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Treatment of Hepatocellular Carcinoma by Intra-arterial Infusion with Mitomycin C

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Abstract. Twenty-nine patients with hepatocellular carcinoma (PHC) were given oral administration of 5-Fu (or Futraful) and intermittent intra-arterial infusion with 10-20 mg of Mitomycin C (MMC). Objective responses such as decreased serum α-fetoprotein level, decrease in the liver size, and prolongation of the survival time were found in 15, 14, and 13 out of 29 patients respectively. Subjective symptoms such as weakness, abdominal pain, and loss of appetite were improved in 7 of 29 patients. Of control patients with PHC who received oral administration of 5-Fu (or Futraful) alone, or intra-venous injection of 4 mg of MMC twice a week, the objective responses were observed in one of 13 patients. This indicates significant therapeutic effect of intra-arterial infusion of MMC on patients with PHC. Patients with severe liver dysfunction, decreased number of peripheral lymphocytes, or high level of serum alkaline phosphatase were unsuitable for this infusion. A significant decrease of serum hemoglobin level was observed as a side effect of intra-arterial infusion of MMC.

Key Words: liver carcinoma, chemotherapy, Mitomycin C

Introduction

Hepatocellular carcinoma (PHC) is progressively fatal, and patients are usually in the inoperable stage when the diagnosis is made. In fact, at the present time, surgical resection has been performed on only about 12% of 2716 patients with PHC[1] and a radical cure is very rare. Chemotherapy still seems to be a reasonable approach for most patients with advanced tumor, and energetic efforts are being concentrated on search for more rational applications of anticancer agents. Recently, in our Department, considerable progress in PHC therapy has been made as the result of studies on the combination therapy of anticancer agents and improvement of technique for administering the drug. Consequently, subjective and objective symptoms of patients with PHC have been improved, and long-time survival has increased in number[2]. In the present study, the treatment of PHC is presented with special reference to the effectiveness of regional chemotherapy by intra-arterial infusion of high dose of Mitomycin C (MMC).

Materials and Methods

1. Subjects

The subjects were 29 patients with PHC who were admitted to our hospital from 1975 to 1978 and given high dosage of MMC by intra-arterial infusion. They consisted of 24 males and 5 females ranging from 40 to 74 years old with an average age of 58 years. As the control, 15 patients were selected from PHC patients who had received no MMC intra-arterial infusion. Diagnosis was made from the findings of scintigraphy, celiac angiography, and blood chemical examinations and was confirmed by liver biopsy or postmortem examinations.

2. Methods of intra-arterial infusion of MMC

Intra-arterial infusion was carried out by the arteriographic technique desceibed by Seldinger[3,4]. A siliconized teflon catheter was inserted percutaneously through the femoral artery, the tip of the catheter was advanced to the celiac artery under the fluoroscopic control, and then 5-20 ml of saline solution with MMC (10-20 mg) was injected in one shot through the catheter. The main anticancer agents used in combination with MMC intra-arterial infusion were 5-Fu (100-300 mg/day, p.o.), Futraful (600-800 mg/day, p.o.) or OK-432 (2-3 KE/week, i.m.). OK-432 is a streptococcal immunopotentiator made from attenuated strain of streptococcus haemolyticus[5]. This has recently been widely used as the non-specific immunopotentiator for malignant diseases. One KE of OK-432 is equivalent to 0.1 mg of lyophilized bacteria.

3. Judgement of therapeutic effects

The efficacy of intra-arterial infusion of MMC against PHC was judged on serum α-fetoprotein (AFP) levels, liver size, and survival time. In addition, clinical evaluations of anticancer drugs were made according to Karnofky's criteria[6]. Those of 0-B, 0-C, and I-A were judged to be improved and 0-0 and 0-A, to be unimproved.

The AFP levels were measured by passive hemagglutination test and single radial immunodiffusion. Size of the liver was examined by palpation and from hepatic scintigraphy. The survival time was measured as the number of days from the time of diagnosis of PHC to the time of death.

4. Effect of MMC intra-arterial infusion on laboratory data

The following laboratory tests were performed to evaluate the effect of MMC infusion and its side effects: peripheral lymphocyte count, serum hemoglobin (Hb), and serum albumin as indicies for evaluating the general condition, GOT, GPT, alkaline phosphatase (ALP), and γ-GTP as indicies for evaluating liver function, and urea N for evaluating renal function. These laboratory data were usually obtained one week prior to, and one week after MMC intra-arterial infusion with exception of some obtained 15 to 25 days before and after the infusion. On the average, these data were obtained 9 days before and after the infusion.

Results

1. Therapeutic effect of MMC intra-arterial infusion

Table 1 shows the changes in AFP levels, iver size, survival time, and clinical evaluation by Karnofsky's criteria[6] in the 29 cases receiving MMC intra-arterial infusion (infusion group) and in the control. The serum AFP levels decreased in 15 out of 29 cases (about 15%) of the infusion group, while no such decrease was observed in the control. Considerable reduction of liver size was found in 14 cases (48%) of the infusion group, while only one cases in the control. As for the survival time, 6 cases (20%) in the infusion group died within 50 days, a smaller percentage compared with the 4 such cases (26%) in the control group. On the other hand, the patients surviving longer than 200 days were found in 13 cases (44%) in the infusion group, while 4 cases (26%) in the control.

According to Karnofsky's criteria, 15 cases in the infusion group (51%) were improved, but 4 cases (26%) in the control. Furthermore, 7 cases (24%) in the infusion group were classified as 1-A, in which improvement of subjective and objective symptoms had continued for more than one month, but no such case was found in the control. These findings indicate the effectivenss of intra-arterial infusion of MMC in patients with PHC.

Table 1 Therapeutic effect of intra-arterial infusion with MMC on patients with hepatocellular carcinoma

MMC one shot	AFP		Hepatomegal.		Surviving days		Thera. effect (Karnofsky)		Combined Chemotherapy
MMC (+) 29	↑	4	↑ →	15	0–50	6	0–0	8	FT-207 : 13 5-FU : 4 MFC : 1 OK-432 : 8
	→	10			50–200	10	0–A	6	
	↓	15	↓	14	200–	13	0–C	8	
							1–A	7	
MMC (−) 15	↑	5	↑ →	8 6	0–50	4	0–0	6	FT-207 : 8 5-FU : 1 MFC* : 1 MMCi.v. : 2 OK-432 : 2
	→	10			50–200	7	0–B	3	
	↓	0	↓	1	200–	4	0–C	1	
							?	5	

※ Combination chemotherapy of MMC, FT-207 and Cytarabine

2. Clinical characteristics of patients responding to MMC intra-arterial infusion.

This infusion was not effectiveness in all patients with PHC. In the infusion group, 15 cases responded to this therapy, but the remaining 14 cases showed no response.

All the patients were staged according to the classification proposed by the international symposium on liver cancer held in Kampala in 1971[7]. Three patients were in functional stage I PHC, 18 patients in stage Ⅱ, and the remaining 8 in stage Ⅲ. In the improved group (0-C, I-A), 3 patients were in stage I, 10 in stage Ⅱ, and 2 in stage Ⅲ. In the unimproved group (0-0, 0-A), 8 patients were in stage Ⅱ and 6 patients were in stage Ⅲ. This indicates that MMC intra-arterial infusion was effective in the patients classified into the earlier stage such as stage I or Ⅱ, but not in patients classified into the advanced stages (Table 2).

Table 2 Relationship between therapeutic effect of MMC and functional and anatomieal stagings for hepatocellular carcinoma

Therapeutic Effect (Karnofsky)	Functional Staging (Vogel) No. of cases		
	I (good)	Ⅱ (moderate)	Ⅲ (poor)
0 – 0	0	4	4
0 – A	0	4	2
0 – C	0	6	2
1 – A	3	4	0

Laboratory findings obtained prior to MMC intra-arterial infusion in the improved group were compared with those of the unimproved group (Table 3). In the former group, hemoglobin (Hb) and albumin were higher, but bilirubin, ALP, GPT, GOT, γ-GTP, and urea N were lower than in the unimproved group. These results suggest

Laboratory findings after intra-arterial infusions with MMC. —— mean

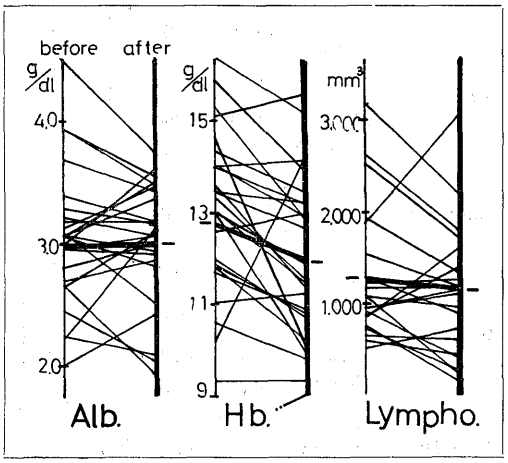

Fig. 1 a

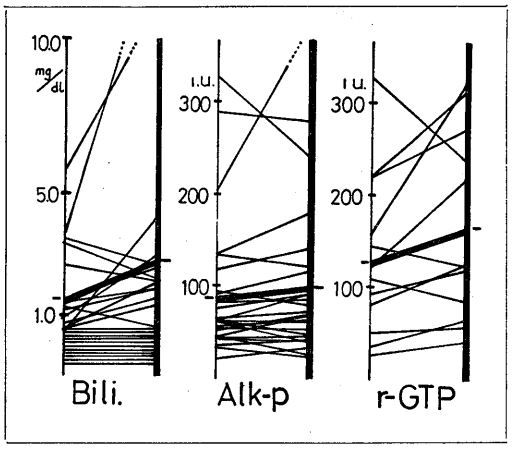

Fig. 1 b

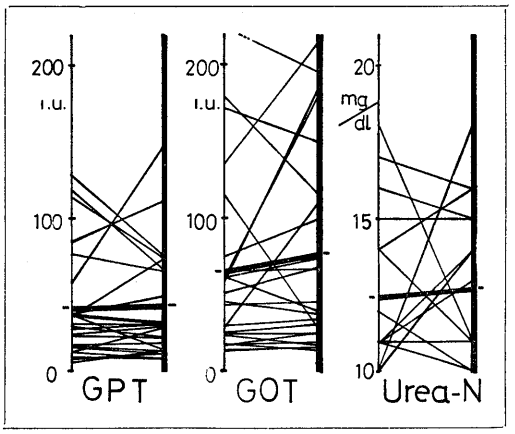

Fig. 1 c

that, in the former group, underlying hepatic dysfunction were relatively mild and nutritional conditions were kept well. In the latter group, the peripheral lymphocyte count was 808.6/mm³, signicantly lower that of 1,601/mm³ in the former group, and the serum ALP level was significantly higher than in the former group.

3. Changes in laboratory findings after MMC intra-arterial infusion

Fig. I-a, b, and c show the comparison of laboratory biochemical findings in all patients before and after MMC intra-arterial infusion. The changes in these findings

Table 3 Change of Laboratory Findings after Intra-arterial Infusion of MMC

Patient Groups			Lympho-cyte /mm³	Albu-min g/dl	Hemo-globin g/dl	Bilirubin mg/dl	ALP u	GOT u	GPT u	γ-GTP u	Urea N mg/dl
unimproved		No. of Cases	12	11	11	11	11	11	11	8	7
(0-0, 0-A)	before Therapy	Mean	708.6 *1)	2.6	11.1	2.1	154.8 *2)	98.4	48.9	160.4	10.4
		SD	120	0.5	2.3	1.7	88.4	64.0	36.4	98.1	2.0
	after Therapy	Mean	543.3	2.8	11.4	6.9	178.3	120.0	58.2	201.4	13.1
		SD	371	0.7	2.1	8.3	104.2	74.3	48.4	93.4	1.8
improved		No. of Cases	15	15	15	15	15	15	15	7	14
(0-C, 1-A)	before Therapy	Mean	1601.6	3.1	13.8	1.1	66.9	61.3	40.9	114.0	13.3
		SD	804	0.5	1.6 *3)	0.9	28.7	48.1	33.4	53.8	2.3
	after Therapy	Mean	1246.4	3.2	12.4	1.6	70.4	65.9	39.0	143.4	12.4
		SD	348	0.5	1.3	1.2	34.4	49.9	28.6	80.2	2.1

*1) and *2) : Statistically significant difference from the group, 0-C and 1-A,
*3) : Statistically significant difference from the group prior to therapy

varied with individual case. As shown in the mean values of the respective findings, it was found that levels of albumin and Hb, as well as lymphocyte count decreased and bilirubin, ALP, γ-GTP, GOT, GPT and urea N increased after the MMC intra-arterial infusion, but these changes were not statistically significant, except the change in Hb levels. The MMC intra-arterial infusion may slightly worsen general conditions, hepatic function and renal function. However, the patients whose laboratory findings rapidly worsened after the infusion resulted in a very poor prognosis.

Table 3 shows the mean values of respective finding before and after MMC intra-arterial infusion in both improved and unimproved cases according to Karnofsky's criteria. There was no statistically significant difference. In the unimproved group, however, all values except the lymphocyte count tended to decrese after the infusion. In the improved group, laboratory findings such as serum albumin and GPT improved slightly after the infusion.

Discussion

Recent advances in the early diagnosis and chemotherapy of liver cancer are resulting in an improvement of subjective and objective symptoms, and prolongation of surviral time in inoperable cases, which have never been experienced before[2]. At present, the theoretical grounds for the optimum administration of anticancer agents are being established on the basis of their mode of cytostatic action[8].

We are of the opinion that combination of intermittent local infusion of cytocidal and concentration-dependent agent such as MMC or Adriacin, at higher concentrations through the hepatic artery, with systemic adminisration of cytotoxic and time-dependent agents such as 5-Fu or FT-207, is an effective chemotherapy for liver cancer.

In the present study, which includes the effectiveness of MMC intra-arterial infusion against PHC, a decrease of serum AFP levels, reduction of liver size, and prolongation of survival time were observed more frequently in the MMC intra-arterial infusion group than in the control group. According to Karnofsky's criteria, most of the improved patients belonged to the infusion group. This indicates, as reported by several investigators[9,10], that delivery of a relatively high dose of cytocidal agents such as MMC by local infusion is also effective against PHC.

The MMC infusion, however, is not effective in all patients with PHC, and some of them worsen rapidly after the infusion. This seems to be the result of improper selection of patients. Therefore, the criteria for selection of patients suitable for this therapy should be established.

Ariel et al[9]. reported that hepatic scintigraphy was useful in the selection of patients for intra-arterial chemotherapy. They divided the liver carcinoma into 4 stages from the anatomical extent of the tumor. According to their classification, MMC intra-arterial infusion was applicable to stage I (less than 10% of the liver involved with cancer) and stage Ⅱ, but stage Ⅲ (cancer occupied 30 to 50% of the liver) and more advanced stages were beyond the indication for this therapy. In order to select patients suitable for MMC infusion on the basis of objective data, all patients treated with the infusion were staged according to Vogel's functional and anatomical classifications[7]. Most of the patients in stage Ⅲ did not respond to this therapy. In other words, MMC intra-arterial infusion seems to be unapplicable to cases having severe portal hypertension, bloody ascites, esophageal varices, liver failure, or cachexy. On the other hand, the therapeutic effect of MMC infusion was observed in about half of the group of stage Ⅱ. These findings indicate that the patients for this therapy should be selected from

the group of Vogel's stage I and Ⅱ on the basis of laboratory data. This study also revealed that, in cases not responding to MMC infusion, the peripheral lymphocyte count was as low as $708.6 \pm 120/mm^3$ and ALP was higher than 156.8 ± 88.4 u. As described previously[11,12], the peripheral lymphocyte count is useful in forecasting the prognosis in patients with PHC.

In the present study, it was found that among the hepatoma patients with slight liver dysfunction, such as patients with Vogel's stage Ⅱ, some were improved remarkable by the MMC infusion, and others were not. One of the reasons for the difference in therapeutic effect on patients with the same stages may be due to the varying sensitivity of cancer cells to anticancer drugs.

Regarding a side effect, MMC intra-arterial infusion showed a tendency to worsen the general condition, hepatic function and renal function. This was more pronounced in cases not responding to the infusion, especially in cases with advanced liver cancer. It indicates that MMC infusion induced severe side effects in advanced cases with liver cancer, but the infusion caused no severe side effect in most other cases. Consequently, this infusion is regarded as the best method against inoperable liver cancer at the present time. However, attention should be paid to a statistically significant decrease in serum Hb levels after MMC infusion. As the decreases arised in a relatively short time, within about 10 days after the infusion, it may be due an increase of hemorrhagic tendency caused by the MMC infusion and then due to development of hemolysis. Accordingly before treatment with MMC, it is necessary to throughly examine the presence of hemorrhagic tendency in patients and to supply a coagulation factor, such as fresh plasma and thrombocytes, in order to prevent hemorrhage.

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