diarrhea in 20%, fever in 35%, and cardiotoxicity in 20% of the patients (Table 3). One patient developed severe hematological toxicity (WBC $<500/mm^3$, platelet count $<100,000/mm^3$) after the first injection and died of complete heart block 1 week later. One patient had a 15% decrease in cardiac ejection fraction after 30 mg/m^2 mitoxantrone, and two developed sinus tachycardia after 14–28 mg/m^2. No other concomitant factors that could have caused tachycardia was identified in the latter patients. Both patients with stable disease died of upper gastrointestinal bleeding at 11 and 59 weeks after the first treatment. There was neither a significant decrease in alpha-fetoprotein levels nor a change in hepatitis B markers in any of the 20 patients studied.

Table 2. Response to treatment

Response	No. of patients
Total	20
Complete or partial remission	0
Stable disease	2
Progressive disease	18

Table 3. Toxicity in 19 evaluable patients

Grade*	1	2	3	4
Leukopenia	0	3	10	6
Anemia	5	4	7	1
Thrombocytopenia	0	2	3	0
Nausea/vomiting	6	3	0	0
Diarrhea	1	2	1	0
Fever	3	4	0	0
Alopecia	3	0	0	0
Cardiotoxicity	3	0	0	1

* Criteria of World Health Organization

Discussion

There was no objective response to mitoxantrone in 20 patients with PHC in this phase II study; the overall median survival of 13 weeks indicated no survival benefit to this group. These negative results are similar to those reported by the Eastern Cooperative Oncology Group [4] and the Cancer and Leukemia Group B Study [3]. The presence of significant posttreatment myelosuppression in these PHC patients indicates that an adequate dose of mitoxantrone was used in this study. The occurrence of hematological and cardiac side effects were higher than those in other reports and were not dose-related [2–4]. Although all patients in the present study had apparently normal liver function tests, as indicated by normal serum bilirubin and serum albumin >3 g% before mitoxantrone treatment, their true liver reserve might be suboptimal, resulting in the abnormal excretion of the drug and a subsequent increase in toxicity. All patients in this study had suffered from hepatitis B infection, and subclinical hepatic impairment might have been present even after seroconversion [6]. From our results, we conclude that mitoxantrone is not the drug of choice in PHC patients with underlying long-term hepatitis B infection.

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