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Primary liver cancer in Hong Kong*

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Summary. From 1984 to 1987, we conducted a series of chemotherapy trials to assess their efficacy and impact on survival in patients with inoperable hepatocellular carcinoma. A total of 18 patients were treated with etoposide at a dose of 200 mg/m^2 given on days 1–3 every 3 weeks for a maximum of 8 courses. No response was observed in any of the 18 patients studied. A further trial using epirubicin at doses of 40 and 75 mg/m^2 again showed no evidence of a tumor response in 14 consecutive patients. The dose of epirubicin was further escalated to 90 mg/m^2. Of the 33 patients treated, 1 (3%) achieved a complete response and 2 (6%) showed a partial response. Although the overall median survival amounted to only 72 days, the survival of the three responders was 15, 13, and 12 months, respectively. Therefore, we believe that the tumor response to epirubicin may be dose-dependent. However, the toxicity was also dose-dependent. To improve the therapeutic index, we are currently evaluating the impact of intrahepatic arterial injection of a lipiodol-epirubicin emulsion.

Introduction

Hepatocellular carcinoma (HCC) is currently the second most common cause of cancer death in Hong Kong [2]. Men are more commonly affected than are women, and a high proportion of cases (more than 80%) are associated with liver cirrhosis. Over 80% of cirrhotic HCC cases are positive for hepatitis B surface antigen (HBsAg), and this incidence is 4–5 times greater than that in Western countries. The close relationship of HCC to hepatitis B viral infection can also be seen in familial clustering of hepatitis B virus infection and HCC.

Clinical features

The first presenting symptom in the majority of HCC cases is abdominal pain or discomfort, which is usually localized in the right hypochondrium. Abdominal distention with hepatomegaly and rapid accumulation of ascitic fluid is another common presentation. Obstructive jaundice is usually a late feature. Physical signs include stigmata of chronic liver disease. Hepatomegaly occurs in the majority of patients. Serum alpha-fetoprotein (AFP) values are elevated in over 80% of HCC cases. Liver-function tests are deranged to varying degrees, with elevations in levels of total bilirubin, alkaline phosphatase, and – to a lesser extent – alanine transaminase being observed.

Diagnostic techniques

Ultrasonography is a safe, noninvasive, and inexpensive diagnostic method. In expert hands it produces high detection rates, and HCC lesions as small as 1–2 cm in diameter may be detected. The lower limit is determined by the severity of accompanying macronodular cirrhosis. HCC is usually hyperechogenic or isoechogenic as compared with the surrounding liver tissue; occasionally, it may be hypoechogenic. The tumor mass may be well-circumscribed or diffuse. Portal vein invasion, biliary tree invasion, hepatic vein thrombosis, inferior vena caval invasion or compression, ascites, splenomegaly, collaterals of portal hypertension, and enlarged lymph nodes can also be seen. Ultrasound is the ideal screening test and is excellent for guided biopsy of suspicious lesions in patients when AFP levels are not diagnostic.

Arteriography is an invasive procedure, but it is safe in expert hands. It is also highly sensitive and is the only imaging method that can pick up HCC lesion as small as 3 cm in diameter. This technique is necessary for the

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Table 1. Clinical characteristics of patients treated with high-dose etoposide

Number of evaluable patients	18
Sex (M/F)	17/1
Age (years):	
Median	51.5
Range	37–75
Karnofsky performance score:	
Median	80
Range	70–100
Clinical jaundice	4/18
Ascites	2/18
Bilirubin (μmol/l):	
Median	11.5
Range	2–134
HBsAg (+)	12/14
AFP (μg/l):	
Median	5,480
Range	5–232,000

Table 2. Clinical characteristics of patients treated with low-dose epirubicin

Number of evaluable patients	14
Age (years):	
Median	47.5
Range	36–70
Karnofsky performance score:	
Median	70
Range	50–90
Number of courses given at	
75 mg/m^2:	
Median	5
Range	2–8
40 mg/m^2:	
Median	3
Range	2–5
Bilirubin (μmol/l):	
Median	14
Range	4–36
AFP (μg/l):	
Median	4,401
Range	10–235,200
Survival (days)	
Median	123
Range	35–304

assessment of tumor resectability and clearly demonstrates the hepatic vascular anatomy. Arteriography is also performed for therapeutic procedures such as embolization, intra-arterial chemotherapy, and chemoembolization. Injection of a small amount of lipiodol UF into the hepatic artery at the end of arteriography may further help in diagnosing small HCC lesions. Lipiodol has been shown to accumulate selectively in HCC and remain there for long periods after its injection into the hepatic artery. Computerized tomography in the presence or absence of intravenous contrast medium is performed as an integral part of the examination of patients with suspected HCC.

Surgery

At present, resection is the only curative measure available for HCC. It can be performed safely when the tumor is localized in a surgically resectable area of the liver. The extent of resection may vary from a simple wedge excision to an extended right hepatic lobectomy in which the right lobe and the median segment of the left lobe are removed. Unfortunately, only 10%–15% of HCC patients have resectable tumors [7]. The 30-day operative mortality for hepatic resection of HCC varies from 4% to 20% [3, 8, 9].

Chemotherapy

High-dose etoposide

Etoposide is a semisynthetic derivative of the podophyllotoxin that is naturally produced by the plant species *Podophyllum peltatum*. A recent study by Melia et al. [5] suggested that the response rate obtained using a conventional dose of etoposide was similar to that obtained using Adriamycin. We repeated the trial using a high dose of etoposide (200 mg/m^2) in 500 ml normal saline, which was infused over a 1- to 2-h period on days 1–3 every 3 weeks for a maximum of eight courses of treatment. The treatment was delayed weekly until a white blood cell count of $>3 \times 10^9$/l and a platelet count of $>100 \times 10^9$/l had been reached.

Total disappearance of the tumor below the costal margin and the xiphoid process was regarded as representing a complete response. A reduction of more than 50% in the liver enlargement below the costal margin plus the xiphoid process was regarded as a partial response. An increase of greater than 25% in the liver enlargement below the costal margin plus the xiphoid process was regarded as an indication of disease progression. World Health Organization (WHO) criteria were used to evaluate toxicity [6].

A total of 18 patients were entered into the study, and their clinical characteristics are shown in Table 1. A total of 61 courses of treatment were given, and the median number of chemotherapy courses was 3 (range, 1–8). No response was observed in any of the 18 patients studied. Nine patients developed grade 1–2 myelotoxicity and three subjects developed grade 3 marrow toxicity. There were only mild to moderate degrees of nausea and alopecia. The overall median survival was 74 days (range, 12–170 days). We conclude that etoposide given at the present dose and on the current schedule has no effect on HCC.

Low- to intermediate-dose epirubicin

Adriamycin is one of the few cytotoxic agents shown to produce a response rate varying from 10% to 30%. However, its clinical use is limited by its cardiotoxicity [10]. A new analogue, epirubicin, has been shown to be less toxic [1].

Table 3. Clinical characteristics of patients treated with high-dose epirubicin

Number of evaluable patients	33
Sex (M/F)	29/4
Age (years):	
Median	46
Range	30–67
Karnofsky performance score:	
Median	80
Range	70–100
Number of courses given:	
Median	2
Range	1–8
Bilirubin (μmol/l):	
Median	17
Range	5– 58
AFP (μg/l):	
Median	5,720
Range	5–750,000
Prothrombin time (s):	
Median	13
Range	12–18
Survival (days):	
Median	72
Range	31–393

We conducted a phase II trial of low- to moderate-dose (40 and 75 mg/m^2) epirubicin between 1985 and 1986. The eligibility criteria for entry into the study included clinical evidence of hepatomegaly with either positive histology for hepatoma or elevated AFP levels of >500 μg/l and bilirubin values of <40 μmol/l. The patients were given 75 mg/m^2 epirubicin by i.v. bolus every 3 weeks for a maximum of eight courses, provided that there was no evidence of disease progression. Since this was the first time the drug had ever been used in Chinese patients, it was considered safer to reduce the dose to 40 mg/m^2 in patients with bilirubin values of >20 μmol/l. The response criteria were similar to those described for the etoposide trial.

In all, 14 patients were evaluable for response and toxicity. Their clinical characteristics are shown in Table 2. A total of 50 courses of epirubicin were given. No response was seen in any of the 14 patients studied. Therefore, the true response rate was certainly <20% at the 95% confidence interval [4].

The treatment was fairly well tolerated. Only 2 of the 14 patients (14%) developed grade 1 hematological toxicity (WHO criteria), with mild to moderate degrees of nausea, vomiting, and alopecia being noted. Pre- and post-treatment echocardiograms were obtained in 50% of the patients and revealed no significant drop in the cardiac ejection fraction.

We conclude that epirubicin given at the present dose and in the current form has no effect on the HCC tumor response and has no major impact on survival. It is relatively well tolerated, despite the reduced liver function noted in many of our patients. Therefore, the use of a higher dose of epirubicin warrants exploration in a future trial.

High-dose epirubicin

The selection criteria for entry into this trial were similar to those used in the low-dose trial except that bilirubin levels had to be <60 μmol/l. We again used the same response criteria applied in previous trials. A total of 33 patients were evaluable, and their clinical characteristics are shown in Table 3.

Following treatment with 90 mg/m^2 epirubicin, 1 of the 33 patients (3%) achieved a complete response and 2 (6%) showed a partial tumor response. Therefore, the overall response rate was 9%. The toxicity was more severe than that produced by the low-dose scheme, with three patients developing grade 3 hematological toxicity and seven patients experiencing grade 2 hematological side effects. The cardiac ejection fraction was determined in five patients, none of whom developed any significant (>10%) drop in this parameter. No treatment-related death occurred. Although the overall median survival interval amounted to only 72 days, the survival of the three responders was 15, 13, and 12 months, respectively.

Therefore, we conclude that the tumor response may be dose-dependent. However, the toxicity was also dose-dependent. Thus, there is a practical limitation on the maximum tolerable dose.

Hepatic arterial infusion of a lipiodol-epirubicin emulsion

To improve the therapeutic index, we are currently evaluating the impact of intrahepatic arterial injection of a lipiodol-epirubicin emulsion for inoperable HCC. Thus far, 19 patients have been treated with escalating doses from 50 to 90 mg/m^2 given every 4 weeks. As yet, we have observed only one partial response on this schedule, but the treatment has been very well tolerated, producing no major toxicity. A higher-dose schedule using 90 to 120 mg/m^2 is now being evaluated to assess its efficacy and impact on survival.

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