Cancer Chemother Pharmacol (1994) 33 (Suppl): S 79–S 83

Cancer Chemotherapy and Pharmacology

Combination therapy consisting of arterial infusion chemotherapy (EPF, EAP) and transcatheter arterial embolization (TAE)

Hiraku Yodono, Shoichi D. Takekawa, Koji Tarusawa, Isao Ikami, Jiro Kanehira, Yoko Saito, Satoshi Takahashi, Taisuke Sasaki, Naoko Nishi, Tamaki Kimura, Shigeo Oikawa, Koichi Shibutani, Atsushi Shinohara, Akira Anbai, Rikako Sasaki, Yukio Sasaki, Hiroshi Noda

Department of Radiology, Hirosaki University Hospital, Hirosaki 036, Japan

Abstract. From January 1988 to January 1993, 45 patients with unresectable advanced hepatocellular carcinoma (HCC) were treated with a new combination therapy consisting of arterial infusion chemotherapy and TAE. The combination therapy was performed according to our treatment schedule as follows: two courses of arterial infusion chemotherapy were given first, and then transcatheter arterial embolization (TAE) using a mixture of Lipiodol and cisplatin powder was performed. Two arterial infusion chemotherapeutic regimens were employed: EPF (etoposide, cisplatin, and 5-fluorouracil) and EAP (etoposide, Adriamycin or Epi-adriamycin, and cisplatin). The anticancer drugs were infused through a catheter inserted into the proper or common hepatic artery. Assessment was made of the anticancer effect and survival rate of each treatment method. The response to each therapy was evaluated on the basis of CT performed prior to and after the treatment. In the EPF·TAE group, the response rate was about 46%, whereas in the EAP·TAE group it was 48%. Overall, 21 of 45 patients attained a regression rate of 50% or more. Furthermore, daughter nodules decreased in size or disappeared in about 67% of 15 patients. Additionally, tumor thrombi tended to show a similar response. In all of the cases, the average duration of survival was 30.3 months, and the 1-year survival value was 68%, the 2-year survival value was 44%, and the 3-year survival value was 35%. These results were superior to those obtained with TAE therapy alone.

Work presented at the Third International Symposium on Treatment of Liver Cancer, Seoul, Korea, 12–13 February 1993

Correspondence to: Hiraku Yodono, Department of Radiology, Hirosaki University Hospital; 53 Hon-cho, Hirosaki 036, Japan

Introduction

In Japan, transcatheter arterial embolization (TAE) therapy is currently thought to be one of the best treatments for unresectable hepatocellular carcinoma (HCC) [9]. In the results we obtained with TAE for HCC, the 1-year survival value was 53%, the 3-year survival value was 18%, and the 5-year survival value was 13%. These are relatively good results, but TAE therapy is conservative, not curative, and it has some limitations. TAE therapy is generally not effective against daughter nodules or tumor thrombi [7]. In 1992, we reported the results of hepatic arterial infusion (HAI) chemotherapy for the first 28 cases of unresectable HCC [12]. HAI chemotherapy showed a good antitumor effect on the main tumor, and it was also effective against daughter nodules and tumor thrombi. We then conceived of combining arterial infusion chemotherapy with TAE for the treatment of unresectable HCC. This paper reports the results of our clinical study of that combination of therapies in the treatment of unresectable HCC.

Patients and methods

Patients' characteristics

From January 1988 to January 1993, 45 patients with unresectable HCC were treated with a new combination therapy consisting of HAI chemotherapy and TAE in our hospital and affiliated institutions. The study population consisted of 34 men and 11 women whose mean age was 60 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], 7 patients were classified as being in stage II; 9 patients, in stage III; and 29 patients, in stage IV. Thus, 65% of the patients were classified as being in stage IV. We employed two arterial infusion chemotherapy regimens: EPF and EAP. The EPF·TAE group consisted of 14 patients and the EAP·TAE group, 31 patients. The EAP·TAE group included more advanced cases (Table 1).

Table 1. Patients' characteristics

Regimen	Number of patients	Men	Women	Mean age (years)	Stage		
					II	III	IV
EPF·TAE	14	10	4	57	5	2	7
EAP·TAE	31	24	7	61	2	7	22

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]

Table 2. Treatment schedule

a) First step: arterial infusion chemotherapy

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 (epi-ADM)	20 (30) mg/m^2	Days 1 and 7

All drugs were given intra-arterially. All patients received two infusion courses

b) Second step: TAE
CDDP·LPD + Gelfoam particles

Table 3. Treatment results regarding the main tumor

Regimen	CR	PR	MR	NC	PD	CR + PR (%)
EPF·TAE (n = 14)	1	5	4	3	0	6/13 (46%)
EAP·TAE (n = 31)	1	14	6	10	0	15/31 (48%)

Table 4. Effects on daughter nodules

Regimen	Decreased or disappeared
EPF·TAE	3/6 (50%)
EAP·TAE	7/9 (78%)

Treatment

The combination therapy was given according to our treatment schedule (Table 2). HAI chemotherapy was performed first, and all patients received two infusion courses; then TAE therapy was performed. The two HAI chemotherapy regimens were given as follows: in the 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, whereas in the 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 (30 mg/m^2 Epi-adriamycin) was infused intra-arterially as one course. All drugs were given through a catheter placed in the proper or common hepatic artery by the method of continuous arterial infusion over a 24-h period. TAE was performed using a mixture of Lipiodol and CDDP powder as reported by us in 1989 [10].

At 1 month after TAE, the response to each therapy was evaluated by comparison of the computed tomography (CT) findings obtained prior to and after the treatment. The evaluation was performed in accordance with the criteria of the JSCT [1], which closely resemble the WHO criteria: complete response (CR), the complete disappearance of all objective evidence of the tumor for more than 4 weeks; partial response (PR), a decrease of 50% or more in the volume of the tumor, with no new lesions; minor response (MR), a decrease of less than 50% but over 25% in the tumor size; no change (NC), a decrease of less than 25% or an increase of less than 25% in the tumor size; and progressive disease (PD), more than a 25% increase in the tumor size or the appearance of new lesions. Furthermore, the survival curves of the two groups were constructed using Kaplan-Meier's method. Also, the responses of daughter nodules and tumor thrombi were evaluated by comparison of the CT findings obtained prior to and after the treatment.

Results

Response to treatment

In the EPF·TAE 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·TAE group, 1 patient showed a CR, 14 showed a PR, 6 showed an MR, and 10 showed NC. In all, 15 of 31 patients, or about 48%, attained a regression rate of 50% or more (Table 3). The difference between the two groups was not significant. Overall, 2 patients showed a CR, 19 showed a PR, 10 showed an MR, and 13 showed NC. The overall response rate obtained in this study was 47%. Daughter nodules were detected in 15 patients by CT, and they had decreased in size or disappeared in 10 of the 15 patients, or about 67%, after the treatment (Table 4). Tumor thrombi showed a similar tendency to respond.

Survival

The survival curves were drawn according to the method of Kaplan-Meier. The average duration of survival was 27.6 months for the EPF·TAE group and 21.7 months for the EAP·TAE group as determined from the initiation of the treatment. In the EPF·TAE group, the 1-year survival value was 50%, the 2-year survival value was 43%, and the 3-year survival value was 34%. In the EAP·TAE group, 1-year survival value was 77% and the 2-year survival

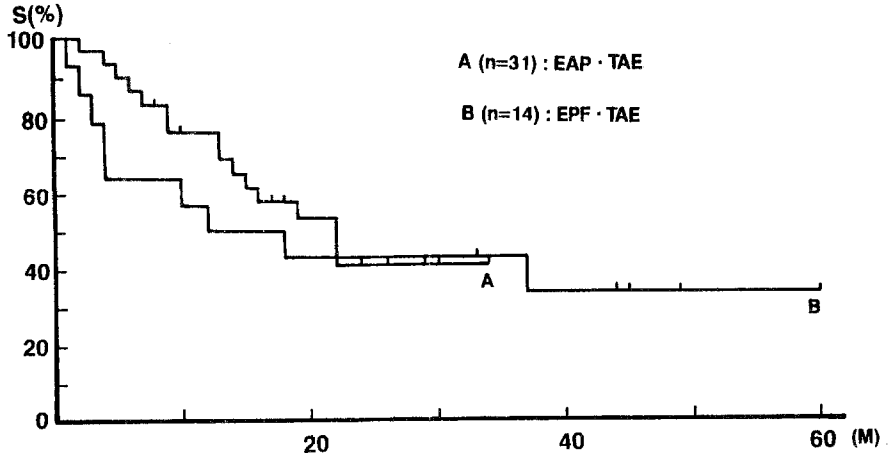

Fig. 1. The cumulative survival of patients with HCC (Kaplan-Meier)

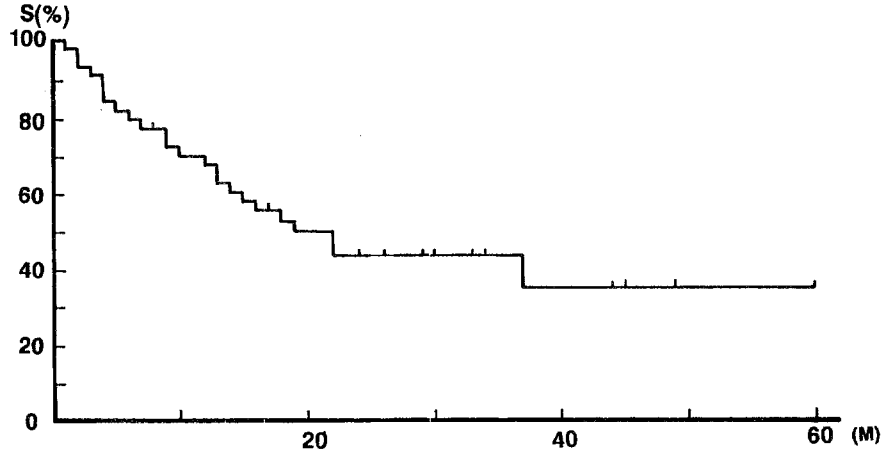

Fig. 2. The cumulative survival of patients (n = 45) with HCC treated with arterial infusion chemotherapy and TAE (Kaplan-Meier)

value was 42% (Fig. 1). There was no significant difference between the two groups according to testing by the generalized Wilcoxon method. Overall, the mean duration of survival was 30.3 months, and the 1-year survival value was 68%, the 2-year survival value was 44%, and the 3-year survival value was 35% (Fig. 2).

Case reports

The first patient was a 53-year-old man with HCC. Two nodules, which were diagnosed as HCC by needle biopsy, were detected by CT in November 1990. After EAP-TAE treatment, the tumors decreased in size and became fibrotic necrosis (Fig. 3). At the time of this writing (January 1993), the patient was alive and healthy.

The second patient was a 72-year-old man with HCC. CT images showed a huge tumor and a daughter nodule in the right hepatic lobe. After EAP-TAE treatment, the huge tumor was greatly diminished in size and the daughter nodule disappeared completely (Fig. 4).

The last patient was a 56-year-old man who had a huge tumor in the left hepatic lobe and a tumor thrombus in the main branch of the intrahepatic portal vein. After EAP-TAE therapy, the main tumor decreased in size and became a cystic mass, and the tumor thrombus also decreased markedly in size (Fig. 5). As of this writing, the patient has survived for 17 months since the treatment.

Cause of death

Of the 45 patients, 24 (53%) patients died, 12 of uncontrolled tumor, 8 of hepatic failure, and 1 each due to myocardial infarction, G-I bleeding, cholangitis, and unknown cause. Of the 8 patients who experienced hepatic failure, 4 died within 6 months of the treatment, whereas the other patients survived for more than 1 year.

Discussion

The best treatment for HCC is tumor resection, if possible [4]. Various efforts have recently been made to treat unresectable HCC with therapeutic modalities such as TAE, percutaneous transhepatic ethanol injection (PEIT) [8], and arterial infusion chemotherapy [5]. TAE therapy is the most popular one for unresectable HCC and has produced rela-

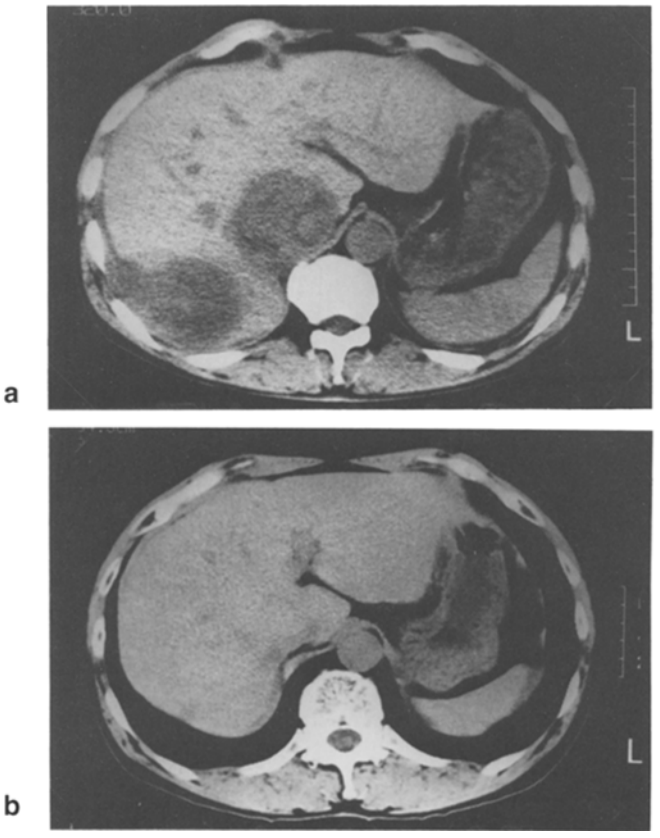

Fig. 3a, b. CT images obtained **a** prior to and **b** after EAP·TAE therapy in a 53-year-old man (**a**) Two nodules are visible in the right hepatic lobe, and the IVC is markedly depressed (**b**) The two nodules have decreased greatly in size and almost disappeared

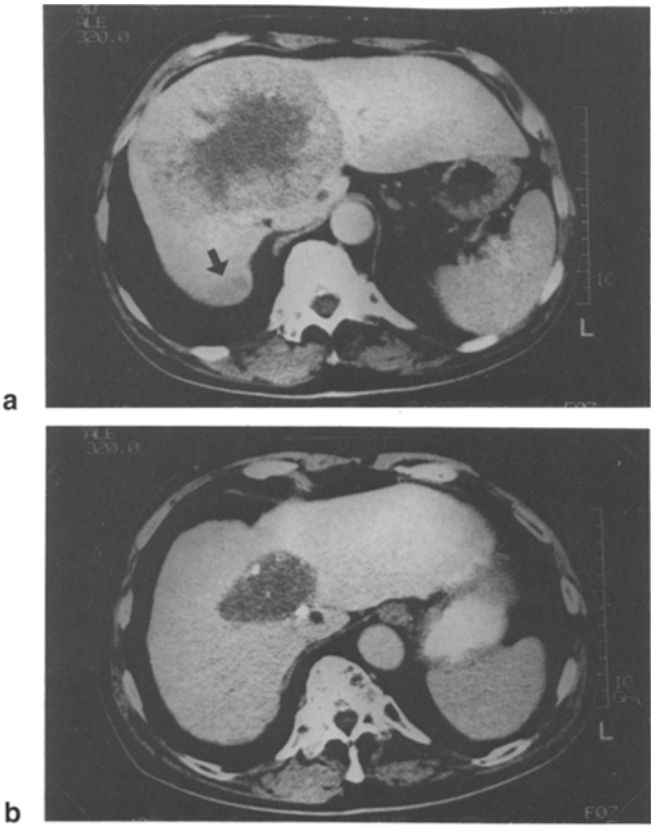

Fig. 4a, b. CT images obtained **a** prior to and **b** after EAP·TAE therapy in a 72-year-old man with HCC (**a**) A large tumor is visible in the liver, and a daughter nodule (↑) is seen in the right hepatic lobe (**b**) The tumor has decreased greatly in size, and the daughter nodule has disappeared completely

tively good results, but they did not satisfy us. PEIT is very effective for small HCC, but it is not useful for advanced HCC. Some researchers, including us, have reported efficacy for arterial infusion chemotherapy given through a catheter placed in the hepatic artery. Melia et al. [3] and Quinn et al. [6] reported that CDDP and etoposide were effective in the treatment of HCC. We reported on HAI chemotherapy using regimens such as EPF and EAP in 1992 [12]. We conceived of combination therapy consisting of HAI chemotherapy and TAE for unresectable advanced HCC and applied it in clinical practice. The results of this study were superior to those obtained with TAE therapy alone, and this combination therapy was more effective against daughter nodules and tumor thrombi, against which TAE therapy is usually ineffective. We thus concluded that this combination of HAI chemotherapy and TAE was exceedingly beneficial in the treatment of advanced HCC. We employed two chemotherapy regimens, but there was no significant difference between them. However, CDDP and etoposide seem to have played an important role in the antitumor effect [12].

In this study, four patients died of hepatic failure within 6 months. HAI chemotherapy may contribute to functional disturbance of the liver. Two patients died due to cholangitis and G-I bleeding, respectively, which might have been aggravated by the HAI chemotherapy. Thus, we have to apply this protocol in clinical practice to patients who have good liver function, no cholangitis, and no cholecystitis. We have to exercise care regarding the management of gastritis, gastric ulcer, and duodenal ulcer during the full term of this therapy.

In conclusion, the combination therapy consisting of arterial infusion chemotherapy and TAE was found to be very effective, and we surmise that it is a new and useful therapeutic regimen for advanced HCC.

References

1. Japan Society for Cancer Therapy (1986) Criteria for the evaluation of the clinical effects of solid cancer chemotherapy (in Japanese). J Jpn Soc Cancer Ther 21: 929
2. Liver Cancer Study Group of Japan (1987) The general rules for the clinical and pathological study of primary liver cancer (in Japanese). Kanehara & Co., Tokyo
3. Melia WM, Johnson PJ, Williams R (1983) Induction of remission in hepatocellular carcinoma. A comparison of VP 16 with Adriamycin. Cancer 51: 206
4. Nagasue N, Yukaya H (1989) Liver resection for hepatocellular carcinoma: results from 150 consecutive patients. Cancer Chemother Pharmacol 23 [Suppl]: S78
5. Nakamura K, Takashima S, Takada K, Fujimoto K, Kaminou T, Nakatsuka H, Minakuchi K, Onoyama Y (1992) Clinical evaluation of intermittent arterial infusion chemotherapy with an implanted reservoir for hepatocellular carcinoma. Cancer Chemother Pharmacol 31 [Suppl I]: S93

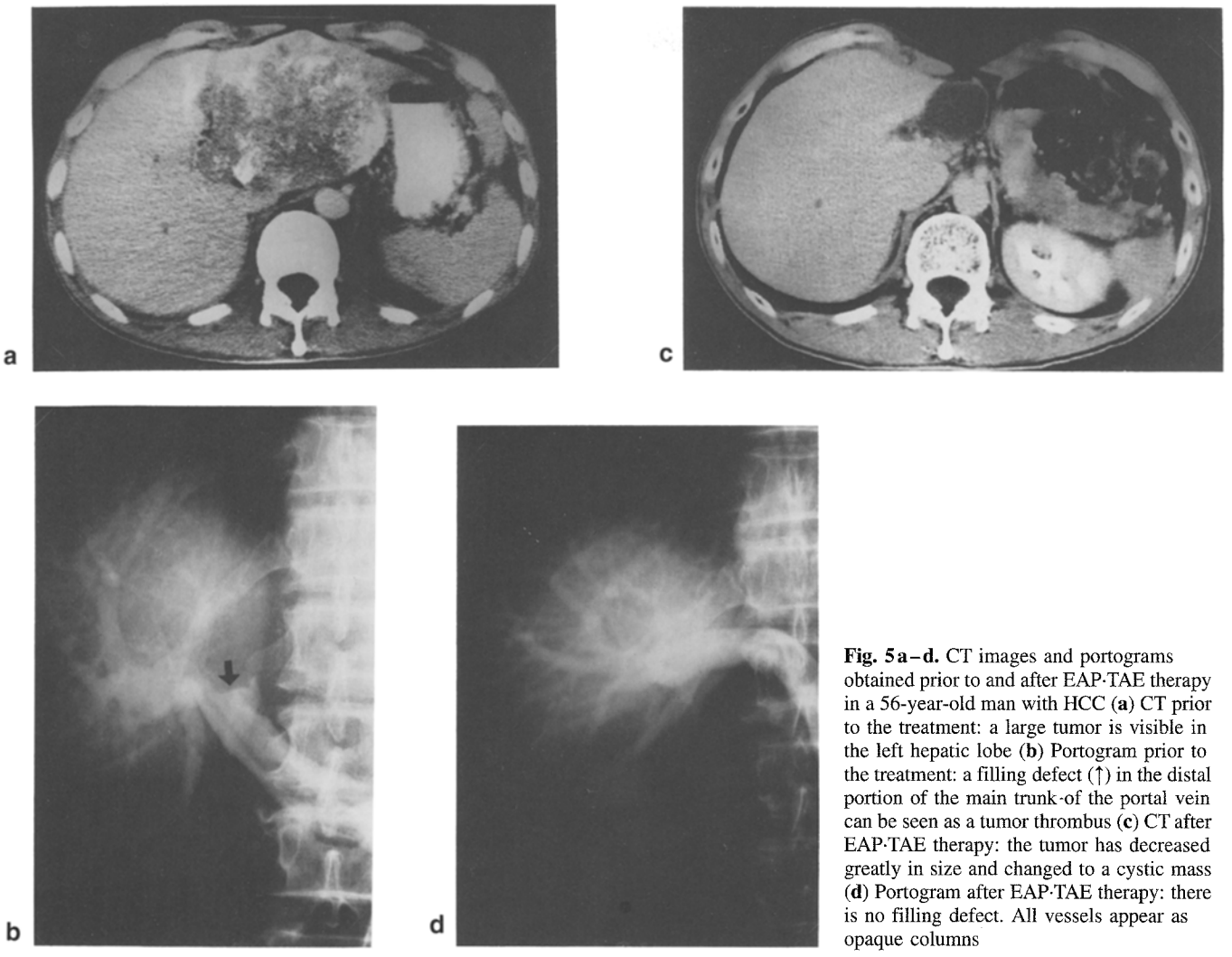

Fig. 5a–d. CT images and portograms obtained prior to and after EAP·TAE therapy in a 56-year-old man with HCC (**a**) CT prior to the treatment: a large tumor is visible in the left hepatic lobe (**b**) Portogram prior to the treatment: a filling defect (↑) in the distal portion of the main trunk of the portal vein can be seen as a tumor thrombus (**c**) CT after EAP·TAE therapy: the tumor has decreased greatly in size and changed to a cystic mass (**d**) Portogram after EAP·TAE therapy: there is no filling defect. All vessels appear as opaque columns

6. Quinn JJ, Altman AJ, Robinson T, Cooke RW, Hight DW, Foster JH (1985) Adriamycin and cisplatin for hepatoblastoma. Cancer 56: 1926
7. Sakurai M, Okamura J, Kuroda C (1984) Transcatheter chemoembolization effective for treating hepatocellular carcinoma. Cancer 54: 387
8. Sugiura N, Takara K, Ohto M, Okuda K, Hirooka N (1983) Percutaneous intratumoral injection of ethanol under ultrasound imaging for treatment of small hepatocellular carcinoma. Acta Hepatol Jpn 24: 920
9. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S (1983) Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 148: 397
10. Yodono H, Saito Y, Saikawa Y, Midorikawa H, Yokoyama Y, Takekawa SD (1989) Combination chemoembolization therapy for hepatocellular carcinoma mainly using cisplatin (CDDP). Cancer Chemother Pharmacol 23 [Suppl]: S42
11. Yodono H, Tarusawa K, Sasaki T, Kanehira J, Saito Y, Takahashi S, Kimura T, Nishi N, Nakamura Y, Takekawa SD (1989) A case with hepatocellular carcinoma effectively treated by intra-arterial infusion of CDDP and other agents. Jpn J Cancer Chemother 16: 3265
12. Yodono H, Sasaki T, Tarusawa K, Midorikawa H, Saito Y, Takekawa SD (1992) Arterial infusion chemotherapy for advanced hepatocellular carcinoma using EPF and EAP therapies. Cancer Chemother Pharmacol 31 [Suppl I]: S89