

Effects of hepatic arterial infusion chemotherapy on unresectable or recurrent hepatocellular carcinoma

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Abstract. We performed hepatic arterial infusion chemotherapy (HAI) on 86 patients with unresectable hepatocellular carcinoma (HCC, 61 patients) or unresectable recurrent HCC after hepatectomy (25 patients). As drug therapy, 250 mg of 5-fluorouracil was injected daily for 14 days using a reservoir embedded in the subcutaneous layer. During this period, 0.4 mg/kg of doxorubicin and 0.12 mg/kg of mitomycin C suspended in Lipiodol Ultra-Fluide were also injected twice intra-arterially. This was defined as one course of HAI, and it was repeated every 3 months. In the patients with unresectable HCC, the 1-, 2-, and 3-year survival rates were 31.5%, 22.4%, and 10.7%, respectively, and the numbers of cases showing a complete response (CR), a partial response (PR), a minor response (MR), no change (NC), and progressive disease (PD) according to the Criteria for the Evaluation of the Clinical Effects of Solid Cancer Chemotherapy established by the Japan Society for Cancer Therapy were 1 (1.6%), 20 (32.8%), 5 (8.2%), 28 (45.9%), and 7 (11.5%), respectively. On the other hand, the 1-, 2-, and 3-year survival rates of the patients with unresectable recurrent HCC were 69.6%, 34.8%, and 14.9%, respectively. The rate of catheter patency after 1 year was 64.1%, and the mean catheter-patency period was 311.9 days. Patients in group A (CR+PR, $n = 21$) survived significantly longer than those in group B (MR+NC+PD, $n = 40$; $P < 0.05$).

In conclusion, since responders to HAI achieve longer survival than nonresponders, the selection of effective drugs is important for this therapy.

Introduction

There are several therapeutic approaches to hepatocellular carcinoma (HCC), including hepatic resection, transarterial embolization, and percutaneous ethanol injection. As recently reported, in our institution, when hepatic resection is not indicated, hepatic arterial infusion chemotherapy (HAI) [1, 2, 5, 8, 9] is performed mainly in patients with unresectable HCC. The purpose of the present study was to clarify the effects and outcome of this treatment.

Patients and methods

Among 502 patients with HCC treated in the Department of Surgery II of Nagoya University School of Medicine between 1981 and 1993, 328 underwent hepatic resection. Because 61 patients were judged to be unresectable due to tumor spread and/or underlying severe liver cirrhosis, they were treated by HAI. These patients included 54 men and 7 women aged 38–74 years (mean, 56.8 ± 8.1 years). Liver cirrhosis was associated in 44 patients (72.1%). According to the TNM classification of the Manual for Staging of Cancer [4], 1 patient (1.6%) belonged to stage I; 12 (19.7%), to stage II; 10 (16.4%), to stage III; 34 (55.7%), to stage IV-A; and 4 (6.6%), to stage IV-B. In all, 25 patients with unresectable recurrent HCC after hepatectomy were also treated by HAI, including 21 men and 4 women aged 40–76 years (mean; 56.7 ± 7.5 years).

Treatment. In the arterial chemotherapy cases, a heparin-coated catheter (PU Catheter; Toray Industries, Inc., Japan) was inserted, and its tip was made to dwell in the hepatic artery, with the other end being connected to a reservoir (Catheter Access; Nipro, Japan) embedded in the subcutaneous layer. We use two kinds of insertion methods for the infusion catheter (Fig. 1): via the femoral artery without laparotomy and via the gastroduodenal artery by laparotomy. In the former method, the gastroduodenal artery is occluded with a metallic coil. In the latter, the right gastric artery is ligated. For drug administration, 250 mg of 5-fluorouracil (5-FU) was injected from the reservoir over a 3-h period daily for 14 days. During the same period, 0.4 mg/kg of doxorubicin (Adriacin; Kyowa Hakko Kogyo Co. Ltd., Tokyo) and 0.12 mg/kg of mitomycin C suspended in an oily medium, Lipiodol (Lipiodol Ultra-Fluide; Laboratoire Guerbet, France), using the same dosage, were injected twice into the hepatic artery from the reservoir on days 1 and 8. This was defined as one course of HAI, and it was repeated every 3 months.

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

Abbreviations: HCC, hepatocellular carcinoma; HAI, hepatic arterial infusion chemotherapy; CR, complete response; PR, partial response; MR, minor response; NC, no change; PD, progressive disease

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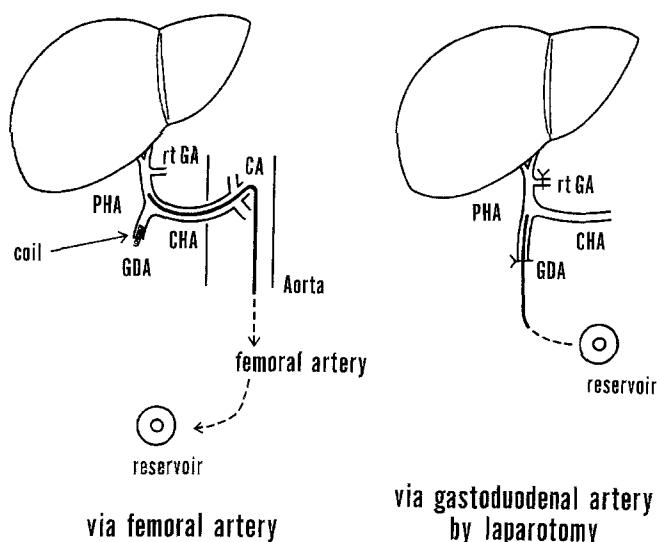


Fig. 1. Route of catheter insertion

Clinical evaluation. The antitumor effect was evaluated by imaging studies and judged by the Criteria for the Evaluation of the Clinical Effects of Solid Cancer Chemotherapy established by the Japan Society for Cancer Therapy [3]. To evaluate the influence of the antitumor effect on survival, the primary cases (61 patients) were divided into 2 groups according to the antitumor effect: a responsive group (CR + PR), group A ($n = 21$), and a nonresponsive group (MR + NC + PD), group B ($n = 40$). These two groups were compared in terms of the survival rate and background factors. The survival curves and the rate of catheter patency were calculated using the Kaplan-Meier method, and the statistical significance of the difference in survival between the two groups was evaluated by the generalized Wilcoxon test.

Results

Response to treatment

The responses of the primary cases consisted of CR in 1 case (1.6%), PR in 20 case (32.8%), MR in 5 cases (8.2%), NC in 28 cases (45.9%), and PD in 7 cases (11.5%). The response rate (CR + PR) was 34.4%. On the other hand, the responses of the patients with unresectable recurrent HCC consisted of CR in 4 cases (16.0%), PR in 8 cases (32.0%), MR in none (0), NC in 8 cases (32.0%), and PD in 5 cases (20.0%). The response rate (CR + PR) was 48.0%.

Survival

The 1-, 2-, and 3-year survival rates of the primary cases were 31.5%, 22.4%, and 10.7%, respectively (Fig. 2). The overall median survival was 356.1 days. However, the patients in group A survived significantly longer than those in group B ($P < 0.05$; Fig. 3). Furthermore, the differences in background factors, except for the sex ratio, between the two groups were not statistically significant (Table 1). The 1-, 2-, and 3-year survival rates of the recurrent patients after hepatectomy were 69.6%, 34.8%, and 14.9%, respectively (Fig. 4).

Table 1. Background factors between Group A and Group B

	Group A ($n = 21$)	Group B ($n = 40$)	
Age	56.86 ± 7.59	56.68 ± 8.62	NS ^a
M/F	21/0	33/7	$P < 0.05^b$
Liver cirrhosis	13/21 (61.9%)	31/40 (77.5%)	NS ^b
Stage:			
I, II, III	9	14] NS ^b
IV	12	26	
KiCG (min^{-1})	0.117 ± 0.042	0.102 ± 0.047	NS ^a

NS, Not significant ^a Student's *t*-test ^b Chi-square test

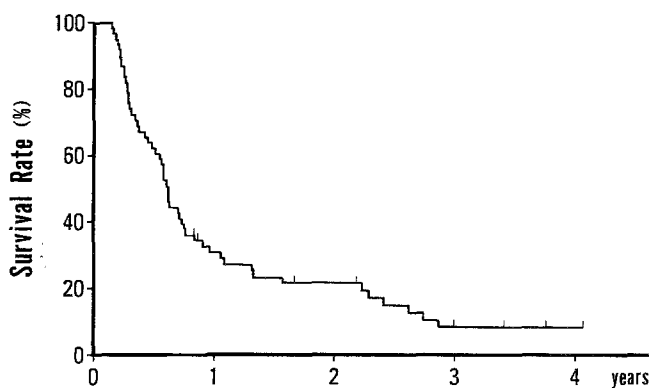


Fig. 2. Survival of unresectable patients with HCC treated by HAI

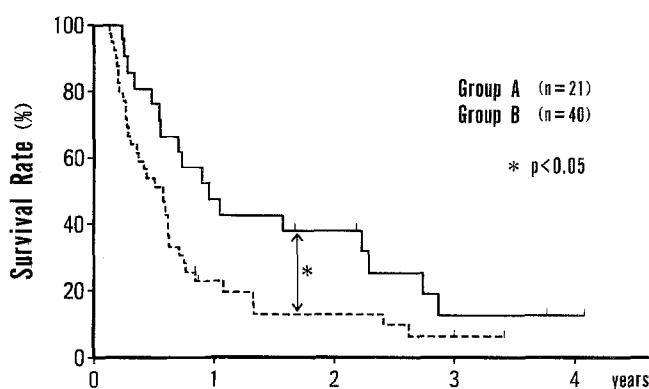


Fig. 3. Comparison of survival according to the antitumor effects between group A (CR + PR, $n = 21$) and group B (MR + NC + PD, $n = 40$)

Complications

Complications developed in relation to the infusion catheter. The 1- and 2-year rates of catheter patency in the primary cases were 64.1% and 57.6% (Fig. 5), and the mean catheter-patency period was 311.9 days. During the course of HAI, complications such as gastroduodenal ulcer (12 patients), liver damage (6 patients), catheter-induced infection (2 patients), bone marrow suppression (2 patients), and dislocated catheter tip (2 patients) were observed. However, no serious complication occurred.

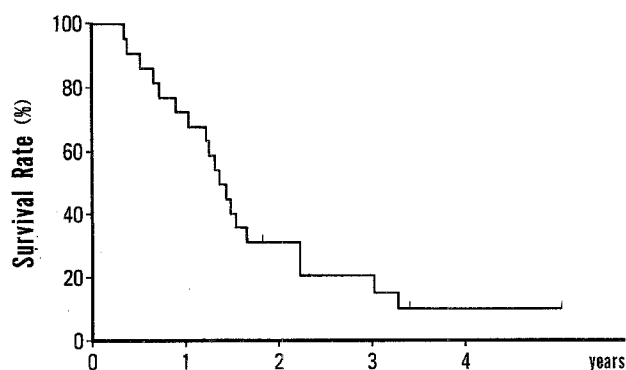


Fig. 4. Survival of unresectable recurrent patients with HCC treated by HAI

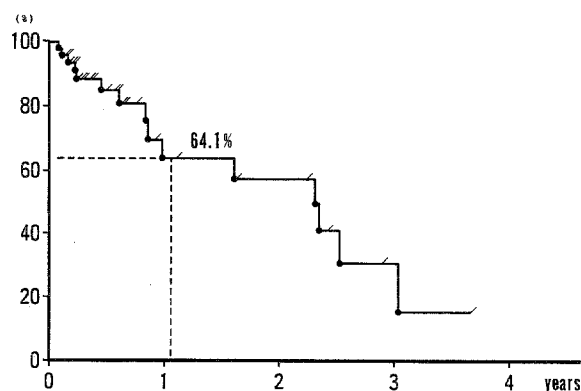


Fig. 5. Rate of catheter patency

Discussion

Thanks to progress in such diagnostic procedures as computed tomography (CT) and ultrasonography, many small HCCs can be detected and surgically treated. However, there are also many patients with unresectable advanced HCC due to tumor spread and/or underlying severe liver cirrhosis. The prognosis for untreated cancer of the liver is very poor [7]. Hepatic arterial infusion chemotherapy (HAI) is one of the effective treatments for unresectable HCC [1, 5, 8, 10]. We reported that HAI employing doxorubicin and mitomycin C suspended in Lipiodol with 5-FU was effective against unresectable HCC [8]. In the present study, the response rate (CR + PR) of 34.4% indicated a relatively favorable outcome. In patients showing a response to chemotherapy, antitumor effects can prolong the survival time.

The long-term prognosis after hepatic resection for HCC has not been satisfactory due to frequent recurrence in the remnant liver [6]. A second resection should be performed if it is feasible on the basis of reevaluation of the function of the remnant liver [6]. However, most cases of recurrent HCC are unresectable because of tumor spread and/or insufficient liver function. In the present study, HAI achieved a satisfactory response in patients with unresectable recurrent HCC.

Our experience suggests that HAI using the reservoir is a favorable drug delivery system, and it promises a relatively good quality of life for the patients. However, catheter occlusion occurs frequently. Management of the catheter to prolong the patent period and combined therapy after catheter occlusion are surmised to be important for improving the effectiveness of HAI in these HCC patients.

In conclusion, since responders to HAI achieve longer survival than nonresponders, the selection of effective drugs is important for this therapy.

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