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Comparison of the anticancer effect of ADMOS alone and ADMOS with CDDP in the treatment of hepatocellular carcinoma by intra-arterial injection

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Summary. A total of 135 patients with hepatocellular carcinoma (HCC) were treated by intra-arterial injection of an Adriamycin/mitomycin C oil (lipiodol) suspension (ADMOS) alone or of ADMOS plus *cis*-diammine-dichloroplatinum (CDDP). In all, 59 patients were treated with ADMOS alone and 76 were treated with ADMOS plus CDDP. A reduction of more than 25% in the tumor size was obtained in 13 of 38 (34%) evaluable patients in the former group and in 39 of 76 (51%) evaluable patients in the latter group. Serum alpha-fetoprotein (AFP) levels decreased by more than 50% in 10 of 17 (59%) and 23 of 33 (70%) patients in the respective groups whose pretreatment AFP level was estimated to be over 200 ng/ml. Overall, the 1-year survival value was 68% and the 2-year value was 41% as determined by the Kaplan-Meier method. No statistically significant difference in survival was observed between the two groups. The initial tumor response correlated with the survival value. No severe complication was encountered except for one case of liver abscess formation. No serious change in the laboratory data was observed following treatment with these regimens. Although the tumor response was significantly better in patients treated with ADMOS combined with CDDP injection than in those treated with ADMOS alone ($P < 0.05$), no significant difference in survival was found between the two groups.

Introduction

Transcatheter arterial embolization (TAE) has been widely used for the treatment of liver tumors, and its therapeutic effectiveness is well recognized. However, TAE has some drawbacks such as severe complications and a higher tendency toward collateral vessel formation [2, 10]. On the other hand, following its injection into the hepatic artery, lipiodol is retained in HCC for long periods [7, 11]. On the basis of this observation, combinations of lipiodol with anticancer drugs such as ADMOS have been used widely for the treatment of HCC. We have also reported our experience with this method in treating HCC [3, 6] and metastatic liver cancer [5].

The therapeutic effectiveness of CDDP as an intra-arterial infusion material has also been reported for the therapy of various cancers, including HCC [8, 9]. The purpose of the present study was to evaluate the effectiveness of CDDP given in combination with ADMOS in the treatment of HCC.

Patients and methods

In all, 59 patients were treated by intra-arterial injection of ADMOS alone (ADMOS-alone) and 76 were treated with ADMOS plus CDDP injection (ADMOS+CDDP). The patients were selected randomly and included various stages of HCC. Table 1 shows the clinical features of both groups.

The diagnosis of unresectable HCC was made by liver biopsy, CT examination, angiography, ultrasonography, measurement of alpha-fetoprotein (AFP) levels, and assessment of the clinical course. ADMOS was prepared by a simple method of dispersing Adriamycin and/or mitomycin C into lipiodol mixed with aluminum monostearate, which serves as a dispersing stabilizer, and was produced under continuous heating at 130° C for 30 min. Under fluoroscopic guidance, a 4.6- to 5.5-F polyethylene catheter was inserted into the proper hepatic artery or a more peripheral branch supplying the liver tumor. ADMOS was carefully infused through the catheter at a rate of 1 ml/min (59 cases, 94 infusions). In the ADMOS + CDDP group, CDDP was injected before or after ADMOS infusion at a rate of 10 mg/min at the same catheter position (76 cases, 179 treatments).

The initial tumor response was evaluated in 114 patients (38 treated with ADMOS alone and 76 treated with ADMOS + CDDP) by CT over a period of 3 months, and the reduction rate was measured by comparing the findings obtained before and after the initial therapy. Measurements were made at the same scanning level, i.e., at the maximal tumor diameter.

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Table 1. Treatment groups

	ADMOS-alone[a]	ADMOS + CDDP[b]
Number of patients	59	76
Sex (M/F)	49/10	63/13
Mean age (years)	59.9	59.2
Total number of injections	94	179
Mean number of injections/patient	1.6	2.3
Mean dose in a single injection:		
Adriamycin (mg)	16.2	10.5
Mitomycin C (mg)	12.5	7.8
Lipiodol (ml)	6.0	3.7
CDDP (mg)	–	135.7

[a] Group treated with Adriamycin/mitomycin C oil suspension
[b] Group treated with Adriamycin/mitomycin C oil suspension plus *cis*-diamminedichloroplatinum

In patients whose pretreatment AFP levels were over 200 ng/ml (17 in the ADMOS-alone group and 33 in the ADMOS + CDDP group), the serial changes in serum AFP were evaluated to judge the anticancer effect. Survival values were calculated according to the Kaplan-Meier method. For evaluation of the therapeutic benefit of adding CDDP, the difference between the survival of the ADMOS-alone group and that of the ADMOS + CDDP group was analyzed statistically.

Results

Tumor response

Table 2 shows the tumor response in the two groups. In the ADMOS-alone group, a reduction of over 25% in the tumor size was observed in 13 of 38 (34%) evaluable patients, whereas in the ADMOS + CDDP group, 39 of 76 (51%) evaluable patients showed at least a 25% reduction. The superiority of ADMOS + CDDP was statistically significant ($P < 0.05$).

A tumor response was also observed in terms of serial changes in serum AFP levels. Excluding patients with a baseline value of less than 200 ng/ml, a decrease of more than 50% in AFP levels was observed in 10 of 17 (59%) patients in the ADMOS-alone group and in 23 of 33 (70%) subjects in the ADMOS + CDDP group. Thus, from the viewpoint of the tumor response, the anticancer effect was better in the ADMOS + CDDP group than in the ADMOS-alone group.

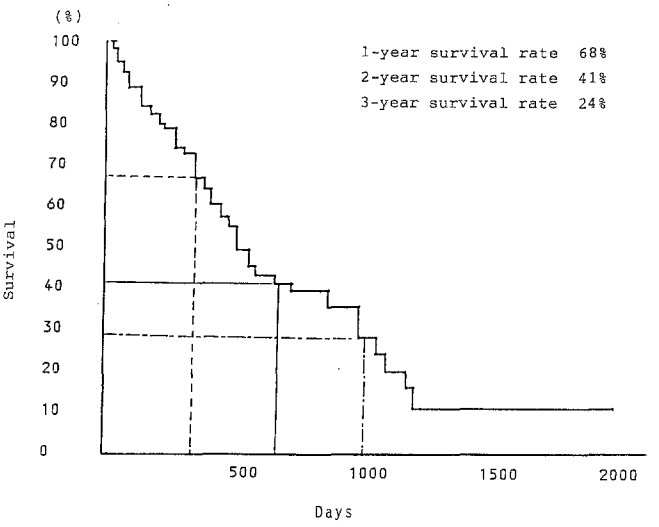

Fig. 1. Survival curve generated for all 135 HCC patients treated by intra-arterial infusion of ADMOS or ADMOS + CDDP

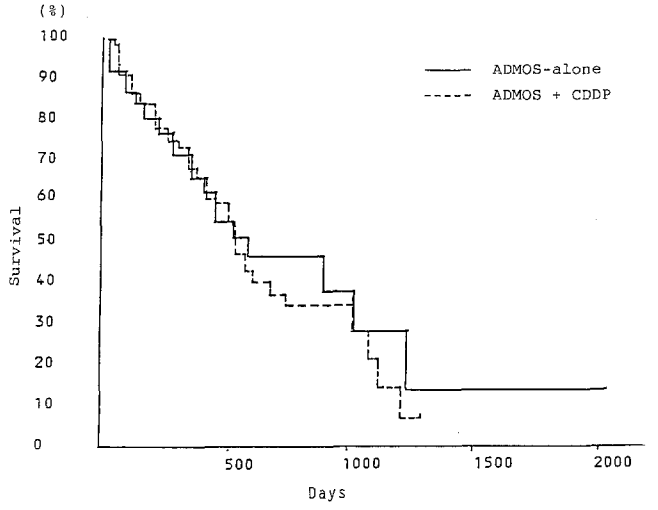

Fig. 2. Survival curves constructed for the ADMOS-alone group ($n = 59$) and the ADMOS + CDDP group ($n = 76$)

Survival

Figure 1 shows the overall survival curve generated for all patients. For all 135 patients in this study, the 1-year survival value was 68%, whereas the 2- and 3-year values were 41% and 24%, respectively. Figure 2 shows the sur-

Table 2. Tumor reduction on CT after intra-arterial therapy

Regimen	Partial response	Minimal response	No change	Progressive disease
ADMOS-alone ($n = 38$)	3 (8%)	10 (26%)	18 (47%)	7 (18%)
ADMOS + CDDP ($n = 76$)	18 (24%)	21 (28%)	27 (36%)	10 (13%)
Totals ($n = 114$)[a]	21 (18%)	31 (27%)	45 (39%)	17 (15%)

Partial response, a reduction of 50%–100% in the tumor size; minimal response, a reduction of 25%–50% in the tumor size; no change, a reduction of 0–25% in the tumor size

[a] Excludes cases lacking a baseline value or follow-up CT and unevaluable cases

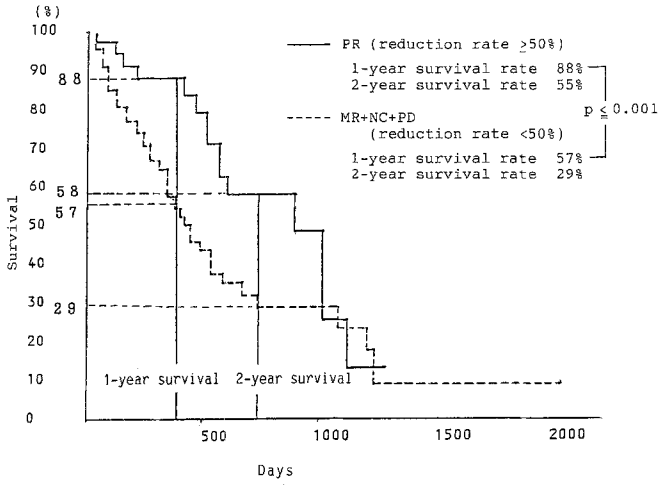

Fig. 3. Survival curves generated for the initial response of the PR group ($n = 21$) and the MR+NC+PD group ($n = 95$)

vival curve as a function of treatment. No statistically significant difference in survival was found between the ADMOS-alone group and the ADMOS + CDDP group (Fig. 2). However, the initial tumor response correlated significantly with the survival value (Fig. 3).

Side effects

Table 3 shows the type and incidence of side effects. One patient who received multiple injections experienced abscess formation and a high fever due to destruction of the bile ducts, but this complication was improved by medication with antibiotics. Another patient who had poor liver function prior to therapy developed a liver disorder. No other severe complication was encountered in either therapy group. A small number of patients complained of fever, nausea, and abdominal pain, but these symptoms were mild and reversible by medication. Transient abnormalities in blood laboratory data were also observed in some cases. The incidence of minor complications other than fever was higher in the ADMOS + CDDP group than in the ADMOS-alone group.

Table 3. Incidence of side effects following 94 treatments with ADMOS and 179 treatments with ADMOS + CDDP

Side effect		ADMOS-alone (%)	ADMOS + CDDP (%)
Symptomatic:			
Nausea/vomiting		26	45
Fever		24	8
Abdominal pain		13	18
Peptic ulcer		1	2
Liver abscess		0	1
Liver disorder		2	1
Laboratory data:			
Hepatic:			
GOT	(>200 KU)	12	25
GPT	(>200 KU)	9	23
ChE	(<800 WU)	19	28
T-bilirubin	(>3 mg/ml)	18	17
Hematologic:			
WBC	(<3 × 10^3/mm^3)	26	29
RBC	(<3 × 10^6/mm^3)	36	48
PLT	(<8 × 10^4/mm^3)	19	29
Renal:			
BUN	(>300 mg/l)	12	19
Creatinine	(>20 mg/l)	3	16

PLT, Platelet count

Discussion

Recently, the prognosis of liver cancers has been improved by the introduction of hepatic arterial embolization techniques. Because the indication for hepatic resection is limited [1], the therapeutic usefulness of TAE in controlling the tumor growth is well recognized.

However, TAE has a few disadvantages as compared with arterial infusion therapy: (1) the indications for cases with a tumor thrombus in the proximal portal vein are limited; (2) collateral circulation develops readily; (3) if permanent occlusion develops, further transarterial approaches are nearly impossible; and (4) the incidence of severe complications seems to be higher [2, 10].

For these reasons, we are likely to choose infusion therapy using ADMOS and/or CDDP without the injection of embolic material for the treatment of liver tumors at our institution. We have obtained clinically satisfactory results in comparison with previous reports on the treatment of HCC by TAE [3, 6].

In the present study, the tumor response in the ADMOS + CDDP group was superior to that in the ADMOS-alone group, and no difference in the incidence of side effects was observed between the two groups. On the other hand, from the viewpoint of survival, no statistically significant difference was found between these two groups. The initial tumor response correlated with the survival value, regardless of the therapy used. The discrepancy between the superiority of the tumor response and the lack of improvement in survival observed for ADMOS combined with CDDP must be individually examined in more detail.

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