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Clinical Trials Summaries

Phase II Study of Ifosfamide (Holoxan®) in Hepatoma*

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INTRODUCTION

THE TREATMENT of hepatoma patients with systemic chemotherapy has thus far yielded a very low response rate and poor survival [1]. There is an obvious need for new active agents. Ifosfamide is a structural isomer of cyclophosphamide which undergoes similar metabolic transformations *in vivo* [2]. Phase II trials of ifosfamide with mesna have demonstrated a clinical efficacy against a variety of neoplasms [3]. Data on the effectiveness of alkylating agents in hepatocellular carcinoma are limited [4]. This study was carried out in order to evaluate the potential value of ifosfamide in hepatocellular carcinoma.

PATIENTS AND METHODS

Patients with histologically confirmed hepatocellular carcinoma were recruited into the study. An eligible patient must have had objective indicators of response to treatment. Hepatomegaly was employed as a measurable lesion when it was histologically proven to contain primary liver cancer and extended at least 6 cm below the costal margin or xiphoid process. Contra-indications for patient eligibility included leukopenia ($<3000/mm^3$) or thrombocytopenia ($<100{,}000/mm^3$), poor renal function (creatinine >1.5 mg%) and abnormal liver function (bilirubin >2.0 mg%). Patients who had poor performance status (<60%) were also considered ineligible for this study.

The types of lesions measured for response were liver tumor, hepatomegaly and lung metastases. Criteria for responses followed WHO criteria [5].

Ifosfamide (Holoxan®) 1.3 g/m^2 was given by intravenous infusion over 4 h and mesna (Uromitexan®) 360 mg/m^2 was given by intravenous injection at time 0, 4, 8 h post ifosfamide. Treatment was given on days 1–5 and recycled every 28 days.

RESULTS

Sixteen patients with histologically proven hepatocellular carcinoma, unresectable, were entered in the study. Three cases were inevaluable, one because of early death and two cases were lost to follow up. The pretreatment characteristics of the 13 evaluable cases are shown in Table 1. All patients were staged prior to treatment according to Olweny *et al.* [6]. Only three cases are stage II_A the others are stage III_A and III_B. Three cases achieved partial response (PR), clearly shown by liver scan, which lasted 4, 10 and 11 months respectively. All responding cases died shortly after disease progression. The overall survival of the PR cases were 4.5, 10.5 and 12 months. Two cases had subjective improvement with no objective response. These two cases survived 6 months each. The non-responding cases died at 3, 5, 6, 7, 8, 8, 9 and 10 weeks.

The most common toxic effects were nausea, vomiting and alopecia. Nausea and vomiting were moderate. Fever usually occurred during treatment

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Table 1. *Patient characteristics and toxicity*

Characteristics		No. of patients
Total entered		16
Number of evaluable		13
Median age in years (range)	45 (25–58)	
Sex M:F	7:6	
Median performance status (Karnofsky)	60%	
Stage II_A		3
Stage III_A		9
Stage III_B (lung metastases)		1
HBsAg and/or HBsAb positive		6 (8 cases studied)
AFP positive		7 (10 cases studied)
Previous chemotherapy		1 (NR to adriamycin)
Side-effects		
Nausea and vomiting		13
Alopecia totalis		13
Hyperpigmentation		10
Anemia		8
Leukopenia and thrombocytopenia (WHO grade 1)		5
Increased serum transaminase and bilirubin		2

and subsided after complete chemotherapy. The median wbc nadir was 3000/mm^3 with a range of 2100–4000/mm^3. The median platelet nadir was 99,000 per mm^3 with a range of 79,000–181,000/mm^3. Episodes of toxic hepatitis occurred in two cases, both were stage III_A. One case had a rapid rise of serum enzymes and bilirubin during treatment, the abnormal enzymes and bilirubin gradually decreased to normal prior to the next course of chemotherapy. The second case had persistently elevated serum enzyme and bilirubin which precluded further treatment.

DISCUSSION

Although the number of patients in this study is small, the response rate of 23% is encouraging, since most patients had advanced disease, which is usually unresponsive to chemotherapy. Also the survival time of two of the three responders is appreciable (10.5 and 12 months). These results should prompt exploration of higher doses of ifosfamide or combinations of ifosfamide with other active agents.

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