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Clinical Trial of Repetitive Portal Administration of Anticancer Drug as a Prophylactic Modality for Liver Metastasis —A Pilot Study of the Optimal Dosage and Reduced Toxicity—

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Abstract: Since 1986, we have been investigating repetitive intraportal administration of anticancer agents as prophylaxis for liver metastasis after gastrointestinal cancer surgery. Intraportal mitomycin C (MMC: 4 mg) was given on the day of operation and on postoperative days 1–6.

A preliminary pharmacokinetic study of intraportal MMC administration was performed in a rabbit model. A high first-pass extraction ratio was found at doses of 0.05 and 0.1 mg/kg, and it decreased at the higher doses of 0.2 and 0.4 mg/kg. The clinical dose of 4 mg corresponded to 0.05–0.1 mg/kg in the rabbit model and was considered to be within the optimal dose range.

The side effects and clinical outcome for patients treated with intraportal MMC were compared with those for a control group. The controls included an MMC (+) group that received intravenous MMC, and a MMC (−) group that did not. The intraportal MMC group showed less toxicity compared with the MMC (+) group and a prospective effect on survival and liver metastasis.

These results suggested that our schedule for repetitive intraportal MMC was adequate.

Key words: Repetitive portal administration, Mitomycin C, Pharmacokinetic study

INTRODUCTION

The most frequent site of recurrence after surgery for colorectal cancer is the liver, and tumor development is caused by the transportal seeding of cancer cells[1)]. The standard systemic adjuvant chemotherapy does not effectively prevent the development of liver metastases[2),3)]. Accordingly, some workers have adopted the intraportal administration of anticancer agents as a prophylaxis for liver metastases. Their studies have indicated that one shot intraportal injection of anticancer agents at the time of surgery was ineffective[4)]. On the other hand, Tayler *et al.*[5)] have successfully prevented the development of liver metastases in patients with colon cancer by using the continuous intraportal infusion of 5-fluorouracil during the postoperative period. The effect of intraportal therapy is considered to depend on the sensitivity of tumor cells to the anticancer drug used and on the dosage and frequency of administration. Accordingly, we have been examining the optimal schedule for intraportal administration using a rabbit-VX2 tumor model. We reported previously that effective prophylaxis required 7 administrations of an appropriate anticancer agent at its optimal dose[6)]. We used mitomycin C (MMC) in subsequent clinical trial, because it is considered to be more effective for gastrointestinal cancer than the

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other agents available, but determining the optimal dosage in humans, by comparison with the animal model[7] was not possible.

This report assesses the validity of our administration schedule by a pharmacokinetic study in a animal model, and the review of side effects and outcome in a clinical trial.

Materials and Methods

Study 1, Pharmacokinetic study of MMC

The pharmacokinetic study was performed using a rabbit model, of which we have reported details previously[6]. Blood samples were taken 1, 3, 5, 7, 10, 15, and 20 min. after intraportal administration (PV) or systemic intravenous administration (IV) of MMC. The doses of MMC tested were 0.05, 0.1, 0.2 and 0.4 mg/kg, and the serum concentration was measured by a bioassay method[8] at Kyowa Medical Analysis Center.

An open two-compartment model[9] was used to analyze the pharmacokinetics. The blood concentration at time "t" (Ct) was computed as follows:

$CT = AeP^{-\alpha t} + Be^{-\beta t}$

A, B, α, β and were determined using a microcomputer and the non-linear least squares method, and then the blood concentration at t0 (C0) and area under the concentration-time curve (AUC) were determined by following formulae:

$C0 = A + B$

$AUC = A/\alpha + B/\beta$

There were two rabbits in each group, and the group mean values were determined. Since the AUC reflects the toxicity to the host, the AUC difference between PV and IV administration shows the degree of reduction in toxicity by intraportal administration. This was defined as the first-pass extraction ratio (E), and was calculated as bellow:

$E = (1 - \text{AUC after PV/AUC after IV}) \times 100$

Statistical significance was examined using Student's t-test. The study was performed in accordance with the guidelines for animal experiments, Yamanashi Medical College.

Study 2, Clinical Trial of intraportal MMC

From January 1986 to December 1990, we performed intraportal MMC administration in 11 patients (2 with gastric cancer, 3 with colon cancer, and 6 with rectal cancer). Their clinical features are described in Table 1. Staging was performed according to the criteria of the Japanese Research Society for Gastric Cancer[10] and Cancer of the Colon and Rectum[11].

Table 1. Profile of the intraportal MMC group

No.	Age	Sex	Disease	Histology	s(a)	n	p	Stage*
1	76	F	Rectum	well diff.	a1	0	0	II
2	62	F	Stomach	poorly diff.	ss	0	0	II
3	68	M	Rectum	well diff.	pm	1	0	III
4	59	M	Rectum	well diff.	a1	0	0	II
5	70	M	Colon	moderately diff.	sm	1	0	III
6	64	F	Colon	moderately diff.	ss	0	0	II
7	62	M	Rectum	well diff.	a1	1	0	III
8	66	M	Rectum	well diff.	ai	1	0	IV
9	58	M	Colon	moderately diff	ss	0	0	II
10	61	M	Rectum	well diff.	pm	1	0	III
11	44	M	Stomach	well diff.	se	1	1	IV

Jan. 1986–Dec. 1990

*The definition of s(a), n,p, and stage are in accordance with 'The General Rules for Gastric Cancer Study in Surgery and Pathology', and 'Clinical and Pathological Studies on Cancer of Colon, Rectum, and Anus'.

Table 2. Profile of the control group

Stage / Disease	I	II	III	IV	V	Total
Stomach	9 (1)	2 (1)	8 (1)	1	/	20 (3)
Colon	0	1	2	1	1	5 (0)
Rectum	1	2	1 (1)	0	0	4 (1)
Anal Canal	0	0	0	2 (1)	0	2 (1)
Total	10 (1)	5 (1)	11 (2)	4 (1)	1 (0)	31 (5)

( ); Number of patients in the control MMC (+) group.

An urokinase-coated catheter was placed into the mesenteric vein draining the resected segment of colon, i.e., a branch of the superior of inferior mesenteric vein. We used the right colic vein in the gastric cancer. An injection wedge was fixed on to the abdominal wall. On the day of operation and the subsequent 6 days, 4 mg of MMC was injected into the portal vein via the catheter. The catheter was removed two weeks after the final injection.

We examined early postoperative complications in the intraportal MMC group compared with the other 31 patients treated in our institution during the same period (control group, Table 2). In order to compare toxicity between systemic and portal administration, we devised two subgroups. These were a control MMC (+) group (5 control patients administered 10 mg of MMC on the day of operation and the 1st postoperative day), and a control MMC (−) group (15 control patients who received no administration of anticancer drugs during 2 weeks after surgery and developed no infections in this period).

The white blood cell count and platelet count was compared among intraportal MMC group and these two subgroups on the 1st, 3rd, 7th, and 14th postoperative day.

Statistical analysis of the mean values are performed with Student's t-test.

Finally, the clinical courses of the colorectal and anal cancer patients given intraportal MMC and the control group were compared. Two control group patients received systemic administration MMC and the patients in both groups received oral futraful as adjuvant chemotherapy for 2 years from the 14th postoperative day.

Results

Pharmacokinetic study of intraportal MMC

The blood concentration at t0 (C0), the area under the concentration-time curve (AUC), and the first pass extraction ratio (E) at each dose of MMC are shown in Table 3. C0 values for the PV group were smaller than in the IV group for doses of 0.05 mg/kg and 0.1 mg/kg, but were about the same at 0.2 mg/kg and 0.4 mg/kg. The AUC values in the PV group were smaller than those in the IV group, and the E values were larger at lower doses (45%, 40%, 40%, and 26% for 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg of MMC respectively). The 4 mg dose administered in clinical use corresponded with a dose of 0.05–0.1 mg/kg in this method. Thus, the high E value of 45–40% indicated the effective reduction of MMC toxicity by intraportal administration.

Complications and toxicity of intraportal administration

Complications associated with catheterization to the mesenteric vein included intraperitoneal bleeding in one patient, portal thrombosis in another, and inability to remove the catheter in three cases (Table 4). However, patients given intraportal MMC displayed no major complications such as wound infection,

Table 3. Pharmacokinetics of mitomycin C using rabbits

Dose	Route	(number)	C0 (μg/ml)	AUC (μg, min/ml)	E (%)
0.05mg/kg	PV	(n=2)	0.097	0.539	45.2
	IV	(n=2)	0.137	0.984	
0.1mg/kg	PV	(n=2)	0.178	0.93	39.6
	IV	(n=2)	0.353	1.552	
0.2mg/kg	PV	(n=2)	0.798	2.076	40.1
	IV	(n=2)	0.797	3.467	
0.4mg/kg	PV	(n=2)	1.203	3.755	26.5
	IV	(n=2)	1.323	5.113	

C0; The blood concentration at t0. AUC; area under the concentration-time curve. E; first-pass extraction ratio. Mean values are shown for C0 and AUC.

Table 4. Complications associated with intraportal or intravenous (control) administration of mitomycin C

Complications	Intraportal group (n=11)	Control group (n=31)
Intraperitoneal bleeding*	1	—
Portal thrombosis	1	—
Retention of the catheter	3	—
Wound infection	0	3
Suture separation	0	0
Pancytopenia	0	3

*Due to catheter removed from the mesenteric vein.

suture separation, or pancytopenia. In addition, the biochemical data remained normal. (data is not shown).

Hematological profiles are shown in Figs. 1 and 2. The mean WBC counts of the control MMC (+) and intraportal MMC groups decreased significantly lower than that of the MMC (−) group. However, on the 14th postoperative day, the count of the intraportal MMC group was higher than that of the MMC (+) group. The mean platelet counts on the 7th and 14th postoperative days were significantly higher in the intraportal MMC group compared with the other two groups.

Clinical course of colorectal cancer patients

Recurrence of colorectal cancer was compared between the intraportal MMC group (n=9) and the control group (n=11). The follow-up period for the intraportal MMC group was 32±18 months and that for the control group was 37±12 months.

No liver metastasis and only one case of lung metastasis were found in the intraportal MMC group (Table 5).

Survival rates were calculated using the Kaplan-Meier method and indicated a better survival for the intraportal MMC group (Fig. 3). However, we did not perform a statistical

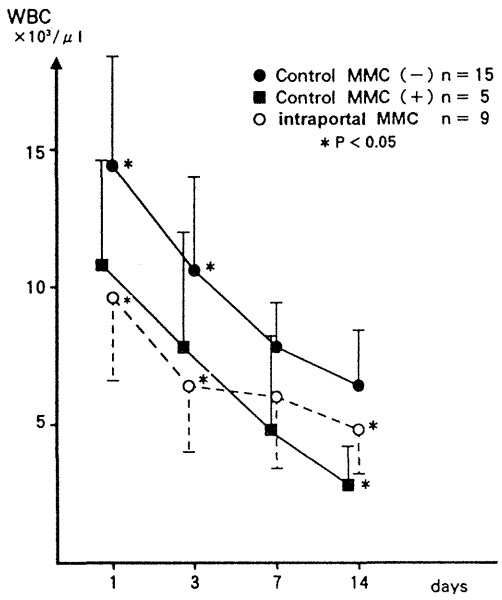

Fig. 1. Mean WBC count during the postoperative period.

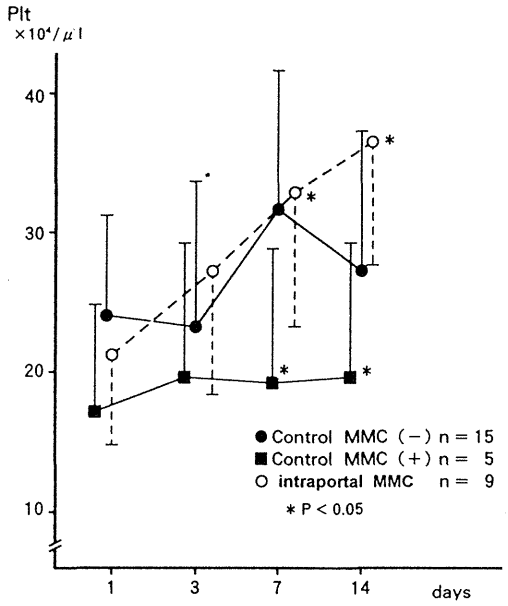

Fig. 2. Mean platelet count during the postoperative period.

Table 5. Sites of reccurence in patients with colorectal cancer in the intraportal MMC and and control group.

	Intraportal group (n=9)	Control group (n=11)
Follow-up period	32 ± 18 month	37 ± 12 month
Liver metastasis	0	3
Lung metastasis	1	2
Bone metastasis	0	1
Local recurrence	0	0
Death	0	5

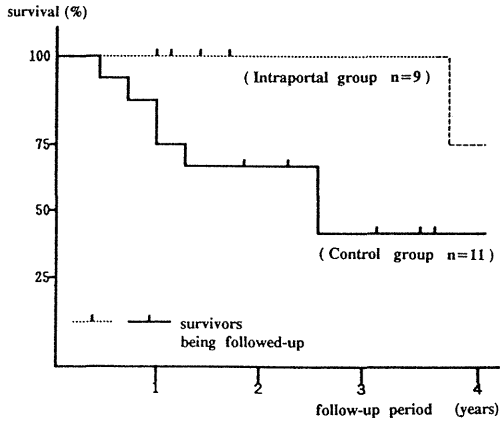

Fig. 3. Survival analysis of colorectal cancer patients (Kaplan-Meier method).

analysis because the number of patients was too small and there were differences in the backgrounds of both groups.

Discussion

Liver metastases receive their main blood supply via the hepatic artery, but they are also supplied by the portal vein[12]. Thus, from the early 1980's it has been postulated that the intraportal injection of anticancer agents might serve as an effective form of prophylaxis for liver metastasis[5),13),14)].

The relative merits of intraarterial injection versus intraportal injection of anticancer drugs to prevent micrometastases are still under discussion. Some workers[15] believe that intraarterial injection is more beneficial even for microscopic tumors, but we decided to use the intraportal technique, for several reasons[16]. At first, drugs injected into the portal vein may be more effective than those injected arterially in combating the spread of tumor cells from the existing malignant area to the endotherium of the sinusoids via the portal vein. Secondly, although the route selected for the anticancer drug varied, the effect of portal administration was the same, that was the thorough distribution of the drug to all parts of the liver. This is critical for the success of a liver metastatic prophylaxia. Additionally, the facility of portal technique comparing with the arterial injection is to be recommended. It does not require the ligation of other blood vessels during the catheter implantation as must be done for intraarterial administration.

Concerning the catheterization procedure itself, we initially experienced the complications of intraperitoneal bleeding and portal thrombosis. Portal thrombosis occurred in a patient whose catheter had been placed via the ligamentum teres into portal vein trunk. It was diagnosed by the sudden onset of fever and all extremely high platelet count, and improved soon after removing the catheter. We subsequently placed the catheter into a branch of the superior or inferior mesenteric vein and situated it so that the tip did not reach the portal trunk. Although slight elevation of the platelet count was seen in the intraportal MMC patients (see Fig. 2), which may suggest latent portal thrombosis, we found no other symptoms to support the presence of portal thrombosis. To prevent intraperitoneal bleeding as occurred in one patient whose catheter was accidentally removed in the early post operative period, we subsequently removed in catheter at two weeks after the final administration of MMC. However, in three patients the catheter could not be removed and remains in situ. Although no problems have been caused retained catheters, some device to allow smooth and safe removal is required.

As to the optimum schedule for MMC, we had been unable to find adequate instructions on the portal administration. So we have been conducting the experimental work to determine the optimal repetitive intraportal administration. The repetition method was decided from the results obtained in a rabbit-VX2 tumor model[6]. According to this experiment we also found that a 7-day course of injections with appropriate dosage, achieve complete suppression of liver metastasis. This animal study used Adriamycin. Its first pass extraction rate (E) was larger at the smaller doses, but a sufficient liver concentration was unattainable at very low doses. We therefore selected the dose which achieved an effective liver concentration and a larger extraction ratio.

It was impossible to determine an adequate schedule for clinical case as same as the experimental model. we selected MMC as a most effective drug against gastrointestinal cancers and decide the dose with 4 mg/body mainly by our clinical experience. However, the results of this study suggest the validity of our schedule. The pharmacokinetic study of MMC showed that the E value was higher at the lower doses as same as Adriamycin, but it is necessary to achieve an effective liver concentration in these dose dependent drugs. We

could estimate that our clinical dosage of 4 mg/body had a high E value and reduced systemic side effects and gave enough concentration of the liver.

An important point to note is that although the intraportal MMC group received 28 mg of MMC during the trial, they suffered less from excess toxicity (estimated by recording the WBC counts during the post operative period) than the control MMC (+) group, who only received 20 mg of MMC injected intravenously. These results are very encouraging, because the safety aspect is one of the most important factors in the usage of anticancer agents as prophylaxis.

Furthermore, the present survival rates and the sites recurrence supported the efficacy of our intraportal administration method. We would however like to further substantiate our findings by treating more patients and increasing the follow-up period.

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