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Arterial infusion chemotherapy for advanced hepatocellular carcinoma using EPF and EAP therapies*

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Summary. Arterial infusion chemotherapy of EPF (etoposide, cisplatin, and 5-fluorouracil) or EAP (etoposide, Adriamycin, and cisplatin) was carried out in 28 cases of advanced hepatocellular carcinoma (HCC) between January 1988 and December 1990, and assessment was made of the anticancer efficacy of each treatment method. In all, 13 patients were treated with EPF therapy and 15 received EAP therapy. The anticancer agents were infused through a catheter inserted into the proper or common hepatic artery. The catheter was inserted via the axillary artery or common femoral artery using Seldinger's method or the cut-down method. The results of each therapy were analyzed in relation to the tumor regression rate and the side effects encountered. The tumor regression rate was determined on the basis of two-dimensional evidence obtained by computed tomography performed before and after treatment. The treatment results were also compared with the results of chemoembolization therapy using a mixture of cisplatin (CDDP), Adriamycin (ADM) and lipiodol. Of the 28 patients treated with arterial infusion chemotherapy, 14 (50%) attained a regression rate of 50% (PR). In all, 46% of the EPF group and 53% of the EAP group achieved a PR. These results were superior to those obtained using chemoembolization therapy. In general, the side effects were relatively mild and transient.

Introduction

Various therapies for unresectable hepatocellular carcinoma (HCC) have been developed. In Japan, transcatheter arterial embolization (TAE) therapy is currently thought to be one of the best treatments for unresectable HCC. The prognosis of patients with HCC has truly been improved by TAE [8]. However, TAE therapy is not curative but conservative, and it has some limitations [5]. In our experience with TAE therapy for unresectable HCC, the 1-year survival value is 53%, the 3-year survival value is 18%, and the 5-year value is 13%. Chemotherapy is generally not effective against HCC, but some investigators have reported that arterial infusion chemotherapy is effective against this disease.

Many new anticancer drugs have recently been developed, and arterial infusion chemotherapy with these durgs has been tested in attempts to investigate their antitumor effects in HCC [6, 9]. For this purpose, we decided to conduct a trial of combination therapy with arterial infusion chemotherapy and TAE in patients with advanced HCC. In this paper we report the results we obtained using arterial infusion chemotherapy for HCC.

Patients and methods

Patients characteristics. From January 1988 to December 1990, 28 patients with unresectable HCC were treated with arterial infusion chemotherapy and TAE in our hospital and affiliated institutions. The study population included 23 men and 5 women whose mean age was 58.1 years (range 15–75 years). According to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer proposed by the Liver Cancer Study Group of Japan [2], 4 patients classified as being in stage II, 5, in stage III; and 19, in stage IV. In all, 13 patients received

Table 1. Patients' characteristics

Regimen	Number of patients	Men	Women	Mean age (years)	Stage[a]		
					II	III	IV
EPF	13	10	3	56.1	3	1	9
EAP	15	13	2	59.9	1	4	10

[a] According to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer proposed by the Liver Cancer Study Group of Japan [2]

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Table 2. Treatment schedule

Drug	Dose	Schedule
EPF regimen:		
CDDP	20 mg/m^2	Days 1 – 5
Etoposide	30 – 40 mg/m^2	Days 1 – 5
5-FU	250 mg/body	Days 1 – 26
EAP regimen:		
CDDP	50 mg/m^2	Days 2 and 8
Etoposide	50 – 60 mg/m^2	Days 4 – 6
ADM	20 mg/m^2	Days 1 and 7

All drugs were given intra-arterially

arterial infusion chemotherapy with EPF and 15 received EAP therapy (Table 1).

Treatment. We employed two arterial infusion chemotherapy regimens, EPF and EAP (Table 2). In EPF therapy, 30 – 40 mg/m^2 etoposide (5 days), 20 mg/m^2 CDDP (5 days), and 5-fluorouracil (5-FU) at 250 mg/body (26 days) were given as one course through the catheter placed in the proper or common hepatic artery. In EAP therapy, 50 – 60 mg/m^2 etoposide (days 4 – 6), 50 mg/m^2 CDDP (days 2 and 8), and 20 mg/m^2 Adriamycin (ADM) (days 1 and 7) were infused intra-arterially as one course.

All patients received two infusion courses. The drug-delivery method was a 24-h continuous hepatic arterial infusion (HAI) through a 4- to 5 – F catheter. The catheter was inserted into the femoral artery by Seldinger's method or by a new technique that we recently developed [1]; in the latter technique, the catheter is inserted into the proper hepatic artery through the aortic arch and descending aorta via the left thoraco-acrominal artery by the cut-down method.

At 1 month after the completion of two courses, the response to each chemotherapy was evaluated by computed tomography (CT) performed before and after the treatment. Objective response criteria were defined as follows: complete response (CR), the complete disappearance of all objective evidence of disease; partial response (PR), a decrease of 50% or more in the size of the tumor; minor response (MR), a decrease amounting to 25% or more but less than 50% in the size of the tumor; no change (NC), a decrease or increase of less than 25% in the size of the lesion; and progressive disease (PD), an increase of 25% or more in the size of the tumor or the appearance of new lesions.

Results

Of the 28 patients treated 13 were given the EPF regimen and 15 received EAP therapy. Overall, 14 subjects (50%) attained a regression rate of 50% or more. In the EPF group, 1 patient achieved a CR, 5 showed a PR, 4 displayed an MR, and 3 showed NC. In all, 6 of the 13 subjects, or about 46%, attained a regression rate of 50% or more (CR + PR). On the other hand, in the EAP group, 8 patients showed a PR; 5, an MR; and 2, NC. In all, 8 of 15 patients, or about 53%, attained a regression rate of 50% or more (Table 3). In our previous experience with TAE [10], 23%

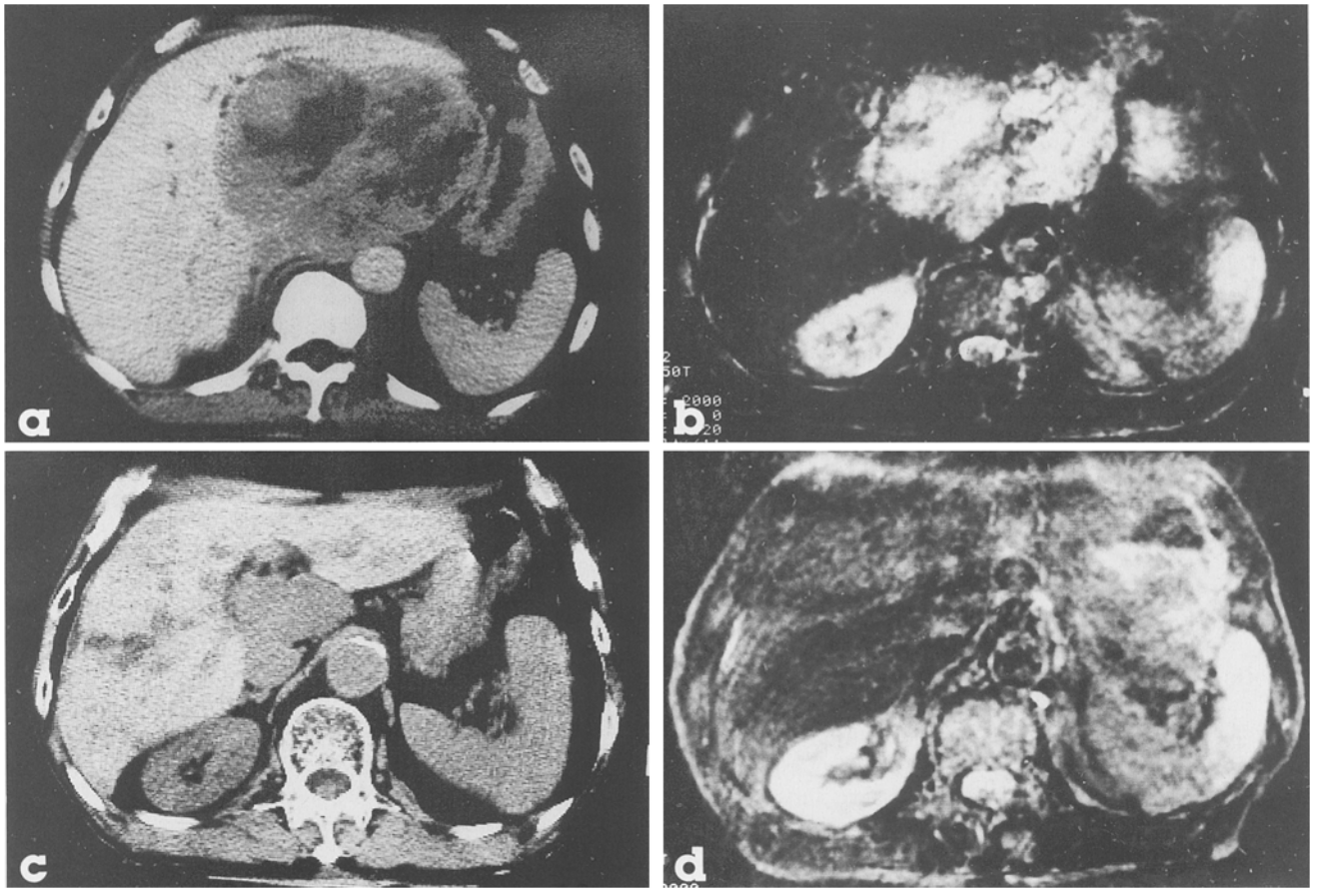

Fig. 1 a – d. CT and MRI images obtained **a, b** prior to and **c, d** after EPF therapy in a 74-year-old man). **a** A large, inhomogeneous tumor is visible in the caudate lobe. The IVC is markedly depressed. **b** The tumor shows high signal intensity at T2 WI on the MRI image. **c** The tumor has decreased greatly in size. **d** The signal intensity of the tumor has returned to normal. The tumor seems to show a change to fibrous necrosis.

Table 3. Treatment results

Regimen	CR	PR	MR	NC	PD	CR + PR (%)
EPF (n = 13)	1	5	4	3	0	6/13 (46%)
EAP (n = 15)	–	8	5	2	0	8/15 (53%)

Table 4. Side effects encountered

Side effect	EPF (n = 13)	EAP (n = 15)
Loss of appetite	9/13 (69%)	13/15 (87%)
Nausea/vomiting	7/13 (54%)	14/15 (93%)
Fever	1/13 (8%)	5/15 (33%)
Alopecia	9/13 (69%)	9/15 (60%)
Hematological toxicity	9/12 (75%)	13/15 (87%)
Liver damage	7/13 (54%)	6/15 (40%)
Renal damage	6/13 (46%)	5/15 (33%)

of 77 patients achieved a PR. Thus, these HAI chemotherapies are superior to TAE in regard to the tumor reduction effect.

Various side effects of the treatments occurred (Table 4). Hematological toxicities such as leukopenia and thrombocytopenia were very frequently encountered. Loss of appetite, nausea, and vomiting were experienced by many patients in the EAP group. Alopecia occurred in over 60% of cases and was attributable to treatment with etoposide and ADM. Liver and renal damage were found at the same frequency in the two groups. Most of these side effects were not very severe and the drugs were well tolerated.

A representative case in the EPF group was a 74-year-old man with a large HCC (T4N0M0 stage IV; IM_0, Vp_3, Vv_3) in the caudate lobe. A low-density mass was detected on the CT scan and a high-intensity signal was visible on the MRI image. After EPF therapy, the mass showed a decrease in size on the CT scan, and its MRI intensity was the same as that of the normal liver tissue (Fig. 1). No recurrence has been detected over the past 3 years. A representative case in the EAP group was a 53-year-old man with a large HCC (T4N0M0 stage IV; IM_0, Vp_3, Vv_3) in the right lobe. The patient had tumor thrombi in the intrahepatic portal vein and IVC. After two courses of EAP therapy, the tumor became very small (81% regression) and the tumor thrombi almost disappeared (Fig. 2).

Discussion

Chemotherapy can be effective when an appropriate method for the administration of anticancer drugs is devised [7]. Melia et al. [3] and Quinn et al. [4] have reported that etoposide and CDDP are effective in the treatment of HCC. In the present successful trial, we concluded that HAI of anticancer drugs, such as EPF and EAP, is quite beneficial in the treatment of HCC. Incidentally, HAI of anticancer drugs was effective in eradicating some daughter nodules and tumor thrombi against which TAE therapy is not usually effective. We were also impressed by the observation that the remission period was prolonged in most of our

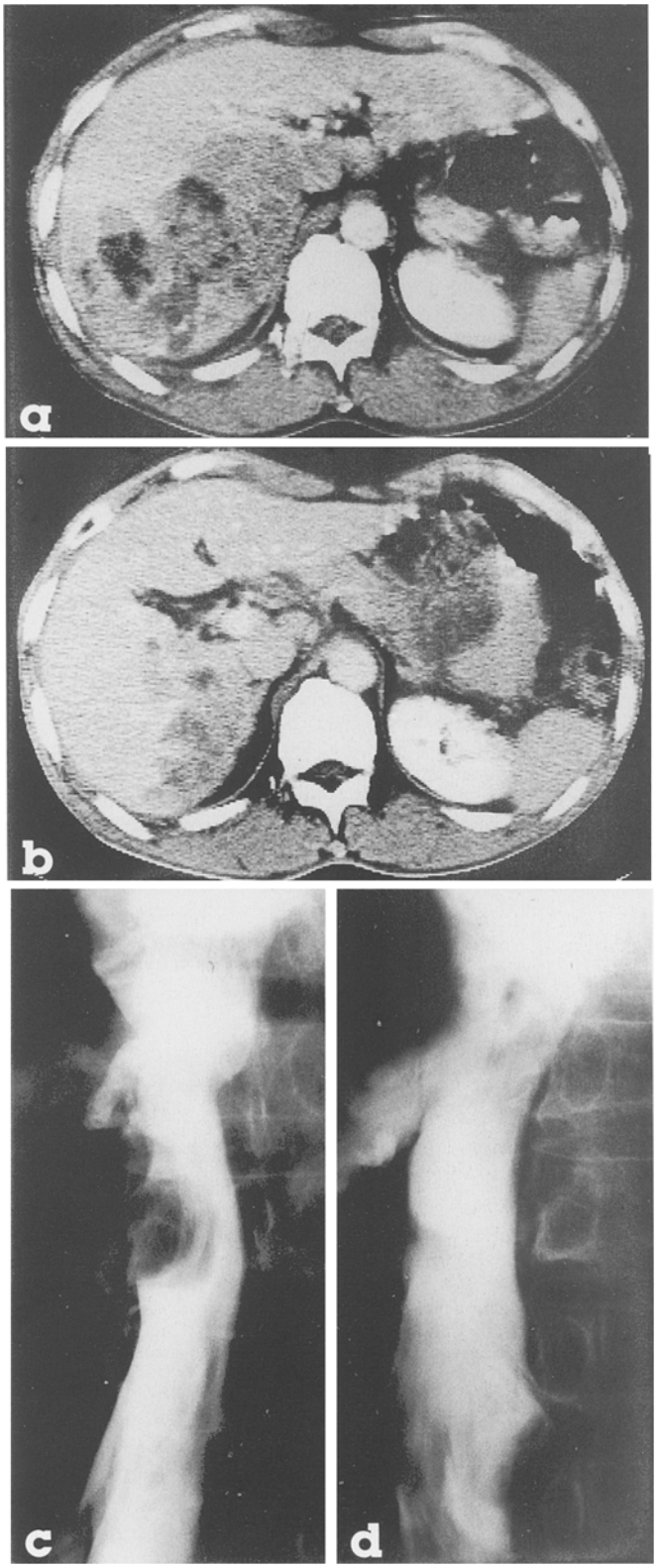

Fig. 2 a–d. CT scans and cavograms obtained prior to and after EAP therapy in a 53-year-old man). **a** CT prior to EAP: a huge HCC is visible in the right lobe. **b** CT after EAP: the tumor has become very small (81% regression). **c** Cavogram prior to EAP: a large filling defect in the IVC can be seen on the cavogram. **d** Cavogram after EAP: the filling defect has almost disappeared

patients. Therefore, combination therapy with HAI chemotherapy and TAE is thought to be reasonable, and we expect to obtain very good results in the near future.

In our protocols, the planned dose was a little smaller than the standard dose. This is very important for reducing the side effects. Most side effects were temporary and well tolerated. However, sepsis occurred in one patient, and severe liver damage due to the treatment was noted after 6 months in another subject; unfortunately, both of these patients died. The sepsis seemed to have been caused by cholelithiasis. The liver damage may not have been caused by the treatment, as the patient had very severe liver cirrhosis; in this case, it was a particular shame that the patient died because the tumor was completely suppressed. In conclusion, although we did not treat a large number of cases in the present study, we at least detected the efficacy of HAI of EPF and EAP. We are convinced that combination therapy with HAI chemotherapy and TAE will improve the outcome of unresectable HCC.

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