Cancer Chemother Pharmacol (1994) 33 (Suppl): S 134–S 138

Cancer Chemotherapy and Pharmacology

Repeated arterial infusion chemotherapy for inoperable hepatocellular carcinoma using an implantable drug delivery system

Takashi Iwamiya, Satoshi Sawada, Yoshio Ohta

Department of Radiology, Tottori University Hospital, Tottori, Japan

Abstract. Arterial infusion chemotherapy has become one of the major treatments for malignant tumors. Since 1988, we have attempted repeated arterial infusion of anticancer drugs using an implantable drug delivery system in 68 patients who had inoperable hepatocellular carcinoma (HCC). Most of our patients could not undergo transcatheter arterial embolization (TAE) because of extreme tumor extension and/or accompanying advanced liver cirrhosis. In most patients we implanted a 5-F catheter via the femoral artery nonsurgically and connected it to a subcutaneously implanted drug delivery system without any difficulty. The treatment consisted of weekly or biweekly intrahepatic one-shot administration of anticancer drugs. As one therapeutic regimen, epirubicin was given alone. Other regimens consisted of combined chemotherapy using two or more of the following drugs: mitomycin C, Adriamycin, 5-fluorouracil, cisplatin, and epirubicin. In some cases, these drugs mixed with Lipiodol were given for targeting and slow release in the liver. The response rate (CR+PR) of the cases was 25.0%. The median survival period was 389.9 days. The 6-month, 1-year, and 2-year survival rates were 75%, 45%, and 17%, respectively. There was no severe side effect or complication except arterial occlusion that precluded further infusion chemotherapy. We think that the implantable drug delivery system will contribute not only to improved therapeutic efficacy for inoperable HCC but also to an improved quality of life for the patients.

Introduction

For inoperable hepatocellular carcinoma (HCC), transcatheter arterial embolization (TAE) and intra-arterial and systemic chemotherapy have been the main conservative therapies [3–5, 14, 19]. However, intra-arterial chemotherapy has usually been carried out as one-shot administration of an anticancer drug(s). Recently, improvement in the material of catheters and the development of an implantable drug delivery system (IDDS) have enabled us to perform long-term arterial infusion chemotherapy on an outpatient basis [7]. In the present study, we applied an IDDS to 68 patients with inoperable HCC and investigated its therapeutic effects.

Patients and methods

From January 1988 to November 1992, a total of 68 patients with inoperable HCC were treated by repeated arterial infusion chemotherapy using an IDDS. Table 1 shows the characteristics of the patient population. The patients included 58 men and 10 women whose age ranged from 28 to 87 years. All of them were unable to undergo surgery for some reason, including the tumor size, tumor extension, metastasis, advanced liver cirrhosis, and/or recurrence after hepatic resection. According to the general rules for primary liver cancer established by the Liver Cancer Study Group of Japan [12], there were 3 cases of stage I disease, 8 cases of stage II disease, 9 cases of stage III disease, and 48 cases of stage IV disease. The patients were also classified into three groups according to Child's criteria. Eight patients were also diagnosed as having diabetes mellitus. In all, 11 patients had received no previous treatment, whereas the other 57 patients had previously undergone some treatment such as operation, TAE, hepatic arterial infusion, and/or percutaneous ethanol injection therapy (PEIT).

We implanted a 5-F polyurethane catheter nonsurgically via the femoral artery or subclavian artery [1]. The approach was decided on the basis of the shape of the celiac trunk as revealed by prior angiography. The transsubclavian approach was carried out by surgical cut-down of the branch of the subclavian artery. The details of the transfemoral approach are as follows (Fig. 1). First, conventional angiography was carried out by Seldinger's technique without a sheath introducer assembly. Following the angiography, the gastroduodenal artery and other vessels were occluded with embolization steel coils to achieve an effective distribution of infused drugs [8]. Then, a 5-F polyurethane catheter was inserted into the hepatic artery over an exchange guidewire and connected to an implanted injection port through a subcutaneous tunnel. It takes about 1 h to complete the implantation procedure. In some cases, a coaxial catheter system was placed in the hepatic artery through a collateral vessel that resulted

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

Correspondence to: Takashi Iwamiya, Department of Radiology, Tottori University Hospital, 36-1 Nishi-machi, Yonago-city, Tottori 683, Japan

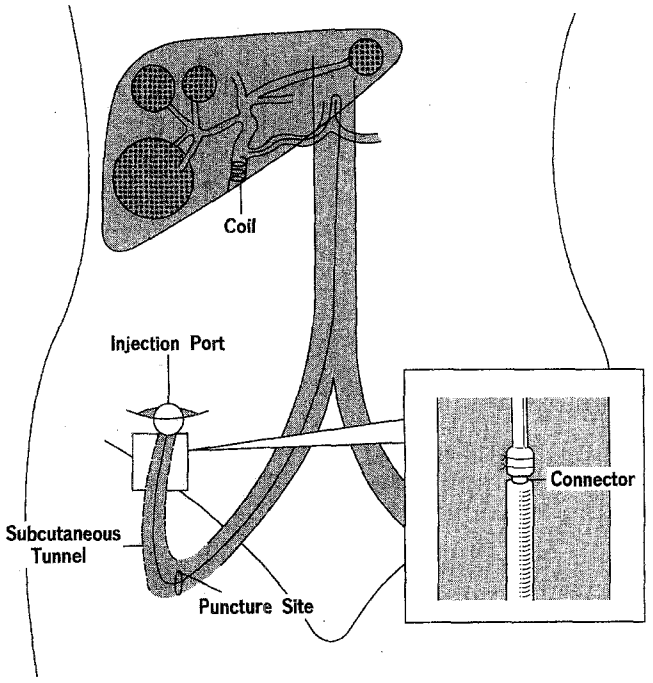

Fig. 1. Schema of the implantable drug delivery system by the percutaneous transfemoral approach

Table 1. Characteristics of patients

Characteristic		No. of patients
Sex	M	58
	F	10
Age (years) (mean age, 60.0):		
	≤39	2
	40–49	9
	50–59	19
	60–69	27
	70–79	9
	⩾80	2
Stage[a]:		
	I	3
	II	8
	III	9
	IV	48
Child's classification[b]:		
	A	37
	B	19
	C	12
Complication		
	DM[c]	8
Total		68

[a] Tumor stage according to the general rules for primary liver cancer established by the Liver Cancer Study Group of Japan [12]
[b] Child's classification [6]
[c] Diabetes mellitus

from repeated TAE. After implantation of the drug delivery system, we confirmed the position of the catheter by X-ray radiography and radionuclide angiography with technetium-99m macroaggregated albumin [21].

The treatment schedule was weekly or biweekly one-shot administration of anticancer drugs. All the patients were divided into two groups on the basis of the therapeutic regimen. Group A consisted of 37 patients who were given epirubicin alone, and group B consisted of 31 patients who were given two or more of the following drugs: mitomycin C, Adriamycin, 5-fluorouracil, cisplatin, and epirubicin. In some cases in both groups, these drugs were mixed with Lipiodol and given for targeting and slow release in the liver [10, 11, 17]. At 4 weeks after the onset of therapy, the therapeutic effect was evaluated by imaging studies and was rated using the criteria of the WHO Handbook for Reporting Results of Cancer Treatment.

The survival rates were calculated using the Kaplan-Meier method and were compared using the generalized Wilcoxon test.

Table 2. Response to therapy

	CR	PR	NC	PD	CR+PR (%)
All cases	1	16	37	14	17 (25.0%)
Stages III & IV	0	14	29	13	14 (24.6%)

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease

Results

We succeeded in the implantation in all cases. Complications included abscess formation at the punctured site and around the injection port in three patients who also had diabetes mellitus and wound hematoma in three patients. They were treated by conservative therapies and cured. Dislocation of the catheter occurred in three patients, who underwent correction of the catheter or recannulation by another approach. In three cases the infusion catheter became obstructed during the therapy, and two of these patients underwent recannulation.

The transfemoral approach was applied to 56 cases and the transsubclavian approach, to 12 cases. Of all the patients who underwent repeated arterial infusion therapy, 41 are presently alive and 27 have died. The major cause of death was liver failure in 32 cases. The number of injections ranged from 1 to 48 (mean, 13.5). The total dose of each drug was as follows: epirubicin, 10–1,030 mg (mean, 269.1 mg); Adriamycin, 4.5–131 mg (mean, 54.8 mg); mitomycin C, 4–100 mg (mean, 34.6 mg); 5-fluorouracil, 500–14,000 mg (mean, 4,884 mg); cisplatin, 50 mg (mean, 50 mg); and Lipiodol, 1–28 ml (mean, 7.6 ml).

Table 2 shows the overall response rate. A complete response (CR) was observed in 1 patient; a partial response (PR), in 16 patients; no change, in 37 patients; and progressive disease, in 14 patients. The overall response rate was thus 25%. In the patients with stage III and stage IV disease, it was 24.6%.

The cumulative survival rate after implantation of the drug delivery system is shown in Fig. 2. The median survival period was 389.9 days. The 6-month, 1-year, and 2-year survival rates were 75%, 45%, and 17%, respectively. When the survival rate was analyzed on the basis of the therapeutic effect, the 1-year survival rate was 58% and the median survival period was 528.3 days for the responders versus 43% and 350.7 days for the nonresponders. However, the difference in the median survival period between the two groups was not statistically significant. The cumulative survival period as a function of the therapeutic

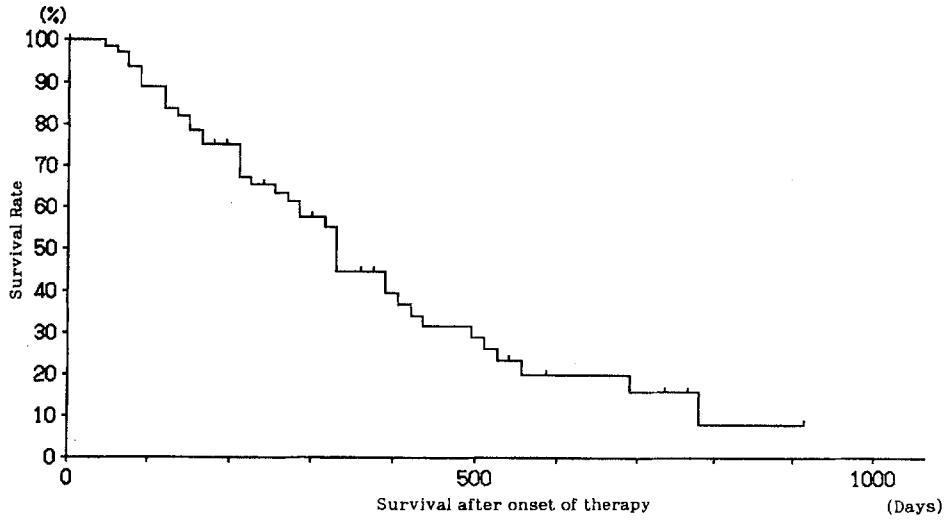

Fig. 2. Survival rate of 68 cases after implantation of the drug delivery system

Table 3. Survival of patients

		Median survival period (days)		Survival rate (%) 1-year	2-year
Total	(n = 68)	389.9		45	17
Stages III & IV	(n = 57)	337		38	8
CR+PR	(n = 17)	528.3	NS	58	31
NC+PD	(n = 50)	350.7		43	14
Group A	(n = 37)	359.8	NS	41	14
Group B	(n = 31)	399.9		48	17
Child's class A	(n = 37)	452.5	P = 0.0158	61	19
Child's class B & C	(n = 31)	297.3		24	12

NS, Not significant

Table 4. Side effects related to the chemotherapy

Side effect	No. of patients (%)
Gastric ulcer	2 (2.9%)
Alopecia	5 (7.4%)
Fever (>38° C)	9 (13.2%)
Anorexia	9 (13.2%)
Hematological toxicity	15 (22.1%)
Obstruction of hepatic artery	5 (7.4%)

regimen also showed no significant difference between group A and group B. With regard to the clinical performance status, the median survival period of the Child's class A cases was significantly longer than that of the Child's class B or C cases (Table 3).

Table 4 shows the major side effects and their incidence. All were transient in nature and were treated by conservative therapies except for three cases of arterial obstruction.

Representative cases

In 57-year-old man, the right lobe of the liver was seen to be occupied by a large tumor on a CT scan (Fig. 3a). At 4 months after implantation of the drug delivery system, a CT scan showed marked reduction in the size of the tumor (Fig. 3b).

In 77-year-old man, the CT scan revealed multiple tumors with a well-enhanced rim in the liver (Fig. 4a). By 7 months after repeated arterial infusion chemotherapy, each tumor had decreased in size and contraction of the right lobe was seen. Dense accumulation of Lipiodol was also seen in the tumor (Fig. 4b). The serum alpha-fetoprotein value decreased from 329,000 to 6.3 ng/ml.

Discussion

TAE is a common therapy, and it achieves good results for inoperable HCC. However, some patients cannot undergo TAE because of extreme tumor extension and/or accompanying advanced liver cirrhosis. Repeated TAE sometimes causes obstruction of the hepatic artery, and this makes further TAE impossible.

The IDDS is designed to permit repeated administration of drugs and blood sampling by percutaneous needle puncture. IDDS is also becoming more accepted for the treatment of metastatic liver tumors [2]. However, for patients with HCC, the use of IDDS has been indicated only for patients who have undergone a noncurative operation [18].

In the present study, we investigated the effect of repeated arterial infusion chemotherapy using an IDDS for inoperable HCC. The 1-year survival rate was 45% and the 2-year survival rate was 17%. These results are far more satisfactory than the results previously reported for conventional arterial infusion therapy [3, 4, 9, 14]. Moreover, significant effects equivalent to those obtained with TAE [13, 19, 20] were observed on the survival rate, although most of our patients could not undergo TAE because of advanced tumor extension and/or poor liver function.

Nakamura et al. [15] reported that arterial infusion chemotherapy with IDDS achieved good results in patients

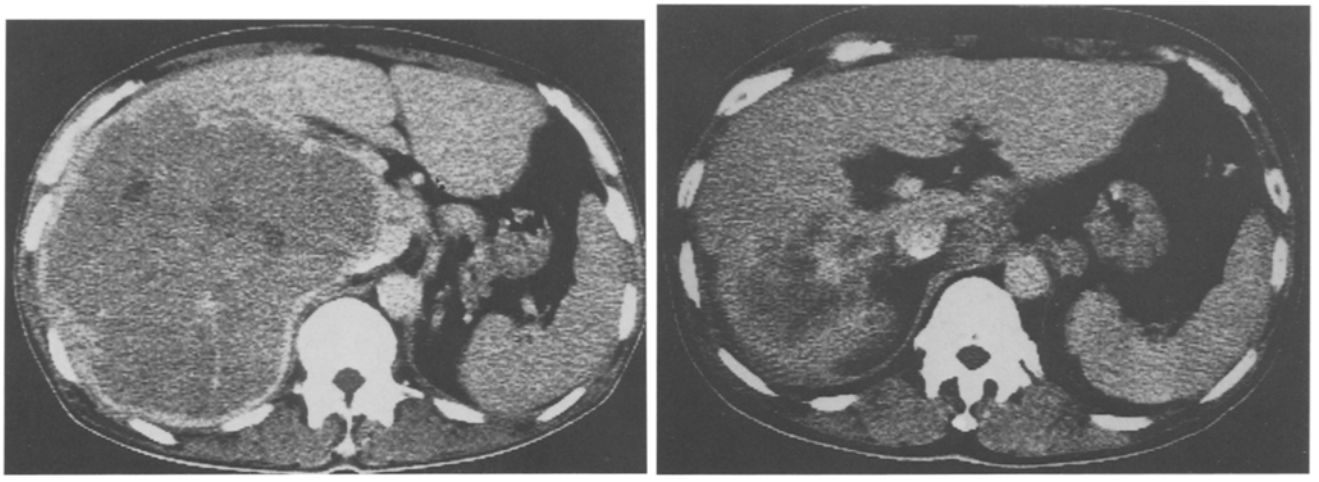

Fig. 3. HCC in a 57-year-old man (**a**) A CT scan reveals a large tumor in the right lobe (**b**) At 4 months after the onset of therapy, a CT scan shows marked reduction of the tumor

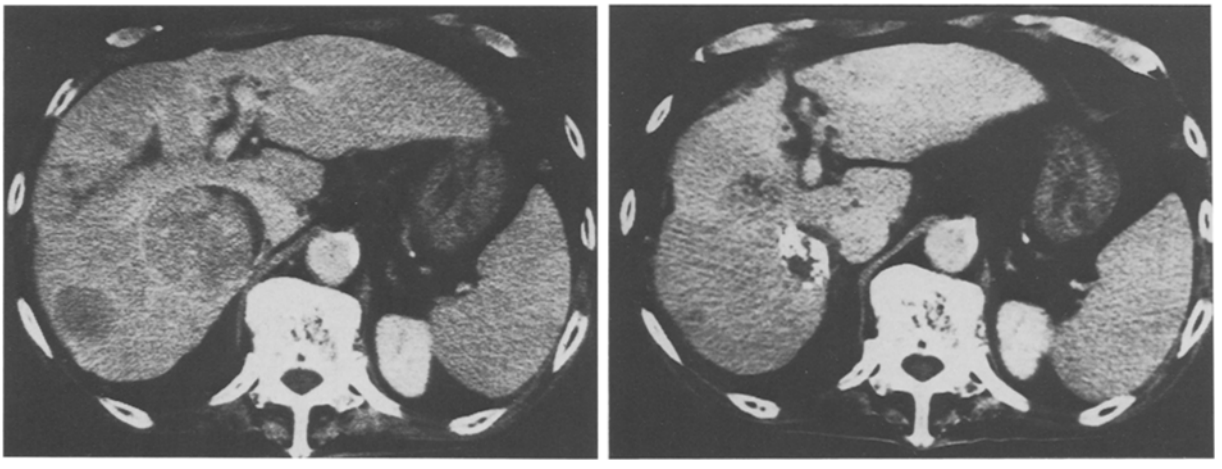

Fig. 4. HCC in a 77-year-old man (**a**) A CT scan reveals multiple tumors with a well-enhanced rim in the liver (**b**) At 2 months after the onset of therapy, a CT scan shows marked contraction of each tumor and dense accumulation of Lipiodol

with HCC, and tumor regression showed a close correlation with the duration of survival. We found no significant difference in the median survival period between the responders and the nonresponders. On the other hand, the reserve liver function was the most significant prognostic factor in the present study. We consider that it is necessary to take account of the patient's liver function during the therapy and closely manage the dose of anticancer drugs in patients with liver cirrhosis.

Some reports have shown that the gastric mucosal blood flow is significantly decreased in patients with liver cirrhosis [16]. Therefore, it is indispensable to occlude the gastric artery and the gastroduodenal artery with steel coils before catheter placement to prevent drug-induced acute gastric mucosal lesions.

The investigation period was not long enough to evaluate the prognosis of the patients in our study, and the survival rates, especially the 2-year survival, can be extended further with a follow-up study of our patients. We should develop a more effective protocol for arterial infusion chemotherapy.

In conclusion, the IDDS will contribute not only to improved therapeutic efficacy for inoperable HCC but also to an improved quality of life for the patients.

References

1. Aoki T, Kimura K, Koyanagi Y, Aoki T, Kusama M, Ashizawa T, Takagi S, Kakuta T, Matsunaga T, Yasuda D, Ohno M, Shibata K (1989) Various methods of catheter placement in hepatic arterial infusion technique of catheter placement via a femoral artery. Jpn J Cancer Chemother 16: 3149
2. Arai Y, Kido C, Endo T (1988) Hepatic arterial infusion (HAI) chemotherapy for liver metastasis from colon, gastric and breast cancer (ca). Proc Am Soc Clin Oncol 7: 102
3. Bern MM, McDermott W Jr, Cady B, Oberfield RA, Trey C, Clouse ME, Tullis JL, Parker LM (1978) Intraarterial hepatic infusion and intravenous Adriamycin for treatment of hepatocellular carcinoma. A clinical and pharmacology report. Cancer 42: 399
4. Cady B, Oberfield RA (1974) Arterial infusion chemotherapy of hepatoma. Surg Gynecol Obstet 138: 381
5. Chan KK, Chlebowski RT, Tong M, Chen HSG, Gross JF, Bateman JR (1980) Clinical pharmacokinetics of Adriamycin in hepatoma patients with cirrhosis. Cancer Res 40: 1263

6. Child CG, Turcatte JG (1964) Surgery and portal hypertension. In: Child CG (ed) The liver and portal hypertension. W. B. Saunders, Philadelphia, p 50
7. Ensminger W, Niederhuber J, Dakhil S, Thrall J, Wheeler R (1981) Totally implanted drug delivery system for hepatic arterial chemotherapy. Cancer Treat Rep 65: 393
8. Granmayeh M, Wallace S, Schwarten D (1979) Transcatheter occlusion of the gastroduodenal artery. Radiology 131: 59
9. Hirai K, Kawazoe Y, Yamashita K, Aoki Y, Fujimoto T, Sakai T, Majima Y, Abe M, Tanikawa K (1989) Arterial chemotherapy and transcatheter arterial embolization therapy for nonresectable hepatocellular carcinoma. Cancer Chemother Pharmacol 23 [Suppl]: S37
10. Kanematsu T, Inokuchi K, Sugimachi K, Furuta T, Sonoda T, Tamura S, Hasuo K (1984) Selective effects of lipiodolized antitumor agents. J Surg Oncol 25: 218
11. Kishimoto W, Nonami T, Nakao A, Harada A, Kuroe K, Haba T, Takagi H (1988) Arterial infusion of anticancer agent and Lipiodol using a totally implanted drug delivery system. Jpn J Cancer Chemother 15: 2531
12. Liver Cancer Study Group of Japan (1983) The general rules for clinical and pathological study of primary liver cancer. Kanehara & Co., Tokyo
13. Liver Cancer Study Group of Japan (1986) Survey and follow-up study of primary liver cancer in Japan. Report 7. Acta Hepatol Jpn 27: 1161
14. Miyamoto H, Ogawa M, Inagaki J, Horikoshi N, Ezaki K, Inoue K, Nagata T, Aiba K, Domyo M (1982) Arterial infusion of combination chemotherapy using Adriamycin and mitomycin C for hepatoma and metastatic tumors of the liver. Jpn J Cancer Chemother 9: 1955
15. 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 implantable reservoir for hepatocellular carcinoma. Cancer Chemother Pharmacol 31 [Suppl I]: S93
16. Nishiwaki H, Asai T, Sataka K, Sowa M (1992) Gastric microcirculation and acute gastric mucosal lesions in patients with hepatic cirrhosis. Hepatogastroenterology 39: 242
17. Sakurai M, Okamura J, Kuroda C (1984) Transcatheter chemoembolization effective for treating hepatocellular carcinoma. A histopathologic study. Cancer 54: 387
18. Shimamura Y, Takenaka Y, Ishii M, Shima Y, Taniguchi H, Kitai Y, Watanabe H, Sugai S, Takashi A, Kitaya T, Matsuyama T, Hasegawa H (1989) Multimodal treatment of hepatocellular carcinoma. Cancer Chemother Pharmacol 23 [Suppl]: S87
19. Yamada R, Sato M, Kawabata M, Nakatsuka N, Nakamura K, Takashima S (1983) Hepatic artery embolization in 120 patients with inresectable hepatoma. Radiology 148: 397
20. Yang CF, Ho YZ, Chang JM, Chiang RH, Lai KH, Lee SD, Tsai YT, Lui WY, Liu TJ, Chen GH (1989) Transcatheter arterial chemoembolization for hepatocellular carcinoma. Cancer Chemother Pharmacol 23 [Suppl]: S26
21. Ziessman HA, Thrall JH, Yang PJ, Walker SC, Cozzi EA, Niederhuber JE, Gyves JW, Ensminger WD, Tuscan MC (1984) Hepatic arterial perfusion scintigraphy with Tc-99m-MAA. Use of a totally implanted drug delivery system. Radiology 152: 167