Doxorubicin for Unresectable Hepatocellular Carcinoma

A Prospective Study on the Addition of Verapamil

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A prospective study was conducted to assess the safety and efficacy of the addition of oral verapamil to intravenous Adriamycin (doxorubicin) for the management of patients with unresectable hepatocellular carcinoma (HCC). All 28 patients studied had histologically verified disease, and cirrhosis was present in 20 of the 21 patients with adequate tissue sampling. The overall median survival was 57 days. Chemotherapy was terminated in seven patients after one course of treatment. Partial response and complete response were noted in four patients (19%) and one patient (4.8%), respectively, among the 21 patients evaluated. Side effects related to the chemotherapy were present in all patients studied. Death from fulminating sepsis occurred in three of the 13 patients with leukopenia. Symptomatic myocardial dysfunction developed in one patient. The addition of verapamil apparently did not potentiate the tumoricidal effect of systemic Adriamycin on HCC but probably did increase its complications. *Cancer* 66:1685–1687, 1990.

AMONG DIFFERENT CHEMOTHERAPEUTIC AGENTS used for the treatment of patients with hepatocellular carcinoma (HCC), intravenous Adriamycin (ADM) (doxorubicin; Adria Laboratories, Columbus, OH) has been studied extensively.[1–5] Although it has generally been accepted as a useful agent, the response rate reported among patients in Hong Kong has been unsatisfactory.[6,7] *In vitro* and *in vivo* experimental data have suggested that the use of verapamil, a calcium-channel blocker, can potentiate the efficacy of ADM on different tumors, especially those that are chemoresistant.[8–10] The addition of verapamil is particularly attractive to us as the majority of our patients with HCC have underlying cirrhosis.[11] Reduction in portal pressure was reported after both chronic oral administration and intravenous bolus injection of verapamil in cirrhotic patients with portal hypertension.[12,13] Furthermore, *in vivo* experimental evidence has suggested that the function of the cirrhotic liver can be improved by chronic verapamil intake.[14] A prospective study was therefore conducted to investigate the potential benefit on the tumoricidal effect of systemic ADM by the addition of verapamil and its related toxic profile.

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Patients and Methods

All patients with unresectable HCC who were admitted to the Department of Surgery, Queen Mary Hospital at the University of Hong Kong, were included in the study if they met the following selection criteria: Karnofsky performance status of 70% or above; histologically proven disease; cirrhotic status of Child-Pugh class A and B status; no pre-existing myocardial dysfunction or cardiac arrhythmia; normal leukocyte count ($\geq 4 \times 10^9$/l) and platelet count ($\geq 80 \times 10^9$/l); total serum bilirubin less than 40 μmol/l; and presence of palpable hepatomegaly. Patients who had had previous surgery, chemotherapy, or tumor embolization for their hepatic neoplasm were excluded.

The protocol was approved by the Ethics Committee, Faculty of Medicine, University of Hong Kong. Informed

consent was obtained from all patients studied. All patients were followed until their deaths. From November 1987 through December 1989, a total of 28 patients were included in the study. There were 26 men and two women (mean age, 52.9 ± 10.6 years).

The following investigations were performed before treatment commenced: complete blood picture, liver function tests, serum alpha-fetoprotein by radioimmunoassay, chest radiograph, and electrocardiogram. Assessment of myocardial function by measurement of systolic ejection fraction was obtained before treatment by echocardiogram. Serum hepatitis B surface antigen (HBsAg) status was documented with reverse passive hemagglutination.

Intravenous infusion of ADM was given at a dose of 70 mg/m^2 that was repeated at a 3-week interval until a limiting dose of 550 mg/m^2 had been reached. At each course of treatment, oral verapamil (40 mg three times daily) was given for 5 days before administration of ADM and continued for 1 day after. All investigations were repeated before each course except for the echocardiogram, which was repeated at the conclusion of treatment.

Before each course of ADM and verapamil, the dose of ADM was reduced by 50% if the leukocyte count dropped below 3×10^9/l or the platelet count was reduced to 100×10^9/l or less. In the presence of either leukopenia (leukocyte count $< 2 \times 10^9$/l) or thrombocytopenia (platelet count $< 80 \times 10^9$/l), all drugs were omitted for 2 weeks or until the counts returned to normal values. Chemotherapy was also terminated if no response was seen after four courses, Karnofsky's performance status dropped below 40%, or there were evidences of cardiotoxicity.

The response was considered to be complete when there was complete disappearance of the palpable liver. A partial response was diagnosed when the sum of the liver span at midline and mid-clavicular lines was reduced by 50%. A lesser reduction or a stable or progressive increase in the size of the hepatomegaly was noted as no response. Complete response and partial response together formed the objective response.

Results

The clinical and laboratory data of the 28 patients studied are listed in Table 1. Although histologic verification of disease was obtained in all patients, detailed information on the adjacent nontumorous liver was only complete in 21 patients, 20 of whom had cirrhosis. All patients except two had a raised serum alpha-fetoprotein level greater than 200 ng/ml (normal, < 20 ng/ml).

Seven patients deteriorated rapidly after one course of treatment and further chemotherapy was not given. Among the remaining 21 patients who had two or more courses, objective response was noted in five (23.8%). Four patients had partial response. One patient had persistent ultrasonographic evidence of residual disease despite complete clinical regression of his hepatomegaly and marked subjective improvement. Reduction of serum alpha-fetoprotein to 20% of the pretreatment titer was noted in another three patients who had no regression of their hepatomegaly.

Side effects of varying severity related to chemotherapy treatment were noted in all patients (Table 2). Twelve of the 13 patients with leukopenia had fever. Blood cultures sampled during the febrile attacks were positive in three patients. All three patients died of fulminating sepsis despite vigorous therapy and broad-spectrum antibiotics.

All patients had normal cardiac function according to evaluation before treatment. Electrocardiograms were normal for all patients before each course and at the conclusion of their chemotherapy. At termination of chemotherapy, repeat echocardiograms in six patients revealed impaired myocardial function in three. Two patients had no symptoms related to their cardiotoxicity. Clinically evident cardiomyopathy with heart failure developed in one female patient who had eight courses of ADM and verapamil 1 month after completion of treatment. In addition to the three patients who died of sepsis, all of the remaining 25 patients died of malignant cachexia. The overall median survival of the 28 patients was 57 days.

Discussion

There has been little clinical data in the literature on the application of verapamil to enhance the tumoricidal effect of different chemotherapeutic agents, especially for primary HCC. The necessary serum concentration of verapamil for potentiating the tumoricidal effect of ADM is uncertain, and adjustment of its optimal dosage was difficult when assay of the serum verapamil level was not

TABLE 1. Clinical and Laboratory Data of 28 Patients With Unresectable Hepatocellular Carcinoma Before Chemotherapy

Variables	Value*
Age (yr)	52.9 (48.8 to 57)
Karnofsky rate (%)	84.5 (81.7 to 87.2)
Alpha-fetoprotein (10^6 ng/ml)	8.14 (−8.11 to 24.4)
Hemoglobin (g/l)	12.6 (11.7 to 13.5)
Leukocyte count (10^9/l)	7.8 (6.8 to 8.8)
Platelet count (10^9/l)	235 (189 to 280)
BUN (mmol/l)	5.6 (4.7 to 6.6)
Creatinine (mmol/l)	0.13 (0.07 to 0.19)
Total bilirubin (μmol/l)	19.4 (14.5 to 24.4)
Albumin (g/l)	33.8 (31.6 to 36)
Prothrombin time (seconds over control)	1.19 (0.69 to 1.71)
Hepatitis B surface antigen†	25

* All values expressed as mean values (95% confidence interval) unless specified.

† Value expressed in number of patients.

TABLE 2. Side Effects of Systemic Adriamycin and Verapamil on 28 Patients With Unresectable Hepatocellular Carcinoma

Side effects	No. of patients (n = 28)
Alopecia	27
Nausea and vomiting	15
Mucositis	9
Leukopenia*	13
Thrombocytopenia	7
Myocardial dysfunction†	3

* Three patients had septicemia.
† Six patients had a posttreatment echocardiogram.

available. In the current study, the verapamil dosage design was based on the report by Kong *et al.*[12] Among their ten posthepatitic, cirrhotic Child's A patients, all had successful reduction of their hepatic venous pressure gradient with 40 mg of oral verapamil given three times daily for 1 month. The serum verapamil concentration achieved with such a regimen also was assumed to be adequate for the potentiation of the chemotherapeutic effect of ADM. When most of our patients had concomitant cirrhosis of varying severity, the duration of verapamil intake before ADM administration was sufficient. A steady-state plasma concentration would be reached 2 days after commencement of continuous verapamil intake among cirrhotic patients.[15]

From this study's results, it is apparent that the current regimen of systemic ADM and verapamil offers little benefit for patients with unresectable HCC. The median survival of 57 days was only comparable to patients who had no antitumor treatment, which was reported in two different randomized trials from Hong Kong.[7,11] When measured in terms of response rate and fatal complication rate associated with treatment, the combination of systemic ADM and verapamil did better than the rates of 8.3% and 25%, respectively, reported by Lai *et al.* with systemic Adriamycin alone.[7] The response rate of 23.8% observed in the current study, however, was only comparable with the 24% response rate that we reported previously for 45 patients.[6] In addition, both frequency and severity of hematologic complications related to ADM were apparently increased when verapamil was also given. None of our patients had leukopenia complicated by fatal fulminating sepsis when ADM was given as a single chemotherapeutic agent. As toxicity of ADM is probably related to the schedule of verapamil,[16] careful monitoring of serum verapamil level, timely cessation of verapamil administration before chemotherapy, and modification of the dosage of chemotherapeutic agents employed should be considered in the design of future clinical trials.

REFERENCES

1. Olweny CL, Toya T, Katongole-Mbidde E *et al.* Treatment of hepatocellular carcinoma with Adriamycin. *Cancer* 1975; 36:1250–1257.
2. Olweny CL, Katongole-Mbidde E, Bahendeka S *et al.* Further experience in treating patients with hepatocellular carcinoma in Uganda. *Cancer* 1980; 46:2717–2722.
3. Johnson PJ, Williams R, Thomas H *et al.* Induction of remission in hepatocellular carcinoma with doxorubicin. *Lancet* 1978; 1:1006–1009.
4. Vogel CL, Bayley AC, Brooker RJ *et al.* A phase II study of Adriamycin (NSC 123127) in patients with hepatocellular carcinoma from Zambia and the United States. *Cancer* 1977; 39:1923–1929.
5. Falkson G, Moertel CG, Lavin P *et al.* Chemotherapy studies in primary liver cancer. *Cancer* 1978; 42:2149–2156.
6. Choi TK, Lee NW, Wong J. Chemotherapy for advanced hepatocellular carcinoma. Adriamycin *versus* quadruple chemotherapy. *Cancer* 1984; 53:401–405.
7. Lai CL, Wu PC, Chan GCB *et al.* Doxorubicin *versus* no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. *Cancer* 1988; 62:479–483.
8. Tsuruo T. Reversal of acquired resistance to Vinca alkaloids and anthracycline antibiotics. *Cancer Treat Rep* 1983; 67:889–894.
9. Rogan AM, Hamilton TC, Young RC *et al.* Reversal of Adriamycin resistance by verapamil in human ovarian cancer. *Science* 1984; 224: 994–996.
10. Pradhan SG, Basrur VS, Chitnis MP, Adwani SH. In vitro enhancement of Adriamycin cytotoxicity in human myeloid leukemia cells exposed to verapamil. *Oncology* 1984; 41:406–408.
11. Lai ECS, Choi TK, Tong SW *et al.* Treatment of unresectable hepatocellular carcinoma: Results of a randomized controlled trial. *World J Surg* 1986; 10:501–509.
12. Kong CW, Lay CS, Tsai YT *et al.* The hemodynamic effect of verapamil on portal hypertension in patients with postnecrotic cirrhosis. *Hepatology* 1986; 6:423–426.
13. Freeman JG, Barton JR, Record Co. Effect of isosorbide dinitrate, verapamil and labetalol on portal pressure in cirrhosis. *Br Med J* 1985; 291:561–562.
14. Reichen J, Le M. Verapamil favorably influences hepatic microvascular exchange and function in rats with cirrhosis of the liver. *J Clin Invest* 1986; 78:448–455.
15. Somogyi A, Albrecht M, Klijems G *et al.* Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. *Br J Clin Pharmacol* 1981; 12:51–60.
16. Przybysz TM, Schenken LL. Schedule dependent potentiation of Adriamycin (ADR) and vincristine (VCR) toxicity by verapamil. *Proc Am Assoc Cancer Res* 1984; 25:332.