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Transcatheter Arterial Embolization and Continuous Intraarterial Infusion Chemotherapy in Hepatoma

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ABSTRAK

Arif Faisal – *Terapi embolisasi intraarterial melalui kateter dengan infus berkesinambungan pada penderita hepatoma*

Terapi embolisasi intraarterial melalui kateter *(transcatheter arterial embolization)* merupakan upaya terapi alternatif pada penderita hepatoma yang sudah tidak dapat dilakukan terapi operasi *(unresectable hepatoma)*. Kemajuan dalam bidang kemoterapi mendorong dilakukannya terapi kombinasi embolisasi dengan infus intraarterial berkesinambungan *(continuous intraarterial infusion)*. Hasil yang dicapai dengan metode di atas cukup efektif, *cumulative survival rate* 66,6% untuk 6 bulan dan 55,4% untuk 1 tahun.

Efek samping terapi kombinasi lebih banyak, tetapi masih dalam batas-batas toleransi. Sebab kematian penderita hepatoma dalam penelitian ini terutama gagal hati *(hepatic failure)*.

Key Words: chemotherapy – arterial embolization – hepatoma – hepatic failure – infusion chemotherapy

INTRODUCTION

Hepatocellular carcinoma (HCC) or hepatoma is the most common form of primary hepatic carcinoma in Indonesia and Asian countries. Hepatoma is perhaps one of the most difficult diseases to treat because of the frequently associated cirrhosis, and patients with this neoplasm have a poor prognosis.

According to the report of The Liver Cancer Study Group of Japan (1979), only 9% of hepatoma patients underwent hepatectomy, because most cases are considered inoperable due to extreme tumor extention at the time of diagnosis. The one-year survival rate after surgery was only 28%. Chemotherapy produced the one-year survival rate 7% and the mean length of survival was 3–6 months.

With the progress in diagnostic procedures in recent years, small hepatoma have come to be detected earlier. Surgical technique has been improved along with development of new chemotherapeutic agents and improvement in the way of delivering drugs to cancer, therefore, the prognosis of these patients may have changed. In patients who had a small cancer (less than 25% of liver area in size) the median survival was 29.0 months. Transcatheter arterial embolization (TAE)

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gave a better survival compared with chemotherapy, whether intraarterial bolus administration of Mitomycin C, systemic Mitomycin C or oral/rectal Tegafur (Okuda *et al.*, 1985). In this study we evaluate 18 patients who have been treated with a new regimen of continuous intraarterial infusion followed by TAE, TAE only and intraarterial infusion only in advanced hepatocellular carcinoma.

PATIENTS AND METHODS

The patients in this study were treated with TAE, IAI (intraarterial infusion) or their combination, for advanced HCC, in the Department of Radiology, Hirosaki University Hospital, Hirosaki City. The study was conducted on 18 patients to whom the initial TAE or IAI treatment for HCC has been performed from June 1989 to June 1990.

Hepatic arteriography was performed prior to TAE and IAI to obtain information about the size, location and feeding arteries of the tumor. Arterial photography was performed to confirm that the main portal vein was not obstructed by tumor. A vascular catheter was inserted selectively in the hepatic artery or its branches that fed the tumor. Other feeding arteries were also embolized as necessary. Lipiodol suspension (3–15 ml) was mixed with Adriamycin (10–50 mg), Mitomycin C (4–20 mg) and CDDP 100 mg. A gelatine sponge (Gelfoam) was added in some cases. Under flouroscopic guidance, the embolic agent and anticancer drugs were injected slowly into the feeding artery through the catheter, until complete arrest of tumor arterial blood flow was noted. Careful and slow injection was needed to prevent backflow of the embolic agent into a proximal artery.

Intraarterial infusion (IAI) was performed as continuous infusion technique through a vascular catheter which was inserted via the femoral artery or a branch of the axillary artery. The tip of a vascular catheter was advanced to the proper hepatic artery. The regimen of anticancer drug infusion is as follows:

a. EEP: Epi-Afriamycin 30 mg/m^2 on day 1 and 6; Etoposide 60 mg/m^2 on day 3 to 5; CDDP (Cisplatin) 50 mg/m^2 on day 2 and 7.
b. EPF: Etoposide 40 mg/m^2 on day 1 to 5; CDDP 50 mg/m^2 on day 1 to 5; 5–Fluorouracil 500 mg/body on day 1 to 14;
c. Etoposide 75 mg 5 days.

The second regimen started 2 weeks after completing the first regimen. Investigation of the result of chemotherapy was done one month after the second course of infusion with USG, CT and MRI. After investigation of the therapy, TAE was performed to occlude the feeding artery with Lipiodol suspension, CDDP 100 mg and gelfoam pieces.

RESULTS

Eighteen patients in this study consisted of 15 males and 3 females, 78% of them with age 56–75 years old, ranging 29–82 between years, average 61.6 years. The main tumor in the liver was located mostly in segment 8, 7, 6, or 5 (Couinaud nomenclature), tumor size between 3 to 16 cm in diameter. The

tumors were measured by angiography and CT. All patients had multiple lesions in the liver.

There were 15 patients (83.3%) with hepatocellular carcinoma and they were associated with hepatic cirrhosis and 7 patients (38.9%) with diabetes mellitus. AFP level was higher in all patients (23 ng–50 000 ng/ml). Fourteen patients in this study showed marked decrease in the AFP level 2 weeks after treatment, but an increase in 4 patients. The survival time in three patients (cases 14, 15 and 18) with increased AFP level was less than 6 months.

HBsAg was positive in 2 patients and HCV (Hepatitis C Virus) was positive in 4 patients. TABLE 1 demonstrated the characteristics of the patients in this study.

TABLE 1.– Characteristics of 18 patients.

No.	Name	Sex	Age	Tumor Site	Therapy	AFP		HBsAg	HCV	DM	Cir.	Side Effect
						Pre	Post					
1	KN	F	82	S8,7,4	TAE	605	92	–	–	+	–	Fever
2	TY	M	54	S7,8,6	TAE	83	49	–	–	–	+	Abd. disc.
3	TO	M	60	S8,7	TAE	203	185	–	–	–	+	Fever
4	KN	M	60	S8,7,6,5,4	IAI/EEP	380	79	–	–	+	+	Diarrhea
5	CF	M	69	S8,4,6	TAE	320	77	–	+	+	+	None
6	TY	M	72	S8,7,5,6,4	IAI/Et+TAE	40	9	–	+	–	+	Fever, nausea, abd. disc.
7	TK	M	56	S2,4,7,8	IAI/EEP+TAE	79	36	–	+	–	–	Fever, nausea diarrh., l.a.
8	HS	M	67	S7,8,5	IAI/Et+TAE	750	400	–	–	–	+	Fever, l.a.
9	TS	M	65	S4,5,6	IAI/EEP+TAE	23	13	–	–	+	+	Nausea, vom., alopecia, b.m.supp., g.u.
10	EK	M	60	S5,7,4	TAE	44	13	–	–	–	+	None
11	FY	M	60	S6,5	TAE	420	510	–	–	+	+	Fever, vom.
12	MK	M	65	S4,5,8,7	TAE	940	440	–	–	+	+	Fever
13	SS	M	61	S7	TAE	26	20	–	–	–	+	Fever
14	FT	M	46	S2,3,4,7,8	TAE	6240	7860	–	–	–	+	Nausea, vom, abd. disc.
15	TJ	M	75	S3,8,7	TAE	7200	8700	–	–	–	+	Vom.
16	MY	M	66	S6,5,7,8,2	IAI/EEP,TAE	9260	168	–	–	–	+	Fever, abd. disc., alopecia, b.m.supp.
17	CK	F	62	S3,6,5,8	TAE	493	95	+	+	+	+	Abd. disc.
18	MI	F	29	RL	IAI/EEP+TAE	50000	60000	+	–	–	–	Fever, vom., l.a., alopecia, b.m.supp.

Note: abd. disc. = abdominal discomfort; vom. = vomiting; RL = right lobe.
b.m.supp. = bone marrow suppression; l.a. = loss of appetite;
diarrh. = diarrhea; g.u. = gastric ulcer;

Continuous intraarterial infusion followed by TAE has been performed in 6 patients; TAE only in 11 patients and IAI only in 1 patient. Correlation of treatment methods, staging of the tumor, liver function grade an survival were shown in TABLE 2.

According to TNM Classification, there were 14 patients (77.8%) in stage IVA, three patients (16.7%) in stage III and only one patient (5.5%) in stage II.

TABLE 2. – The correlation of treatment methods, tumor staging, liver function grade and survival.

Case Number	Treatment Methods	Tumor Staging	Function Grade	Survival
1	TAE	IV A	3	24 months, died
2	TAE	III	4	1 month, died
3	TAE	II	4	16 months, alive
4	IAI/EEP	IV A	5	1 month, died
5	TAE	IV A	4	14 months, alive
6	IAI/Et + TAE	IV A	4	19 months, died
7	IAI/EEP + TAE	IV A	4	3 months, died
8	IAI/Et + TAE	III	5	14 months, died
9	IAI/EEP + TAE	IV A	4	19 months, alive
10	TAE	IV A	3	15 months, alive
11	TAE	IV A	3	20 months, died
12	TAE	IV A	5	26 months, alive
13	TAE	III	5	11 months, alive
14	TAE	IV A	5	1 month, died
15	TAE	IV A	3	1 month, died
16	IAI/EEP + TAE	IV A	4	7 months, died
17	TAE	IV A	3	26 months, alive
18	IAI/EPF + TAE	IV A	4	4 months, died

Fever, nausea, vomiting and abdominal discomfort were found as common side effects of the treatment, and all side effects were higher in IAI + TAE treatment method (TABLE 3). Alopecia and bone marrow suppression are also the side effects due IAI + TAE treatment in two patients.

TABLE 3.– The side effects of treatment.

Side Effects	IAI + TAE	TAE	IAI	Total
Fever	5	5	–	10
Nausea/vomiting	4	3	–	7
Abdominal discomfort	2	2	–	4
Loss of appatite	3	–	–	3
Diarrhea	1	–	1	2
Alopecia	2	–	–	2
Bone marrow suppression	3	–	–	3
Gastric ulcer	1	–	–	1
Total	21	10	1	32

In this study, the cumulative survival rate was 66.6% at 6 months and 55.4% at 1 year. Seven out of 18 patients are still alive in about 1 year or more (FIGURE 1). Four patients died of hepatic failure, two patients died of GI bleeding and one patient died of hepatic failure and GI bleeding. The other 4 patients died of metastases and septic shock (TABLE 4). Hepatic failure and GI bleeding were the leading causes of death in this series (63.6%).

If recurrence of the main tumor was recognized, TAE was performed to control it. There were 8 patients in whom TAE was carried out more than once.

TABLE 4. – The causes of death in 11 patients

Causes of Death	IAI + TAE	TAE	IAI	Total
Hepatic failure	2	2	–	4
GI bleeding	–	1	1	2
Hepatic failure + GI bleeding	1	–	–	1
Lung metastases	1	–	–	1
Brain metastases	–	1	–	1
Lung & brain metastases	–	1	–	1
Septic shock	1	–	–	1
Total	5	5	1	11

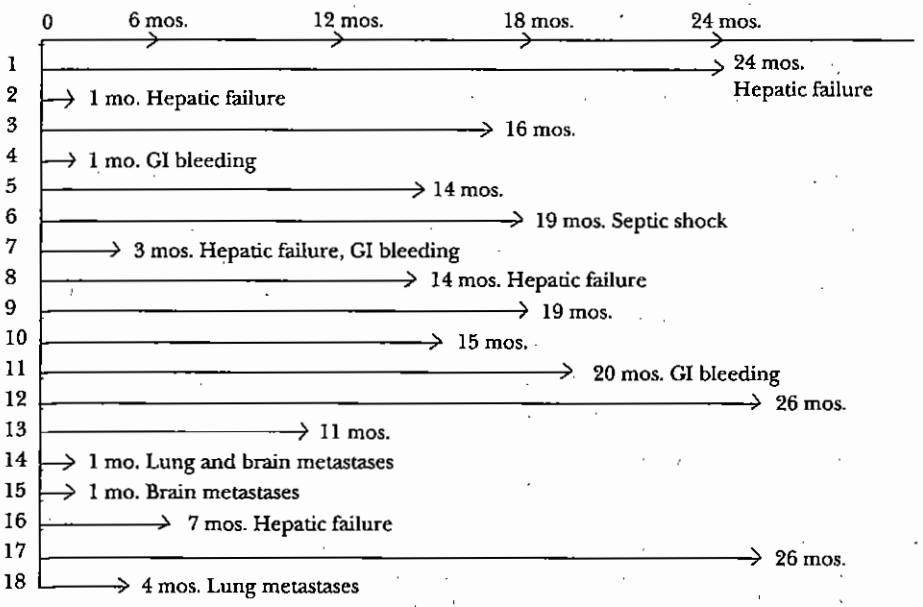

FIGURE 1. – Length of survival and cause of death.

DISCUSSION

The rationale for the use of hepatic arterial embolization in the treatment of hepatoma is that it is fed by arterial blood (Yamada *et al.*, 1983). The principle of TAE technique is to obliterate the feeding arteries for the tumor and cause its necrosis.

The result of treatment of hepatoma had been reported by many authors, and the methods of therapy and evaluation were different by different authors. Combination of TAE and anticancer drugs showed higher survival rate than TAE or anticancer drugs alone. Hirai *et al.* (1989) reported that the one-year survival rate for anticancer drugs only was 22% and the combination of TAE with anticancer drugs was 66.2%. Summary of the results of different treatment methods have been reported previously (Faisal, 1991).

Yamada *et al.* (1990) reported recently the result of combination of TAE and Adriamycin and Mitomycin C without iodized oil; the cumulative one-year survival rate was 51%. Beside that, some cases of small hepatoma with diameter less than 5 cm were treated by TAE only (because of the presence of advanced liver cirrhosis) and their one-year survival rate was 72%. Of course, the result of TAE in small hepatoma was excellent, because TAE was very effective on main nodules, but has little effect on daughter nodules (small intrahepatic metastases), tumor emboli in the portal or hepatic vein and intracapsular invasion (Nakamura *et al.*, 1988).

According to Sasaki *et al.* (1987) the effectiveness of TAE with Cisplatin and Gelfoam in hepatoma before hepatic resection was in 65% of the patients the tumor size was reduced to less than 50% of that before therapy. Histological findings showed 75% of the main nodules were completely necrotic and the necrosis of daughter nodules, tumor embolus in the portal vein or hepatic vein, intracapsular and extracapsular invasion were detected. The concentration of platinum in the tumor tissue was significantly higher than that in the non-tumorous tissue.

According to the report by Nakamura *et al.* (1989) the results of transcatheter oily chemoembolization of hepatoma using Doxorubicin as anticancer drug, its tissue concentration in the tumor and non-tumor were different. In all patients, concentrations of Doxorubicin were higher in tumor tissues, and the drug remained in tumor tissues with iodized oil acting as the carrier of the anticancer drug. In their report, the cumulative survival rate was 82% for 6 months and 53.8% for 1 year. These survival rates were better than those patients who underwent embolization with gelatin sponge, then received an anticancer drug (67.4% for 6 months and 45.2% for 1 year).

Yodono *et al.* (1989) reported the efficacy of TAE in using Cisplantin (CDDP) mixture with Lipiodol suspension. Higher rate of tumor regression were obtained with the simple mixture of Cisplatin and with Cisplatin/Adriamycin, indicating that the antitumor effect of these mixtures were greater than those of Adriamycin/Mitomycin C mixtures. In this report it was stated that the effect of chemoembolization on daughter nodules was not significant.

Small nodules such as daughter nodules and intrahepatic metastases do not have capsules, and so have a blood supply that makes them resistent to conventional TAE therapy (Wakasa *et al.*, 1990). Participation of the portal vein as a feeding vessel is essential to explain the differences seen between the primary tumors and the satellite nodules. The existence of a tumor capsule seems to be related to the efficacy of arterial embolization and chemoembolization.

The regimen in performing intraarterial infusion for hepatoma have been created by many centers. Charnsangavej *et al.* (1990) used the regimen as follows: 5-day infusion of Floxuridine (100 mg/m^2 for each day), Doxorubicin (40 mg/m^2 for 2 hours on day 1), and Mitomycin C (10 mg/m^2 for 2 hours on day 2). When the patient is jaundiced, the dose of Doxorubicin can be reduced to 10 mg/m^2. The treatment is repeated every 4 weeks. A response rate is 62% with a median survival of 11.5 months. In our study, we used a different regimen with some other anticancer drugs and then followed by TAE after 2–course of

intraarterial infusion. In recent study about continuous intraarterial infusion chemotherapy using the different regimen showed partial regression of hepatoma in 50% patients (Yodono, personal communication).

The Liver Cancer Study Group of Japan (1984) reported the histologic findings of hepatoma 55.6% were of massive type and angiography demonstrated hypervascular lesions in 89.2%. HBsAg was positive in 34.1%, and 78% of the cases were associated with cirrhosis. Hepatic failure was reported as the leading cause of death in hepatoma. The results of our study is similar to this report.

Liver cirrhosis is commonly underlying hepatoma (including in our study). Chuang *et al.* (1990) reported that natural killer cell activity was markedly decreased in hepatoma and liver cirrhosis. It was suggested that the decreased activity might be related to the coexistent liver disease and might be one of the causes for the early development and invasion of hepatoma.

High incidence of fever, nausea and vomiting as side effects of treatment were detected in this study and these were also reported by Yamada *et al.* (1990) and Nakamura *et al.* (1989). Fever may be considered to be caused by resorption of the necrotic tumor tissue. These side effects are transient and usually slight.

CONCLUSION

The result of this study suggests that transcatheter arterial embolization (TAE) and continuous intraarterial infusion chemotherapy or combination of both methods are effective therapy for advanced hepatocellular carcinoma.

The cumulative survival rates were 66.6% at 6 months and 55.4% at 1 year. Hepatic failure and GI bleeding were the leading causes of death.

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