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TACE and Continuous Intraarterial Infusion Chemotherapy in Advanced Hepatocellular Carcinoma

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INTISARI

Arif Faisal – *Kemoembolisasi dan kemoterapi pada karsinoma hepatoselular*

Penelitian ini mengemukakan dua cara terapi pada karsinoma hepatoselular lanjut serta membandingkan hasil yang dicapai pada 20 pasien. Berdasarkan respon tumor masing-masing setelah terapi, ternyata kemoterapi dengan infus berkelanjutan menunjukkan hasil yang lebih baik dan lebih efektif. Akan tetapi cara pengobatan itu juga menyebabkan efek samping yang lebih berat.

Kedua cara terapi di atas memberikan angka ketahanan hidup (*survival rate*) 70% untuk 6 bulan dan 40% untuk 1 tahun. Sebagian besar pasien dalam penelitian ini mengalami gangguan fungsi hepar yang berat dan stadium penyakit sangat berperan terhadap hasil terapi.

Key Words : hepatocellular carcinoma – transcatheter arterial chemoembolization – infusion chemotherapy – anticancer drugs – angiography

INTRODUCTION

Primary liver cancer or hepatocellular carcinoma (HCC) or hepatoma has a very poor prognosis for patients. Approximately 80% of patients with this malignancy are associated with hepatic cirrhosis.

Several modalities have been performed to improve the survival rate of patients to gain the quality of life. Surgical resection of the liver is the treatment of choice, but indication for operation is limited due to the highly advanced state of the tumor and the severe hepatic dysfunction. Only 9% to 28% of patients with HCC could be candidated for surgical treatment and the median survival were 21.6 to 46 months (The Liver Cancer Study Group of Japan, 1979 & 1984; Okuda *et al.*, 1977; Patt *et al.*, 1988).

The unresectable HCC chemotherapy showed a less efficacy in comparison with transcatheter arterial embolization (TAE) in combination with anticancer drugs and

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iodized oil (Hirai *et al.*, 1989; Takayasu *et al.*, 1989). Recently, continuous hepatic arterial infusion of anticancer drugs had been developed and it seemed to be effective in main tumor and daughter nodules (Tarusawa *et al.*, 1990, Yodono *et al.*, 1989).

In this study, the results of treatment using continuous hepatic arterial infusion of anticancer drugs followed by TAE and the results of transcatheter arterial chemoembolization (TACE) in advanced hepatocellular carcinoma will be evaluated. The tumor response and the side effects will also be discussed.

MATERIALS AND METHODS

Twenty patients with advanced HCC, who were treated with intraarterial infusion and TACE from July 1990 to June 1992, at the Department of Radiology, Hirosaki University Hospital School of Medicine, Hirosaki City, Aomori-ken, were retrospectively studied. The patients who had recieved previous therapy with percutaneous ethanol injection (PEI) into the tumor were not included in this study. The diagnosis of HCC was established by a combination of sonography, computerized tomography (CT), magnetic resonance imaging (MRI) angiography, biopsy, and alfa-fetoprotein (AFP) assays. Retrospective and randomized study will be done to these patients.

Intraarterial infusion chemotherapy was carried out to 10 patients as continuous infusion method through a vascular catheter (4-5 Fr). The catheters were inserted via femoral artery by Seldinger's technique or into the proper hepatic artery through the aortic arch and descending aorta via the left thoraco-acromial artery by cut-down method. The regimen of anticancer drugs were EEP protocol, consisted of Epi-adriamycin 30 mg/m^2 on day 1 and 6, Etoposide 60 mg/m^2 on day 3 to 5, and Cisplatin (CDDP) 50 mg/m^2 on day 2 and 7. The second regimen started 3 weeks after completing the first regimen. All patients had 2 courses of therapy. Evaluation of the results of chemotherapy was done one month after the second course of infusion with sonography, CT and MRI. Laboratory examination was performed every week. TAE was performed after evaluation of therapy to occlude the feeding artery with Lipiodol suspension, CDDP 100 mg and gelatine sponge (gelfoam) pieces.

TACE therapy was performed in other 10 patients by inserting 4-5 Fr arterial catheter via femoral artery by Seldinger's technique. The tip of the catheter was located selectively in the hepatic artery or its branches wich fed the tumor. Another feeding arteries were also embolized if needed. The mixture of anticancer drugs with Lipiodol suspension were injected slowly into the feeding artery, through the catheter under fluoroscopic control, until complete arrest of tumor arterial blood flow was noted. The anticancer drugs that had been used were as follows: Adriamycin 30 mg (2 patients); Epi-adriamycin 40 mg (1 patient); Farmorubicin 18-60 mg (4 patients); Mitomycin C 3-10 mg (4 patients); SMANCS (Styrene-maleic acid neocarzinostatin) 7 ml (1 patient). Some patients received more than one anticancer drugs. Gelfoam pieces were added to TACE technique in most of the patients. Evaluation of the results were done one week and one month after TACE therapy by sonography, CT, and MRT.

The evaluation of the results of therapy in both methods were focused on the tumor regression, which calculated from the tumor size before and after therapy by imaging technique. The regression of the tumor was defined as follows: CR (complete regression) was the disappearance of the tumor mass; PR (partial regression) was a 50% or greater

reduction; MR (minor regression) was a 25% to 50% reduction; NC (no change) was less than 25% reduction, or when the tumor continued to grow less than 25% of the tumor size; PD (progressive disease) if the tumor continued to grow greater than 25% of the tumor size.

Staging of the hepatic tumor was based on TNM classification as follows, stage I: T1 N0 M0; stage II: T2 N0 M0; stage III: T3 N0 M0 or T1-3 N1 M0; stage IVA: T4 N0–1 M0; stage IVB: T1–4 N0-1 M1 (Sugahara & Tobe, 1988).

The liver function grade has been adjusted to the limits of laboratoric parameters for blood examinations, which was applied by the Department of Radiology, Hirosaki University Hospital. The liver function grade was set in 5 grades of conditions as demonstrated in TABLE 1. The grade of the liver function depends on the laboratoric data values of the patients. Each grade needs more than three abnormal value of laboratoric data.

The efficacy of continuous intraarterial infusion using EEP anticancer drugs and TACE therapy was assessed, especially on tumor response rate, survival and side effects of anticancer drugs.

TABLE 1. – Laboratoric parameters for liver function grade

	Data	1	2	3	4	5
Alb.	(g/dl)	4.0	3.5	3.0	2.5	2.5
T Bil.	(mg/dl)	0.5	1.0	2.0	3.0	3.0
ChE	(u/l)	1000	800	600	300	300
	(pH)	1.0	0.8	0.6	0.3	0.3
PT	(%)	100	80	60	40	40
KICG	(/ml)	0.15	0.10	0.06	0.03	0.03
ICGRmax	(mg/kg/min)	2.0	1.0	0.4	0.2	0.2
HPT	(%)	100	70	50	30	30

Note: Alb = Albumin (N:3.8-5.0)
T Bil. = Total bilirubin (N: 0.2-1.2)
ChE = Cholinesterase (N: 800-1800)
PT = Prothrombin time (N: 70-140)
KICG = Disappearance ratio of ICG (N: 0.168-0.206)
ICGRmax = Indocyanin green test in maximal dose (N: over 2)

RESULTS

Twenty patients in this study were divided into 2 groups treated by 2 methods of treatment: 10 patients were treated with continuous intraarterial infusion chemotherapy and 10 patients with TACE therapy. The location of the tumors were mainly in the segment 5, 6, 7, 8 (Couinaud nomenclature) and most patients had multiple daughter nodules, and one patient with hepatic vein invasion. Patients characteristics of the two groups are shown in TABLE 2.

The intraarterial infusion method using EEP anticancer drugs was done in 7 males and 3 females patients, the median age is 57 (ranging from 41–74) years old. In this method 8 patients had liver cirrhosis, HBsAg was positive in one patient, but HCV was positive in 5 patients. It was also recorded the coincidence of diabetes mellitus (3 pa-

TABLE 2. – Patients characteristics and the therapy methods

	EEP infusion	TACE
Total no. of patients	10	10
Males: females	7 : 3	10 : 0
Median age (yr)	57 (range: 41-74)	64 (range: 52 - 77)
Liver cirrhosis	8	10
HBsAg positive	1	1
HCV positive	5	9
Diabetes mellitus	3	6
Ascites	1	2
9AFP (ng/ml):		
before therapy	70 - 270.000	320 - 1.230.000
after therapy	12 - 132.000	36 - 1.010.000

Note: HBsAg : Hepatitis B surface antigen
HCV : Hepatitis C virus
AFP : Alfa-fetoprotein

tients) and ascites (1 patient). AFP level was high in all patients. The decrease of AFP level to normal limits was observed in 4 patients only, but all patients had AFP level decreased after completing the therapy. In overall 20 courses of EEP infusion had been performed.

There were 10 males in the TACE therapy group. The median age was 64 (ranging from 52–77) years old. All of the patients were associated with liver cirrhosis, only one patient was HBsAg positive and 9 patients were HCV positive. Diabetes mellitus was found in 6 patients and 2 patients with ascites. AFP level was very high in one patient (1.230.000 ng/ml) and all patients in this group had a high AFP level. After TACE therapy, AFP level decreased in 8 patients, none of them reach the normal limits, and increased in 2 patients.

The stage of tumor in the EEP infusion therapy patients were very advanced, all of them within the stage III to IVB (100%). However, in TACE therapy only 50% were in the same stage. The liver function grade of the EEP patients were 50% in grade 4 to 5, on the other hand only 20 % of the TACE therapy patients was in the same grade. Therefore, the patients treated with EEP infusion were in more advanced disease with severe dysfunction of the liver. TABLE 3 demonstrates the tumor stage and liver function grade of the patients.

The tumor regression after EEP infusion and TACE therapy can be seen in TABLE 3. In patients who received EEP infusion therapy, the response rate were: CR, PR, MR, and NC, in 1, 3, 2, and 4 patients, respectively. It means, with EEP infusion method produced CR and PR 40% of the patients. TACE group patients demonstrated none with CR, PR in 1 patient, MR 2 patients, and NC 6 patients. In this method NC was higher than EEP infusion therapy.

Ten patients died at the end of this study, 6 in EEP infusion therapy and 4 in TACE therapy (TABLE 4). All of the death patients in EEP group were in the stage III to IVB and the liver function grade are 3 to 5. Advanced stage of the tumor and a very low hepatic functional reserve in the remaining liver were indications of very poor condition of those patients. Therefore, the death cases was higher in this group.

TABLE 3. – Tumor stage, liver function grade and tumor regression in 20 patients.

	EEP	%	TACE	%
Tumor stage				
II	0	0	5	50
III	6	60	2	20
IVA	2	20	2	20
IVB	2	20	1	10
Total	10	100	10	100
Liver function grade				
2	2	20	2	20
3	3	30	6	60
4	4	40	2	20
5	1	10	0	0
Total	10	100	10	100
Tumor regression				
CR	1	10	0	0
PR	3	30	1	10
MR	2	20	2	20
NC	4	40	6	60
PD	0	0	1	10
Total	10	100	10	100

CR : complete regression MR : minor regression PD : progressive disease
PR : partial regression NC : no change

TABLE 4. – Tumor stage, liver function grade and tumor regression in 10 died patients.

Tumor Stage	EEP	TACE	Liver Function	EEP	TACE	Tumor Regression	EEP	TACE
II	0	0	2	0	0	CR	0	0
III	3	2	3	1	3	PR	2	0
IVA	1	1	4	4	1	MR	1	0
IVB	2	1	5	1	0	NC	3	3
						PD	0	1
Total	6	4	Total	6	4	Total	6	4

The survival period of all patients for 6 months and one year were 70 and 40% respectively. One patient was still alive 24 months after TACE therapy and one patient after EEP infusion therapy was alive for 20 months. Among the died patients, tumor recurrence as a cause of death were in 6 patients, 1 patient with pulmonary metastasis, 1 patient died by hepatic failure, and 2 patients died outside the hospital with unknown causes. FIGURE 1 demonstrates the survival time, tumor regression and the cause of death.

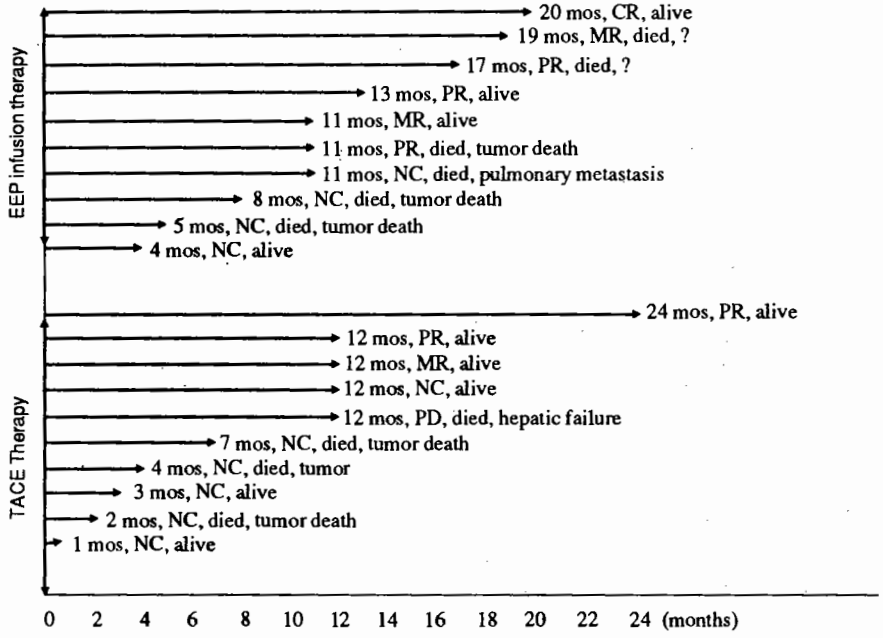

FIGURE 1. – The length of survival, tumor regression and cause of death.

The side effects of the treatment were also observed in this study. These side effects were higher in the EEP infusion method than the TACE. Abdominal pain and nausea/vomiting occured in both methods of therapy, but the incidence of fever seemed to be higher in TACE therapy. Pancytopenia, alopecia and lost of appetite were significantly predominant in EEP infusion method. Renal failure occured in one patient. Blood BUN and creatinine levels were 47 and 2.7 mg/dl respectively, after the second course of EEP infusion therapy; no spesific treatment had been given to this patient, except glucose and normal saline solution until BUN and creatinine levels decreased. This patient died 10 months later by tumor recurrence. Most of the side effects in this study were mild to moderate and still tolerable. TABLE 5 summarized the side effects of therapy for both method in 20 patients in this study.

TABLE 5. – The side effects of therapy.

Side effect	EEP	TACE
Abdominal pain	8	9
Fever	3	7
Nausea/vomiting	6	6
Pancytopenia	8	0
Alopecia	8	0
Lost of appetite	2	0
Renal failure	1	0

DISCUSSION

Hepatic chemoembolization could be defined as the simultaneous infusion of chemotherapy and embolic agents with dual aim of provoking tumor ischemia and increasing the dwelling time of the drugs. The basic mechanism of therapeutic effect was thought to be the combination of selective embolization by iodized oil at the level of the neovasculature in the tumor, and the selective delivery of the long-acting or slow releasing anticancer agents.

There were three factors permitting the safety and effectiveness therapy of hepatic tumor with percutaneous transcatheter arterial embolization. The liver had dual blood supply, the liver tumors were supplied by the hepatic artery and the portal vein, and the catheterization technique was accessible percutaneously into the hepatic artery circulation (Pentecost *et al.*, 1992).

After Nakakuma *et al.* (1983) reported intraarterial administration of iodized oil, Lipiodol (Laboratorie Guerbet, Aulnaysous-Bois, France) were used as an embolic material to treat advanced HCC. Since then, TAE therapy using Lipiodol in combination with anticancer drugs were applied for hepatic neoplasm. The efficacy of Lipiodol and anticancer drugs (TACE) to prolong survival rate of HCC patients had been reported by Hirai *et al.* (1989), they were 66.2% for 1 year and 36.5% for 2 years; and Takayasu *et al.*(1989) reported also 53 and 24% for 1 and 2 years, respectively.

The limitation of embolization in treating HCC were the presence of tumor thrombi in the branches of the portal vein, very big tumor, relatively hypovascular tumor and the nonencapsulated tumor (Sato *et al.*, 1985; Yang *et al.*, 1989; Wakasa *et al.*, 1990).

Intravascular administration of anticancer drugs had been used to control hepatic tumor and intrahepatic invasion. The results of the treatment were varied. The methods of therapy as well as anticancer drugs toxicity had a great influence on the prognosis. Sciarrino *et al.* (1985) reported the limited efficacy of intravenous injection of Adriamycin in HCC, its cumulative survival rate was 34% for 6 months and 13% for one year. Melia *et al.* (1983) studied the efficacy of intravenous administration of Etoposide and Adriamycin in HCC, the response rate showed 18% in Etoposide and 28% in Adriamycin regimen. Both regimens could not produce a significant difference in survival rate. Another study was done by Patt *et al.* (1988) with a conclusion that intraarterial route was more effective and had a better response than intravenous injection. The response rate reported were 73% in the intraarterial administration of anticancer drugs, but only 4% in the intravenous route.

In this study continuous intraarterial infusion chemotherapy using EEP regimen showed CR and PR in 40% (4 of 10) patients. Most patients in TACE therapy had lower response rate or NC (6 of 10 patients), and CR could not be seen in this group. Yodono *et al.* (1989) treated advanced HCC patients in two groups with different anticancer drugs regimen, the results demonstrated that CR and PR were 46% in one group and 53% in the other group of patients.

Although 90% of all patients in this study associated with liver cirrhosis and hepatic virus infection, 80% of EEP and 60% of TACE patients survived for 6 months. But, it was lower in EEP therapy with survival time for 1 year. Reducing of the hepatic functional reserve and the very advanced of hepatic tumor making unable to enhance the

survival period. They were the reasonable causes of death for a higher total death in the EEP therapeutic patients.

Pancytopenia, as a myelosuppression effect due to drug toxicities, occurred in most patients with EEP infusion therapy. This side effect was also reported by Melia *et al.* (1983) and Yodono *et al.* (1989). One patient in this study, as reported also by Kajanti *et al.* (1986), developed renal failure after EEP infusion and it might be related to tubular necrosis of the kidney in using Cisplatin. Hydration of patient, to prevent kidney damage, should be maintained prior and after drug infusion. Various side effects in both treatment methods were similar to other reports (Nakamura *et al.*, 1989; Yamada *et al.*, 1990). Most of mild and moderate side effects were tolerable and could be inhibited by conventional treatment.

CONCLUSIONS

1. Although the number of patients were small, this study concludes that continuous intraarterial infusion chemotherapy (EEP regimen) and TACE therapy were effective to treat advanced hepatocellular carcinoma (HCC). Patients with favorable prognostic factors have a possibility to gain the survival period.
2. Regarding to the response of tumor could be seen on the efficacy of continuous intraarterial chemotherapy. Complete regression were obtained in a higher percentage by selective infusion chemotherapy method.
3. The survival rate of all patients with both treatment methods were 70 and 40% in 6 months and 1 year respectively. Patients with severe hepatic dysfunction and more advanced hepatic tumor could not have a longer survival.
4. Bone marrow suppression (pancytopenia) and alopecia were predominant side effects in patients with continuous intraarteral infusion therapy. Reversible renal failure also occurred in one of this group of patients. Abdominal pain and fever seemed to be higher in TACE therapy.

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