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Short communication

Phase II study of high-dose ifosfamide in hepatocellular carcinoma

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Summary. A phase II study of high-dose ifosfamide in hepatocellular carcinoma was conducted among 17 Chinese patients. The dose of ifosfamide used was 2.5 g/m^2 daily given as a continuous infusion for 5 days. In all, 15 patients were evaluable for tumour response. There was no complete or partial responder. The treatment was well tolerated. The most frequent toxicity was alopecia, which occurred in 11 patients, and 5 patients developed mild haematological toxicity. There was no evidence of liver or bladder toxicity. Overall, 14 patients were evaluable for survival. The median survival was 92 days (range, 30–568 days). We conclude that high-dose ifosfamide is well tolerated but ineffective in hepatocellular carcinoma in Chinese patients.

Introduction

Hepatocellular carcinoma is the second most common cause of cancer death in Hong Kong [3]. It is an aggressive disease, with the median survival of untreated patients being 8–12 weeks. The only hope of cure is surgical resection, which results in a 5-year survival of around 26% [5]. However, the majority of patients present with inoperable disease [4].

Several cytotoxic agents have been tried with little success [2]. Ifosfamide, a new alkylating agent of the oxazaphosphorine group, has demonstrated clinical efficacy against several malignant tumours [1]. Its main side effects are myelosuppression, haemorrhagic cystitis and encephalopathy. The myelosuppression produced by ifosfamide is less severe than that induced by cyclophosphamide, and the cystitis can usually be prevented by mesna rescue. Ifofosfamide-induced encephalopathy usually occurs at daily doses exceeding 3 g/m^2. There have been previous studies with ifosfamide in hepatocellular carcinoma. Thongprasert et al. [8] conducted a phase II study in 16 patients using 1.3 g/m^2 ifosfamide and mesna uroprotection. In 13 evaluable patients, the response rate was 23%; the duration of survival for these 2 responders was 10.5 and 12 months, respectively. In view of this finding, we conducted a phase II study using higher doses of ifosfamide in Chinese patients with hepatocellular carcinoma.

Patients and methods

Patients under the age of 70 years who had histologically proven hepatocellular carcinoma were eligible for the present study. All of these patients had inoperable disease, with inoperability being determined by bilobar disease, evidence of extrahepatic spread or invasion of the inferior vena cava or main portal vein as determined by ultrasound examination. Exclusion criteria for the study were as follows: poor liver function (total bilirubin, >60 μmol/l), inadequate bone marrow function (a WBC of $<3 \times 10^9$/l or a platelet count of $<100 \times 10^9$/l); a Karnofsky performance score of <50 and concurrent serious medical illness.

Eligible patients were given a continuous infusion of ifosfamide at a dose of 2.5 g/m^2 daily for 5 days. Mesna rescue was given as a continuous infusion at a daily dose of 2000 mg/m^2 for 6 days. The patient also received hydration pre- and posttreatment. Urine was tested daily for red

Table 1. Patients' clinical details

Total number of patients	17
Sex (M/F):	
M	15
F	2
Median age (years)	50 (range, 28–67)
Median Karnofsky performance score	100
Median alpha-fetoprotein level (ng/ml)	704 (range, 0–287,000)
Median bilirubin (μmol/l)	9 (range, 3–59)
Median albumin (g/l)	39 (range, 35–44)
Median number of courses	2 (range, 1–4)
Median survival (days)	92 (range, 30–568)

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Table 2. Tumour responses

Complete or partial	0/17
Static	8/17 (47%)
Progressive	7/17 (41.2%)
Unknown	2/17 (11.8%)

Table 3. Treatment toxicity

	WHO grade			
	1	2	3	4
Haematological	4	1	0	0
Liver	0	0	0	0
Alopecia	2	4	5	0
Nausea/vomiting	0	6	0	0

blood cells. Cycles were repeated every 3 weeks for a maximum of six cycles.

Toxicity was evaluated using WHO criteria [9]. Treatment was delayed weekly if the WBC was $<3 \times 10^9$/l and/or the platelet count was $<100 \times 10^9$/l. Response was assesed after three cycles and/or on cessation of the treatment by clinical examination, determination of alpha-fetoprotein levels and ultrasound examination. A complete response was defined as the complete disappearance of disease as determined by clinical examination and on ultrasound images. A partial response was defined as a reduction of $\geqslant 50\%$ in the liver enlargement below the costal margin at the mid-clavicular line and the xiphoid process. Static disease was defined as either no change or a response amounting to less than a partial response. The rest were defined as progressive disease. The survival interval was calculated from the initiation of treatment until the time of death.

Results

A total of 17 patients were registered for the study. In all, 2 patients defaulted after receiving only one or two cycles and were therefore not available for evaluation of response and survival, and 1 patient defaulted after completing three cycles and was not evaluable for survival. The patients' clinical details are listed in Table 1. The tumour response is shown in Table 2. These results were generally disappointing, including no complete or partial responses, a 53% rate of static disease and a 47% rate of progressive disease. The median duration of survival for the 15 evaluable patients was 92 days (range, 30–568 days). At the time of this writing, 3 patients had survived for 71, 105 and 588 days, respectively. The toxicity of the treatment is shown in Table 3. The chemotherapy was well tolerated, with no evidence of encephalopathy, liver toxicity, cystitis or haematuria being observed.

Discussion

Hepatocellular carcinoma is an extremely aggressive disease, with surgery being the only hope of cure. In patients presenting with inoperable disease the outlook is uniformly grim. Various chemotherapeutic agents have been tried with little success. In earlier studies we obtained only a 9% rate of response to high-dose 4′-epidoxorubicin and no response at all to high-dose etoposide [6, 7]. The study conducted by Thongprasert et al. [8] produced a 23% response rate, but we have not been capable of reproducing this result, even using a higher dose of ifosfamide. One possible explanation for this failure may be that a different disease entity is involved in our Chinese population, which is even less responsive to chemotherapy than are other racial groups. We conclude that although ifosfamide is well tolerated at the present dose and schedule, it is ineffective against hepatocellular carcinoma, and a truly effective drug against this virulent tumour has yet to be found.

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References

1. Brade WP, Herdrich K, Varini M (1985) Ifosfamide pharmacology, safety and therapeutic potential. Cancer Treat Rev 12: 1–47
2. Falkson G, Macintyre J, Moertel C, et al. (1984) Primary liver cancer: an Eastern Cooperative Oncology Group trial. Cancer 54: 970–977
3. Institute of Radiology and Oncology (1986) Cancer incidence in Hong Kong. Cancer Registry, Medical and Health Department, Hong Kong
4. Liver Cancer Study Group of Japan (1984) Primary liver cancer in Japan. Cancer 54: 1747–1755
5. Okamoto E, Yamanaka N, Toyosaka A, Tanaka N, Yabuki K (1987) Current status of hepatic resection in the treatment of hepatocellular carcinoma. In: Okuda K, Ishak KG (eds) Neoplasms of the liver. Springer, Berlin Heidelberg New York Tokyo, p 356
6. Shiu W, Mok SD, Leung N, Li M, Zacharia A, Li A, Martin C (1987) Phase II study of high dose etoposide in hepatocellular carcinoma. Jpn J Clin Oncol 17: 113–115
7. Shiu W, Leung N, Li M, Leung WT, Li AKC (1988) The efficacy of high dose 4′-epidoxorubicin in hepatocellular carcinoma. Jpn J Clin Oncol 18: 235–237
8. Thongprasert S, Klunklin K, Phornphutkul K, et al (1988) Phase II study of ifosfamide in hepatoma. Eur J Cancer Clin Oncol 24: 1793–1796
9. World Health Organization (1979) Handbook for reporting results of cancer treatment, World Health Organization, Geneva