Phase 2 Study of High Dose Etoposide (VP16-213) in Hepatocellular Carcinoma

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Abstract

A phase II study of etoposide (VP16-213) in hepatocellular carcinoma was conducted among 18 Chinese patients. There was no observable tumour response but the treatment was relatively well tolerated with an overall median survival interval of 74 days.

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Key words: Etoposide—Hepatocellular carcinoma

Introduction

Hepatoma is now the second commonest cancer among men in Hong Kong[1]. From all the chemotherapeutic agents, adriamycin is probably the most active against this type of cancer[2]. A recent study[3], however, showed the response rate with a conventional dose of VP16-213 to be similar to that of adriamycin. Etoposide (VP16-213), is a semi-synethetic derivative of the podophyllotoxins which are produced naturally from the plant species, *podophyllum peltatum*. This paper describes a phase 2 study among Chinese patients of high dose VP16-213 in hepatoma.

Materials and Methods

The selection criteria for patients included: clinical evidence of hepatomegaly with positive histology or an alpha foetal protein of more than 500 μg/l, and a Karnofsky performance (KP) score equal to or greater than 50. Eligible patients were given 200 mg etoposide/m^2 in 500 ml normal saline, infused over a 1–2 hour period on days 1–3 every three weeks, with a maximum of eight courses of treatment. Treatments were delayed every week until a white blood count $\geq$ 3000/l and a platelet count $\geq$ 100,000/l were reached. The total disappearance of the tumour below the costal margin and the xiphoid process was regarded as being a complete response. A reduction of more than 50% in the liver enlargement below the costal margin plus the xiphoid process was regarded as being a partial response. A greater than 25% increase in the liver enlargement below the costal margin plus the xiphoid process was regarded as being an indication of disease progression. World Health Organisation (WHO) criteria were used to evaluate toxicities[4].

Results

Eighteen patients participated in the study. Nine had a histologically proven hepato-

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Table I. Clinical Characteristics of Patients

Age:	Median	51.5
	Range	37-75
Sex:	M : F	17 : 1
KP score:	Median	80
	Range	70-100
Hb (g/l):	Median	12
	Range	7-16
Clinical jaundice		4/18
Ascites		2/18

KP, Karnofsky performance.

Table II. Laboratory Results of Patients

Bilirubin (μmol/l):	Median	11.5
	Range	2-134
ALP (IU/l):	Median	255.5
	Range	121-650
ALT (IU/l):	Median	50
	Range	7-405
AFP (μg/l):	Median	5480
	Range	5-232000
HBs Ag (+):		12/14
PT (seconds):	Median	15
	Range	14-16
APTT (seconds):	Median	37
	Range	32-46

ALP, alkaline phosphatase; ALT, alanine transaminase; AFP, alpha foetal protein; HBs Ag, surface antigen of B Hepatitis virus; PT, prothrombin time; APTT, activated partial thromboplastin time.

Table III. Haematological Toxicity of Patients

WHO grade	
0	6/18
I	5/18
II	4/18
III	3/18
IV	0/18

WHO, World Health Organisation.

cellular carcinoma, all showing a trabecular histological pattern. Among the nine patients, the six with an alpha foetal protein (AFP) of more than 500 μg/l were histologically positive for hepatocellular carcinoma. Diagnoses for the remaining nine patients were based on an AFP level of more than 500 μg/l together with clinical evidence of hepatomegaly. Fifteen patients were suffering from abdominal pain on presentation, one had jaundice and two, an epigastric mass. Their clinical characteristics are shown in Table I and their laboratory findings in Table II. Four out of the 18 patients had had surgery prior to the study. Two patients had had a laparotomy for rupture of the hepatocellular carcinoma. One patient had had a right hepatic lobectomy, 1 year prior to the study. One patient had had a cholecystectomy and T-tube drainage for his jaundice, caused by a tumour thrombus obstruction in the common bile duct. A total of 61 courses of treatment was given, the median number of chemotherapy courses being three (range 1–8). There was no response in any of the 18 patients studied. Mean white blood counts and platelet counts prior to treatment were 10.1×10^9/l and 279×10^9/l, respectively. Haematological toxicities are shown in Table III. Most marrow toxicity occurred after two courses of chemotherapy. There were only mild-to-moderate degrees of nausea and alopecia. Fourteen patients had died by the time this analysis was carried out, the overall median survival being 74 days (range 12–179).

Discussion

Despite recent advances in the diagnosis and treatment of various cancers, the outlook for inoperable hepatoma remains rather grim. Many chemotherapeutic agents have been shown to have very little effect and no major impact on survival[5]. The differences in survivals in various study series are probably due to the selection criteria. It has been shown that liver function and Karnofsky performance score are important prognostically[6]. Hitherto, the key to treatment success has depended on early detection[7].

Our study failed to demonstrate any antitumour activity with high dose VP16-213 in patients with advanced hepatoma. The

treatment was, however, relatively well tolerated. This paper re-affirms the resistance of this type of tumour to chemotherapy, and the search for a new agent is still a matter of urgency if this group of patients is to be salvaged.

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