A Random Phase II Study of Mitoxantrone and Cisplatin in Patients With Hepatocellular Carcinoma

An ECOG Study

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Of 86 patients entered in an Eastern Cooperative Oncology Group (ECOG) random Phase II study of mitoxantrone (DHAD) and cisplatin (DDP) in primary liver cancer, 69 were eligible. Nine of the 13 ineligible patients were excluded after a pathology review. Sixty-one percent of the patients were North American, and 39% were South African. The most common severe or the worst toxicity on DHAD was hematologic; and to DDP, hematologic and vomiting. Of the 69 eligible patients, 21 experienced severe, life-threatening or fatal toxic reactions. Two patients treated with DDP had partial responses. With a 95% confidence interval, the true response rate to DHAD was less than 8%, and to DDP, less than 17%. The median survival time was 14 weeks on both drugs. Assuming a proportional hazards model, factors that are significantly associated with survival are patient performance status, the presence of the symptoms, raised bilirubin and hepatomegaly, and clinical evidence of cirrhosis. Any differences between survival rates for South African and North American patients were largely explainable by these factors.

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PATIENTS WITH HEPATOCELLULAR carcinoma occasionally respond after treatment with a variety of agents. No cytostatic agent has given a response rate of greater than 20% in random, stratified clinical trials.[1–5] Phase II trials of new drugs, therefore, offer the best hope. Combinations of single agents shown to be inactive on their own are unlikely to be effective.

In this study we investigated two agents, mitoxantrone hydrochloride and cisplatin. Beginning in 1983, a pilot study of dihydroxyanthracenedione (DHAD) in 19 patients with hepatocellular carcinoma was done in Pretoria, South Africa using a dose of 14 mg/m^2 every 3 weeks. Hemopoietic suppression and occasional nausea were the only documented toxicity. Two partial responses were observed. DHAD therefore appeared to be a new agent worthy of further testing in patients with this disease.[6]

Cisplatin (DDP) has a broad spectrum of antineoplastic activity, and it therefore seemed reasonable to evaluate the effect of this agent in patients with hepatocellular carcinoma. There were no published data of controlled clinical trials of DDP in this patient population when this study was undertaken. Based on the pilot study EST P-D 878 by ECOG, we decided to use DDP in doses of 75 mg/m^2 every 21 days in this trial.

Patients and Methods

Eighty-six patients were entered into the study. All patients had to have histologically confirmed hepatocel-

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The following institutions also participated in this study: Albany Medical College, Albany, NY; Albert Einstein College of Medicine, Bronx, NY; Case Western Reserve University, Cleveland, OH; Hahnemann Medical College, Philadelphia, PA; Medical College of Ohio, Toledo, OH; University of Minnesota, Minneapolis, MN; New York University Medical Center, New York, NY; Northwestern University Medical Center, Chicago, IL; Hospital of the University of Pennsylvania, Philadelphia, PA; University of Pittsburgh, Pittsburgh, PA; University of Rochester Cancer Center, Rochester, NY; Roswell Park Memorial Institute, Buffalo, N; Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; SUNY-Downstate Medical Center, Brooklyn, NY; and Tufts University, Walpole, MA.

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lular carcinoma. Histology was reviewed by the ECOG pathology panel. To be eligible for study, a patient had to have an area of known, malignant disease to serve as an objective indicator of response to treatment. Hepatomegaly was considered a measureable lesion when it had been histologically proven to contain primary liver cancer and when it extended at least 5 cm below the costal margin or xiphoid process. A liver scan could be used if the liver contained proven carcinoma and if the scan had a clearly defined perfusion defect measuring at least 5 cm in diameter. Patients also had to have an ECOG performance status (PS) of 0, 1, 2, or 3.[7] Also required were adequate hematologic function (WBC $\geq 4000/\mu l$, platelets $\geq 100000/\mu l$) and renal function (creatinine ≤ 1.5 mg or BUN ≤ 30 or blood urea ≤ 50 mg).

Patients

Of the 86 patients entered in the study, four were canceled and 13 were ineligible. Nine of the ineligible patients were excluded after a pathology review by a panel although they had been considered to have primary liver cancer by the contributing institutions. Of these nine patients, four were found to have cholangiocarcinoma, and five did not appear to have primary liver cancer. Of the remaining four ineligible patients, three had cardiac disease, and one had no measurable disease. Twenty-eight patients (39%) were from South Africa, and one of these was ineligible because of pathology. (Patients who were bedridden (PS 4) or who had portal systemic encephalopathy were not eligible.)

Seventy-four percent of the eligible patients were men and 55% were white. Forty-nine percent of the patients were more than 60 years old. Seventy-eight percent had PS 1 or 2, and 76% had lost weight in the past 6 months. The most common disease symptoms were abdominal pain (81%), hepatomegaly (87%), abdominal swelling (60%), and reduced appetite (48%). Only 10% had respiratory metastatic disease symptoms, and 21% had gastrointestinal metastatic disease symptoms. Twenty-one percent of the patients had cirrhosis associated with their disease (as indicated on the on-study form by the investigator). Note that cirrhosis is often very difficult to confirm in a biopsy sample, and it is very likely that the true proportion of patients with cirrhosis was much higher than 21%. Twenty-one percent had lung metastases, and 6% had bone metastases. Seventeen percent of the patients were HBsAg positive, 35% anti-HBs antigen positive, 52% had elevated alpha-fetoprotein, 25% had raised bilirubin, and 20% had raised gamma globulin at the time of entry into the study. Informed consent was obtained.

The two random treatments were mitoxantrone—14 mg/m^2 by intravenous (IV) infusion every 3 weeks and cisplatin—75 $mg/m^2/d$ every 21 days, administered after prehydration and forced diuresis with furosemide and mannitol. Doses were modified for hematologic toxicity for both drugs, and DDP was discontinued if serum creatinine rose more than 50% above the baseline. Follow-up blood counts were required weekly, and control kidney and liver functions were required before each cycle of treatment. The criteria for response and toxicity were those of ECOG.[7]

Statistical Methods

The main goal of the study was response; survival and duration of response were secondary goals. The goal for the number of patients was 30 per treatment arm, ensuring that if the true response rate was 20%, then with 90% probability, at least three responses would be observed. The use of random Phase II trials allows the rapid testing of promising, new therapies in a controlled population. Furthermore, running such trials builds up a valuable data base of information, which can then be used to study the disease. This design is routinely used by ECOG to study several disease sites.

Survival was measured from time of entry to the end of the study. In analyzing the data the log-rank test[8] was used to test for an association between individual patient factors and survival. A multivariate proportional hazards model[9] was used to model the simultaneous effects of various patient characteristics on survival. Exact binomial confidence intervals in the response rates were calculated.[10] Kaplan-Meier curves[11] were used to display survival by various patient characteristics.

Results

Toxicity

Twenty-one of the 69 eligible patients experienced severe, life-threatening, or fatal toxicity (Table 1). There was one fatal reaction to DDP. This patient had a cardiac arrest and died during treatment. Four patients had life-threatening toxic responses, three DHAD and one to DDP. Of these four, one patient on DDP experienced convulsions and seizures for approximately 8 days, beginning 10 days after the beginning of treatment. One patient on DDP experienced life-threatening leukopenia (WBC count, 700) on days 1 through 5 in the third cycle of treatment. Another patient on DDP experienced leukopenia (WBC count, 900) on days 10 through 20 of cycle 1, and had life-threatening fever as well. A third

TABLE 1. Severe or Worse Toxic Reactions of 21 Patients With Primary Liver Cancer

	DHAD	DDP	Total
Vomiting	0	3	3
Skin, mucous membrane	1	1	2
Neurologic	0	2	2
Hematologic	12	3	15
Infection	1	0	1
Liver	1	0	0
Cardiac	1	1	2
Fever	1	0	1
Edema	1	2	3

DHAD: dihydroxyanthracenedione; DDP: cisplatin.

patient on DDP experienced life-threatening sepsis. This patient also had severe hematologic and liver toxicity. The most common severe or worse toxic reaction to DHAD was hematologic. The most common toxic reactions to DDP were hematologic problems and vomiting.

Response

Two patients treated with DDP had partial responses. One who had a partial response for 272 days relapsed and died 5 weeks later. Another patient had a partial response lasting 82 days and died 2½ months later. Both patients were white North Americans. One patient was a man and the other, a woman. With no observed responses, the 95% upper confidence interval in the response rate to DHAD is (0%, 8%). The 95% upper confidence interval for the response rate to DDP is (0%, 17%).

Survival

Sixty-eight patients have died, and one was still alive after 33 months. The median survival time on both treatments was 14 weeks. A proportional hazards model[9] suggested several prognostic factors for survival (Table 2), including PS ($P = 0.014$), disease symptoms

TABLE 2. Primary Liver Cancer and Factors Associated With Survival

Factor	Favorable outcome	Unfavorable outcome	*P* value*
Hepatomegaly	absence	presence	0.007
Bilirubin	normal	raised	0.007
Performance status	ECOG 0–1	ECOG 2–3	0.014
Cirrhosis (clinical)	absent	present	0.031

* From a proportional hazards model.[9]

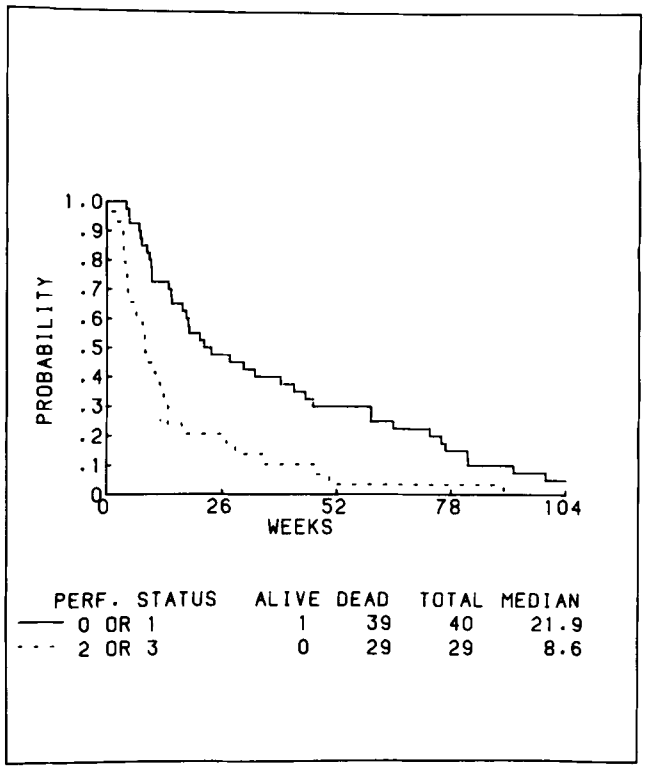

FIG. 1. Hepatocellular carcinoma and survival by performance status.

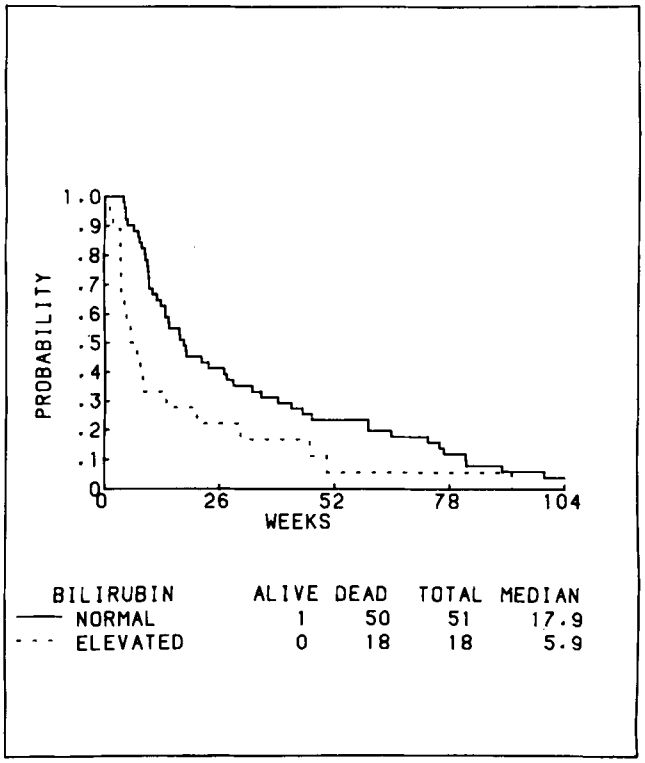

FIG. 2. Hepatocellular carcinoma and survival by bilirubin.

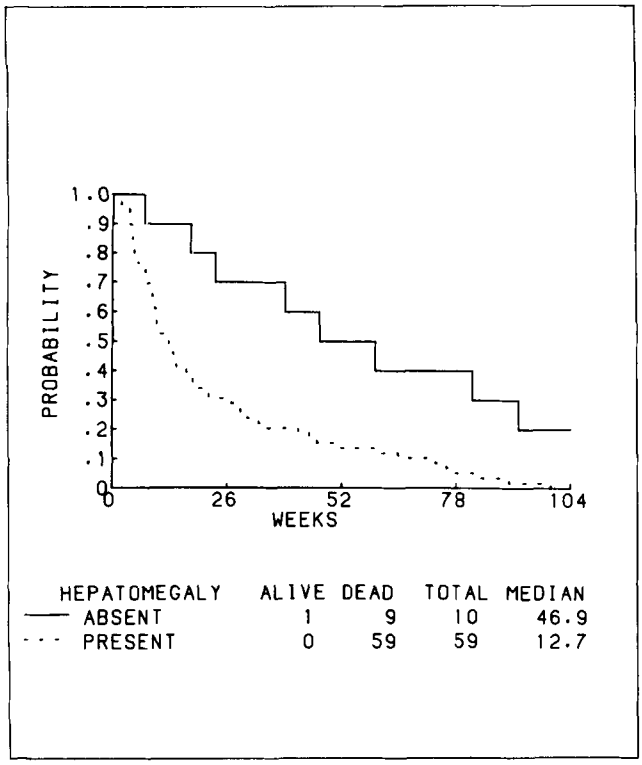

FIG. 3. Hepatocellular carcinoma and survival by hepatomegaly.

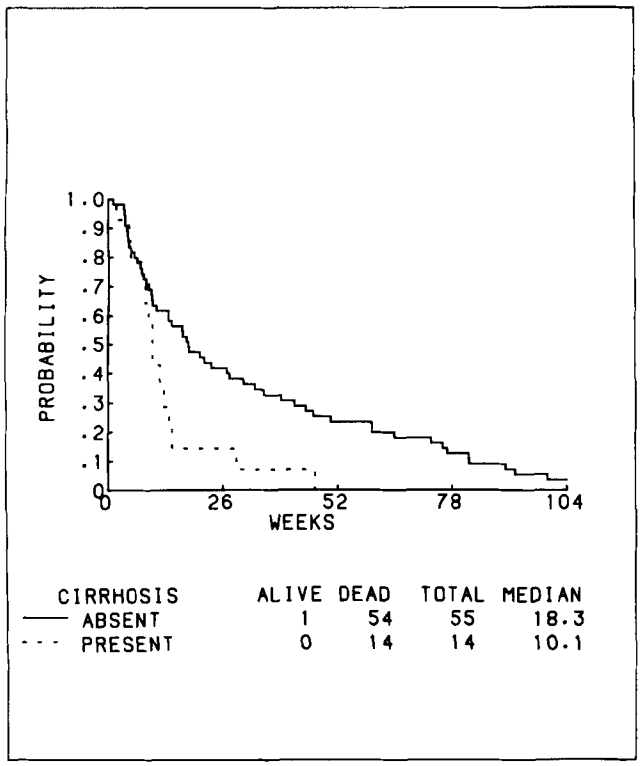

FIG. 4. Hepatocellular carcinoma and survival by cirrhosis.

of hepatomegaly (P = 0.007), presence of cirrhosis as reported on the flow sheets (but not necessarily confirmed histologically) (P = 0.0310, and elevated bilirubin (P = 0.007). The median survival time for patients with a PS of 0 or 1 was 23.4 weeks compared with a median of 8.6 weeks for patients with a PS of 2 or 3 (Fig. 1). The median survival time for patients with normal bilirubin was 17.7 weeks compared with only 5.9 weeks for patients with elevated values (Fig. 2). The median survival time for patients with no hepatomegaly was 46.9 weeks compared with 12.7 weeks for patients with hepatomegaly (Fig. 3). Patients with cirrhosis had a median survival time of 10.1 weeks compared with 18.3 weeks for patients without cirrhosis (Fig. 4).

Although both country of origin and race appeared to be associated with survival when analyzed individually using a log-rank test,[8] neither variable remained significant after accounting for the factors in Table 2.

Discussion

Causing no observed responses among 34 analyzable patients, DHAD does not appear active as a single agent in treating primary liver cancer. The upper 95% confidence interval in the response rate was (0%, 8%). In cancer and leukemia Group B patients there is a reported response rate of 6% with this agent.[12] Causing two partial responses among 35 analyzable patients in this trial, cisplatin (DDP) is unlikely to be active. The upper 95% confidence interval is (0%, 17%). Furthermore, with a 26% rate of severe or worse toxicities, DDP is unlikely to be worth further study for this population of patients. Melia *et al.* have reported a response in one of 13 patients treated with DDP,[13] and the Southeastern Cancer Study Group reported a response in one of 20 patients with primary liver cancer.[14]

The negative results underline the importance of this type of trial, which shows that the impression from pilot trials that both of these drugs are valuable for patients with primary liver cancer was erroneous. The median survival time of 14 weeks is not significantly different from that obtained with other agents that have been adequately tied in patients with primary liver cancer.

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