

Fundamental Investigations on Local Chemotherapy for Liver Cancer

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Introduction

The liver is the organ with the most frequent occurrence of metastatic malignant tumor, and malignant tumor of every part spreads to the liver.

And it is said that the number of metastatic liver cancers is more than twenty times as many as that of primary liver cancers, and 20 to 50% of all cancers spread to the liver²⁴⁾. Surgical removal of liver cancer, not only primary cancer but also metastatic cancer is limited.

ISHIKAWA summarized that the rate of surgical removal of primary liver cancer is 25.8% and its two years survival rate is 30.3%¹³⁾.

The result of the operation for liver cancer is the worst as compared with cancer of other organs.

On the other hand, the cases in which cancer has already spread to the liver at the time of the first abdominal operation were found to be at the rate of 5 to 13% and about 10% of autopsy cases of cancer showed the metastases to the liver¹⁴⁾¹⁹⁾²¹⁾. And as regards the radiation therapy, liver parenchyma is said to be vulnerable to radiation owing to its sensitivity to radiant rays.

Judging from these points, local chemotherapy is greatly promising.

Anticancer drugs inhibit the growth of malignant tumor, but they also injure the normal cellular tissues of the host and so we should try to intensify the effects of anticancer drugs and to lessen their side effects as much as possible by improving the method of administration.

As to the liver, especially, it is convenient to carry out local chemotherapy as the inflow vessels and outflow vein of the liver are clearly divided.

Since the injection of anticancer drugs into the hepatic artery¹⁷⁾ was developed by MILLER and CRIMAN in 1961, a remarkable effect on liver cancer was observed.

STORER and others observed the effects of the injection of anticancer drugs into the portal vein²⁶⁾.

The investigation on the distribution of anticancer drugs in various body fluids and

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organs, such as the liver, and the inactivation of these drugs by the normal liver or the liver cancer tissue following such local chemotherapy are very important in order to clarify the problems on the effect of this therapy and in the prevention of side effects.

Chapter I

Inactivation of MMC or 5-FU by the normal liver, the metastatic lesion of liver, and the tumor tissue in vitro.

1. The method to measure the concentration of anticancer drugs.

The concentration of anticancer drugs in various organs or body fluids was measured by bioassay.

In practice, the Band culture method (OKUBO) in bioassay was used in this experiment²²⁾.

As test organisms *E. Coli B* for the measurement of MMC and *St. aureus 209-P* for 5-FU were used. The minimum inhibition concentration is 0.0025 mcg/ml and 0.025 mcg/ml, respectively (Table 1).

Table 1. Various conditions of measurement of anticancer agents concentration.

Method of measurement	Band culture method	
Anticancer agents	MMC	5-FU
Strain of test organisms	<i>E. coli B</i>	<i>Staph. aureus 209-P</i>
Number of organisms	$1.0 \times 10^7/\text{ml}$	$6.5 \times 10^7/\text{ml}$
Medium	Nutrient agar	M. H. medium
Incubation time at 37°C (hrs.)	5 to 7	7 to 9
Minimum inhibition concentration (mcg/ml)	0.0025	0.025

(1) Inactivation of MMC and 5-FU by the normal liver tissue of dogs.

Materials and methods

The fresh tissue of the normal liver was placed into the physiological saline solution, homogenized and made into 50% emulsion.

Five ml of this homogenate were mixed with an equal volume of MMC or 5-FU solution in vitro at 37°C and drug levels in the mixtures were measured every 15 minutes for two hours after the mixing.

Results

MMC was inactivated by more than 40%, and 5-FU by 20% immediately after the mixing, and each of them retained 28% and 44% of activity, respectively, 60 minutes later, and only a low % and 30% 120 minutes later.

The lower the concentration of anticancer drugs was, the stronger the inactivation became.

But when the liver homogenate was treated with heat of 100°C for 5 minutes, not much inactivation occurred (Fig. 1).

- (2) Inactivation of MMC and 5-FU by the normal liver tissue and the metastatic lesion of liver in man.

Results

The homogenate of the normal liver tissue inactivated MMC by 70 % and 5-FU by 20%, respectively, immediately after the mixing and only a low % and 27% of activity, respectively, remained 60 minutes later, and this inactivation progressed still further until 120 minutes later.

With the homogenate of the metastatic lesion of liver, a drop in activity was observed by 75% in MMC and by 20% in 5-FU. Although the inactivation progressed gradually in the course of time, each one of them still kept 10% and 60% of its activity, respectively, 120 minutes later (Fig. 2).

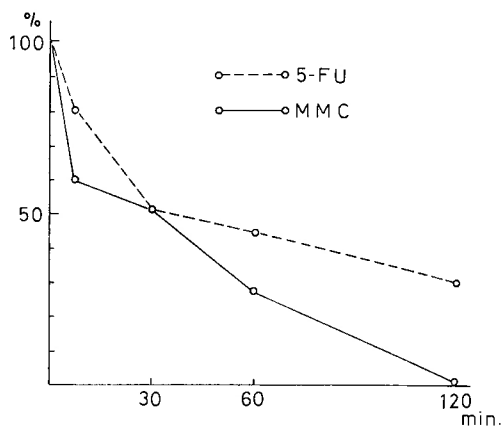


Fig. 1 Inactivation of MMC and 5-FU by dog liver homogenates (37°C , in vitro)

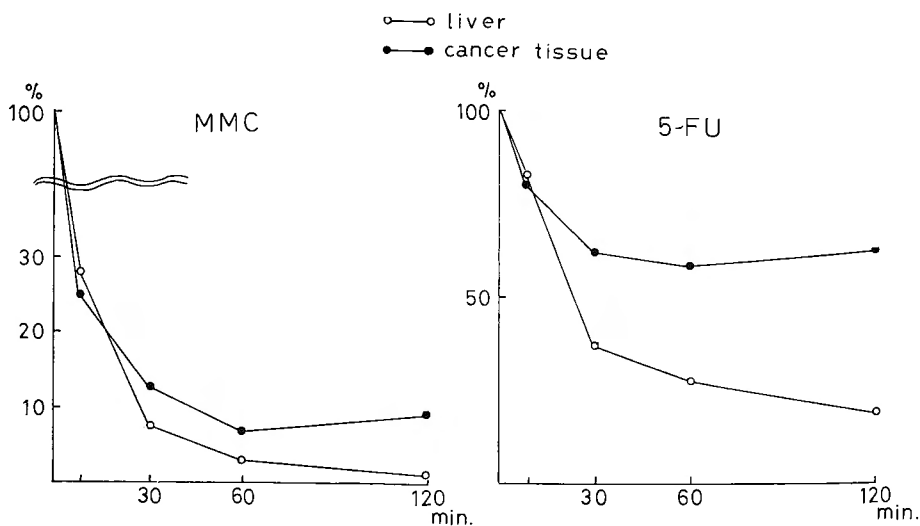


Fig. 2 Inactivation of MMC and 5-FU by human liver homogenates and cancer tissues (37°C , in vitro)

Chapter II

The concentration of anticancer drugs in various organs and body fluids following various types of administration of MMC or 5-FU into the blood vessels which flow into the liver.

Materials and methods

The method to collect samples of various body fluids is shown in Fig. 3.

Adult mongrel dogs weighing 6~11kg were used. The dogs were anesthetized by intramuscular injection of Ketamine chloride at the dose of 10mg/kg.

During surgery, air way was provided by an endotracheal intubation and oxygenated by AIKA's time-cycled respirator with the room air under positive pressure of 20cm H₂O and with controlled respiration of 20 times per minutes.

MMC or 5-FU was administered by various methods.

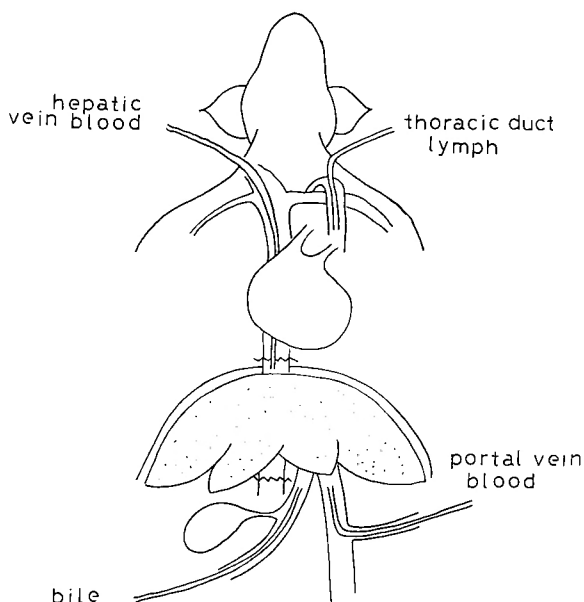


Fig. 3 Position of sampling tubes in dogs.

- (1) Concentration of MMC and 5-FU in various body fluids (hepatic vein blood, bile and thoracic duct lymph) following drip infusion into the mesenteric vein.
- a) Ten mg of MMC in 500ml of the physiological saline solution were injected into the mesenteric vein at the speed of 5ml/min. by drip infusion. And after the initiation of injection body fluids samples were collected at every standard time after infusion.

Result

The concentration in the hepatic vein blood and the thoracic duct lymph increased rapidly in the course of time, and especially the concentration in the thoracic duct lymph increased remarkably, showing about 5 times as much as that in the hepatic vein blood and nearly 100 times as much as that in the bile 80 minutes later. And the amount of lymph flow showed several times as much as that prior to drip infusion. Drug levels in the bile hardly increased from 40 minutes after infusion (Fig. 4).

- b) Two hundred and fifty mg of 5-FU in 500ml of the physiological saline solution were injected into the mesenteric vein similar to the way of MMC.

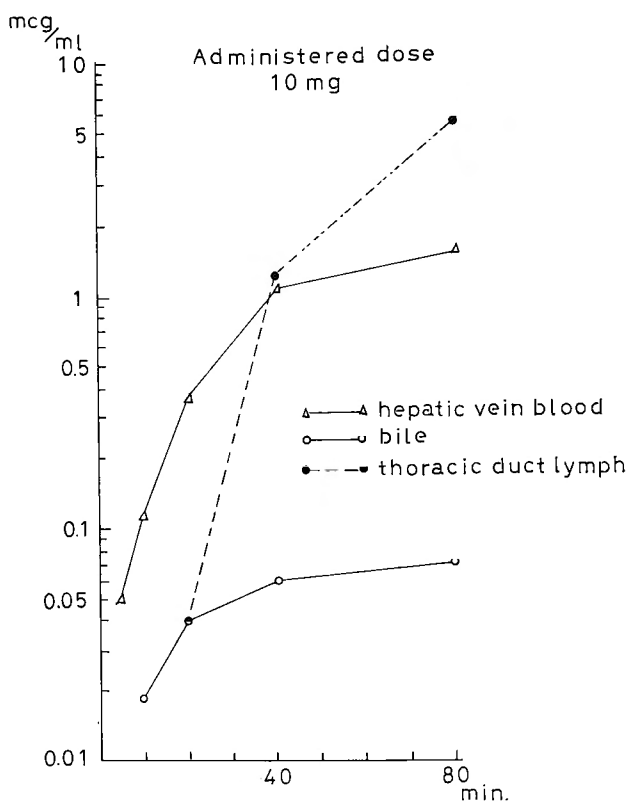


Fig. 4 Fluids levels of MMC in dogs following drip infusion into the mesenteric vein.

Results

Drug levels in the hepatic vein blood arrived at a peak value of 5.5 mcg/ml 20 minutes later and maintained the levels of 4~5mcg/ml thereafter.

The concentration in the thoracic duct lymph was not observed 5 and 10 minutes after infusion and showed a value of 3.5mcg/ml 20 minutes later. Then it decreased to 1mcg/ml.

This showed rather the opposite tendency to that in the case of MMC. The concentration in the bile increased in the course of time and showed a value of more than 10 times as much as that in the hepatic vein blood and was more than 100mcg/ml 80 minutes later.

It showed high excretion into the bile in contrast with MMC (Fig. 5).

- (2) Concentration of MMC and 5-FU in various body fluids (hepatic vein blood, bile and thoracic duct lymph) following one shot injection into the proper hepatic artery.

Two mg of MMC in 10 ml of the physiological saline solution were injected into the proper hepatic artery by one shot injection.

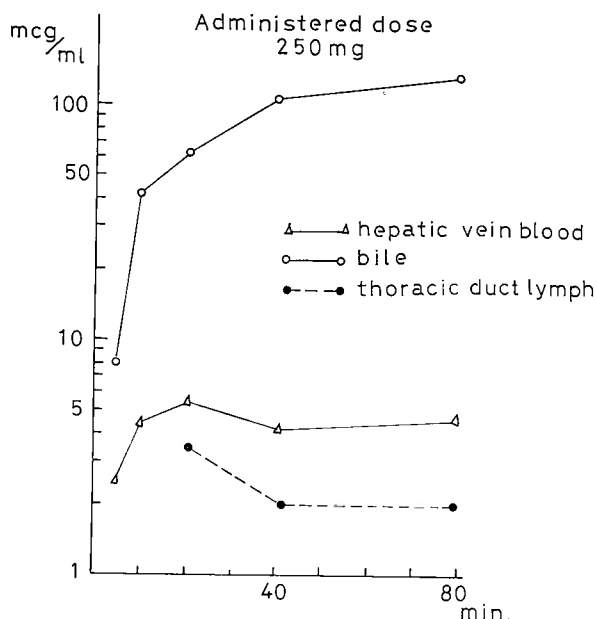


Fig. 5 Fluids levels of 5-FU in dogs following drip infusion into the mesenteric vein.

Results

The concentration in the hepatic vein blood showed a value of 1mcg/ml 5 minutes after injection, but it decreased in the course of time and showed only a value of 0.04 mcg/ml 80 minutes later. The concentration in the bile and thoracic duct lymph showed peak values of 0.15 and 0.5mcg/ml, respectively, 20 minutes later and then decreased in the course of time.

A fairly high concentration of MMC was found after the passage through the liver.

When 250mg of 5-FU in 5ml of the physiological saline solution were injected, the concentration in the hepatic vein blood showed a value of 55mcg/ml 5 minutes later and then it decreased in the course of time.

The concentration in the bile was higher than that in the thoracic duct lymph in contrast with MMC and showed peak values of 100mcg/ml and 60mcg/ml, respectively, 20 minutes later, and then decreased in the course of time.

Higher concentration of MMC was found in the thoracic duct lymph, while that in 5-FU in the bile, and both of them showed the same tendency in the changes of drug levels (Fig. 6).

- (3) The difference between drug concentration in the portal vein blood and that in the hepatic vein blood when MMC or 5-FU was injected into the mesenteric vein by drip infusion.

Ten mg of MMC or 250 mg of 5-FU in 500ml of the physiological saline solution were injected into the mesenteric vein by drip infusion at a speed of 5ml/min.

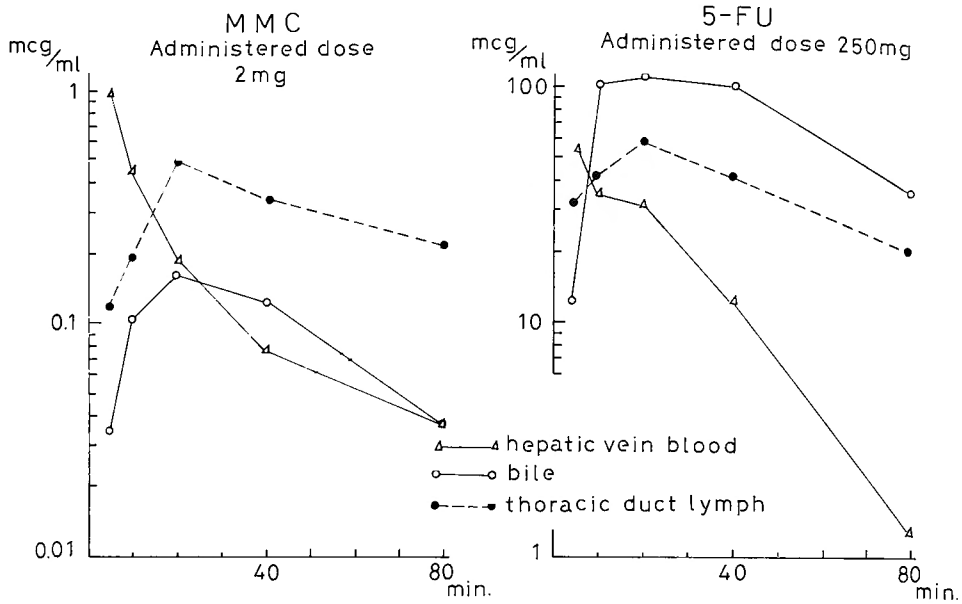


Fig. 6 Fluids levels of MMC and 5-FU in dogs following injection into the proper hepatic artery.

Drug levels in the portal vein blood and the hepatic vein blood were measured in the course of time.

Results

Comparing the concentration in these samples at 40 minutes and 80 minutes after the initiation of drip infusion, the concentration of MMC decreased by 23~25%, while that of 5-FU decreased by 62~67% and the decrease in the latter was more remarkable (Fig. 7).

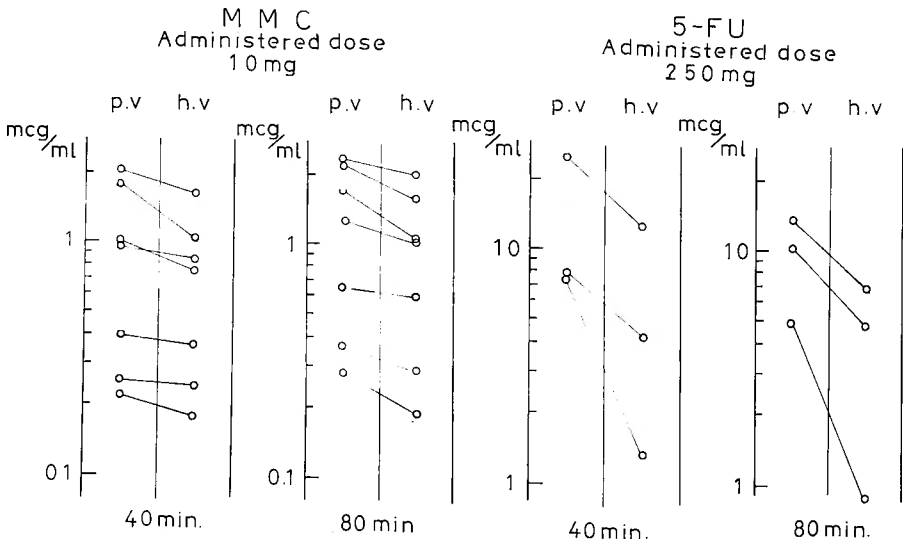


Fig. 7 Difference of MMC and 5-FU levels between the portal and hepatic venous blood in dogs following drip infusion into the mesenteric vein.

- (4) The difference between drug concentration in the proper hepatic artery blood and that in the hepatic vein blood when MMC or 5-FU was continuously injected into the common hepatic artery.

Ten mg of MMC or 250mg of 5-FU in 500ml of the physiological saline solution were injected continuously into the common hepatic artery at a speed of 25ml/8 min. with Mela food pump through the tube inserted into the common hepatic artery via the left gastric artery.

Results

Comparing the concentration in these samples at 40 minutes and 80 minutes after the initiation of injection, the concentration of MMC decreased by 71~77%, while that of 5-FU decreased by 21~32%.

The decrease of MMC concentration was remarkable as compared with that in the case of injection into the mesenteric vein (Fig. 8).

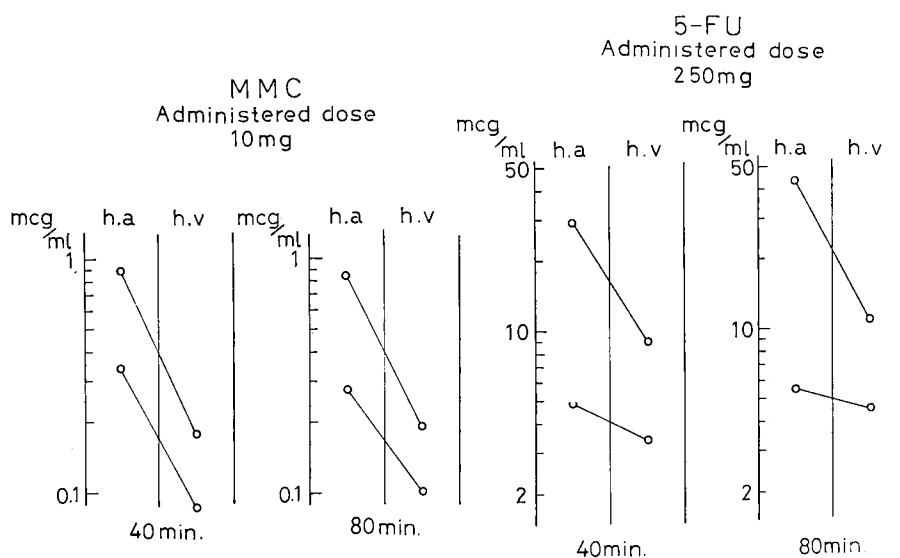


Fig. 8 Difference of MMC and 5-FU levels between proper hepatic arterial and hepatic venous blood in dogs following continuous infusion into the common hepatic artery.

- (5) The effect of the occlusion of the proper hepatic artery on drug levels in the hepatic vein blood when MMC or 5-FU was injected into the mesenteric vein by drip infusion.

Ten mg of MMC or 250mg of 5-FU in 500ml of the physiological saline solution were injected into the mesenteric vein by drip infusion.

The proper hepatic artery was occluded with a Bulldog's clamp 5 minutes before the initiation of injection.

Results

Following the occlusion of the proper hepatic artery drug levels in the hepatic vein blood showed a slightly augmented decrease (Fig. 9).

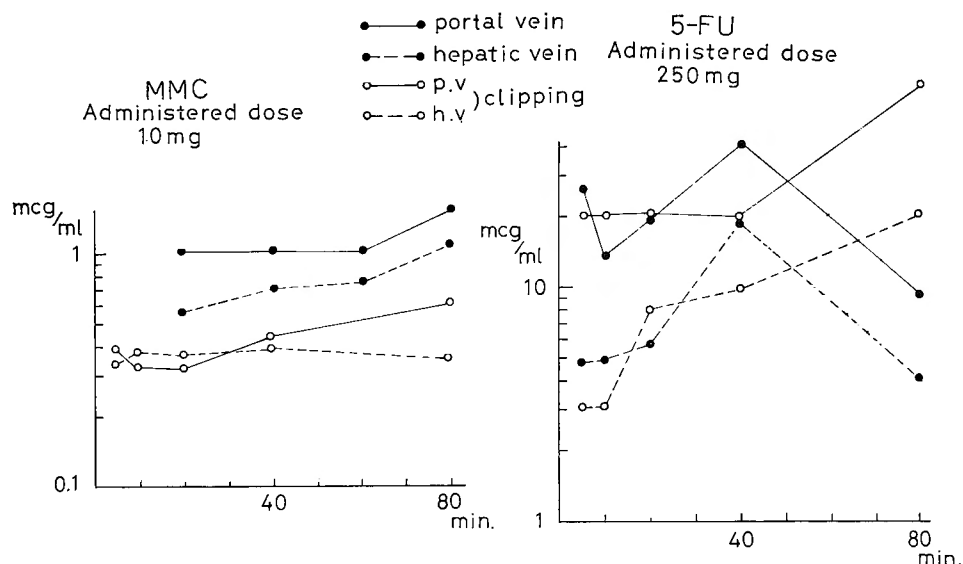


Fig. 9 Influence of the proper hepatic artery clipping following drip infusion into the mesenteric vein.

- (6) The effect of previous administration of V. B₆ on drug levels in the hepatic vein blood when MMC was injected into the mesenteric vein by drip infusion.

Thirty mg of V. B₆ were administered intravenously 5 minutes before MMC was injected into the mesenteric vein by drip infusion.

Results

Drug levels in the hepatic vein blood decreased remarkably as compared with those in the portal vein blood, showing a decrease of 50~60 %, whose rate was two or three times as much as that when V. B₆ was not administered.

And this premedication will be effective in preventing side effects on such occasions (Fig. 10).

- (7) The concentration of MMC which was not found in the hepatic vein blood, but was found in the portal vein blood when it was injected into the mesenteric vein by drip infusion.

One half mcg/ml of MMC were injected into the mesenteric vein at a speed of 10ml/min.

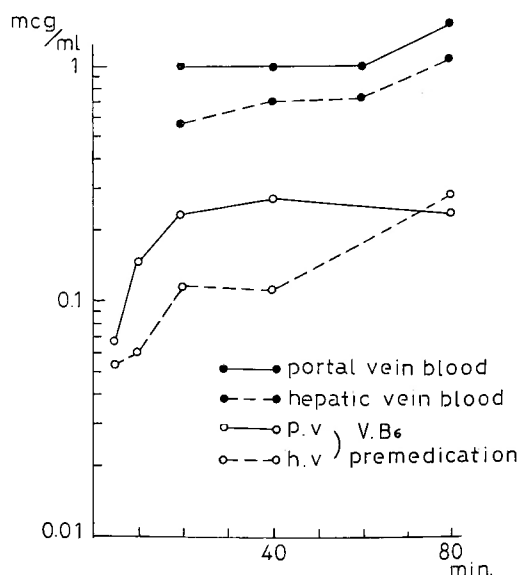


Fig. 10 Effect of V. B₆ premedication at drip infusion of MMC into the mesenteric vein (MMC 10mg/500ml).

Results

MMC was not found in the hepatic vein blood at the concentration of 0.006 mcg/ml in the portal vein blood.

It was always found in the hepatic vein blood at the concentration of more than 0.01mcg/ml in the portal vein blood.

When MMC was found in the portal vein blood and was not found in the hepatic vein blood, it is reasonable to think that anticancer drug was either inactivated by the liver tissue or incorporated into this tissue.

In the case of injection into the mesenteric vein, the concentration in the bile was very low as compared with that in the hepatic vein blood and moreover the concentration in the thoracic duct lymph was low till 40 minutes later.

There will be little side effects in these low concentrations, but we can not expect an antitumor effect of MMC, as its effect is dependent on the drug concentration (Fig. 11).

- (8) The drug concentration in the bone marrow when MMC was injected into the mesenteric vein by drip infusion.

Ten mg of MMC in 500ml of the physiological saline solution were injected at a speed of 5 ml/min. by drip infusion. After finishing the infusion the concentration of MMC in the bone marrow of long bone, such as the thigh bone, shin bone, etc., was measured, but MMC could not be observed at all.

- (9) The effect of the performance of the portacaval shunt on drug levels in the hepatic vein blood when MMC or 5-FU was injected into the proper hepatic artery by one shot injection.

In order to simplify the blood vessels which flow into the liver, carrying out the end-to-side anastomosis between the portal vein and the inferior vena cava, the portal vein blood was shunted into the inferior vena cava.

Ten mg of MMC in 20 ml of the physiological saline solution or 250 mg of 5-FU in 5ml of the physiological saline solution was injected into the proper hepatic artery by an one-shot injection.

Results

In the case of MMC, the performance of the end-to-side portacaval shunt hardly affected the drug concentration in the hepatic vein blood, but in the case of 5-FU, it showed about two times as much as the concentration, as compared with that before

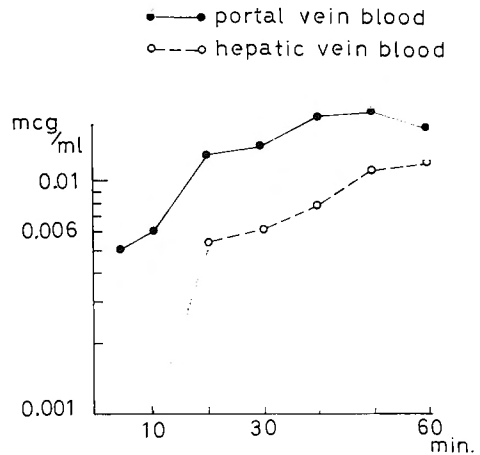


Fig. 11 Blood levels of MMC in dogs following drip infusion into the mesenteric vein (MMC 0.5mcg/ml, 10ml/min)

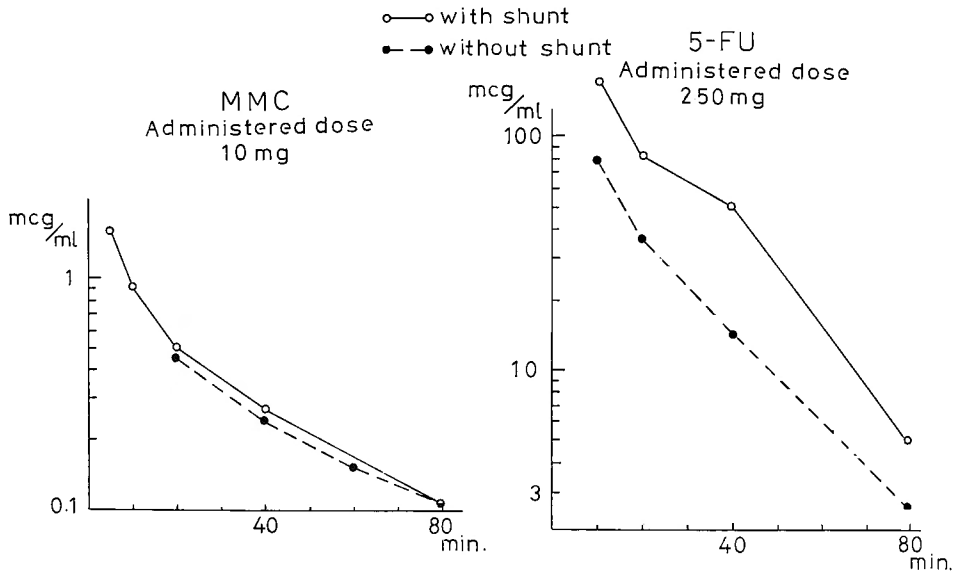


Fig. 12 Blood levels of MMC and 5-FU in the hepatic vein in dogs with or without portocaval shunt following an one-shot injection into the common hepatic artery.

shunting (Fig. 12).

- (10) The drug levels in the liver tissue when MMC or 5-FU was injected into the mesenteric vein by drip infusion or into the proper hepatic artery by an one-shot injection.

Ten mg of MMC in 500ml of the physiological saline solution were injected into the mesenteric vein by drip infusion.

And 10mg of MMC in 10ml of the physiological saline solution or 250mg of 5-FU solution were injected into the hepatic artery by an one-shot injection.

Results

MMC was not found in the normal liver tissue.

As for 5-FU, it was found in this tissue at the rate of 38mcg per 1g of liver tissue.

This meant that MMC is strongly inactivated by the liver.

- (11) The drug concentration in the peripheral blood when MMC was injected by an one-shot into the celiac artery of the patient with metastatic liver tumor.

Ten mg of MMC in 10 ml of the physiological saline solution were injected by an one-shot by Seldinger's method into the celiac artery and the concentration of MMC in the peripheral blood was measured in the course of time.

Results

Ten minutes after injection, drug levels in the peripheral blood showed a value of 0.14 mcg/ml and then decreased gradually in the course of time and 80 minutes later they showed only the value of 0.06mcg/ml.

- (12) The drug concentration in the peripheral blood when MMC was injected continuously

into the common hepatic artery of the patient with metastatic liver tumor.

The concentration of MMC in the peripheral blood was measured during a continuous injection into the common hepatic artery with the infusion pump.

Every sample showed a value less than 0.0025mcg/ml, minimum inhibition concentration of the Band culture method.

- (13) The drug concentration in the peripheral blood when 5-FU was injected into the peripheral vein of the patient with metastatic liver tumor.

After injection of 500mg of 5-FU into the cephalic vein, blood samples were collected from the opposite cephalic vein in the course of time and the drug concentration was measured.

Results

Ten minutes after injection of 500mg of 5-FU into the cephalic vein, drug levels in the peripheral vein blood showed a value of 35mcg/ml, and 80 minutes later 2.6mcg/ml, but 160 minutes later 5-FU was not detected.

Discussion

It is very important to know the relation between the tumor and the system of blood vessels which come in and out when we carry out local chemotherapy for liver tumor.

Especially, the liver differs from other organs because it has the complex blood vessels mechanism such as the hepatic artery, the hepatic vein, and the portal vein.

Seventy-five to 85% of blood flow in the normal liver comes from the portal vein, and as for the nutritive vessels of the liver cancer, SEGALL described in 1923, that the inflow blood vessel of the tumor was the branch of hepatic artery for metastatic liver tumor²⁵⁾.

And BREEDIS & YOUNG, FISHER, and HEALEY described that the nutritive vessel of the primary liver tumor, the metastatic liver tumor, and experimental liver tumor lesion were chiefly the hepatic artery⁴⁾⁵⁾⁸⁾¹¹⁾.

And the approach through the hepatic artery was the first choice for local chemotherapy of liver tumor.

But ACKERMAN and others reported that the relation between the hepatic artery and the portal vein was changeable with the size and with the progress of tumor growth, and that the vascular plexus of tumor was even replaced into the portal vein system reversely due to the rapid change of the artery system which was superior to others¹²⁾.

HONJO and others reported that the primary liver tumor in the cholangioma type was chiefly supplied with the hepatic artery system but that in the hepatoma type was supplied much with the portal vein system rather than the hepatic artery. And the metastatic liver tumor was under the control of the portal vein system at the periphery of the tumor but under the control of the hepatic artery in its central portion¹²⁾.

Therefore, it is needless to say that we can not disregard the approach through the portal vein system.

Now it is very important to clarify how MMC and 5-FU are inactivated and how they

are excreted when they are given into the hepatic artery or into the portal vein by various methods of administration in carrying out the local chemotherapy.

MMC and 5-FU were rapidly inactivated by the normal liver tissue, but were not inactivated remarkably by the metastatic liver tissue.

FUJITA and ITO showed similar results⁹⁾¹⁵⁾.

It is thought to be reasonable that when MMC was injected into the mesenteric vein by drip infusion, the concentration in the hepatic vein blood increased in the course of time, but it is noteworthy that the flow of thoracic duct lymph increases and the concentration in the thoracic duct lymph rapidly increases at the same time on such an occasion.

This method will be available for cases in which the metastatic lesions in the liver and left supraclavicular nodes are observed clinically, because the drug concentration in the thoracic duct lymph even comes up to 5mcg/ml by infusing 10mg of MMC in 500ml of the physiological saline solution.

A significant increase in excretion into the bile was not observed.

As for MMC, HATTORI and others made clear that it was the concentration in blood that influenced chiefly upon antitumor effect and 10mcg/ml was the least effective concentration and the concentration less than 10mcg/ml had definitely no legal effect and caused only side effect¹⁰⁾.

On the contrary, 5-FU need not give high concentration by an one-shot injection because 5-FU was a pyrimidin metabolic antagonist and was enclosed in a tumor cell which was synthesizing DNA and exhibited an expected effect by inhibiting DNA synthesis.

MENDELSON reported that antitumor effect of 5-FU was rather expected by drug injections which can maintain a standard concentration, even if a low concentration, for a long period of time¹⁶⁾.

When 5-FU was injected into the mesenteric vein by drip infusion, the concentration in the bile increased remarkably as compared with the concentration in the hepatic vein blood and the thoracic duct lymph.

The concentration in the bile showed a high value of about 100mcg/ml as compared with those of 3~4 mcg/ml in the hepatic vein blood and 1mcg/ml in the thoracic duct lymph.

Immediately after the injection of MMC into the proper hepatic artery by an one-shot injection, MMC showed the high levels in the hepatic vein blood, that is, the concentration showed the highest value of 1.4mcg/ml 5 minutes after the injection of 2mg of MMC, and still higher concentration in the thoracic duct lymph.

As for the method of administration of the concentration-dependent antitumor drugs, an antitumor effect can not be expected by the methods except for an one-shot injection.

The intravenous injection of 2~4mg of MMC is performed in combination with other drugs. However, in the author's opinion, this method not only increases side effects, but also it can not exhibit a sufficient antitumor effect.

Following the injection of 5-FU into the proper hepatic artery by one-shot, high drug

levels were observed in the hepatic vein blood, the thoracic duct lymph and the bile, as compared with the case of injection into the mesenteric vein by drip infusion, that is, it showed 10 to fifty times as high as concentration.

As for the injection by the infusion pump, the drugs were injected into the common hepatic artery, and the difference between the concentration in the proper hepatic artery blood and that in the hepatic vein blood was investigated.

But, when 10mg of MMC in 500ml of the physiological saline solution was injected continuously, drug levels in the proper hepatic artery blood did not come to 1mcg/ml at the highest concentration, the concentration in the hepatic vein blood was less than 0.2 mcg/ml.

In other words, though 20mcg/ml of MMC were injected into the common hepatic artery continuously, the concentration in the proper hepatic artery remained below 1mcg/ml.

It seems that we can not expect an antitumor effect unless a fairly large amount of MMC is injected.

In the case of continuous injection of 250mg of 5-FU, the concentration in the proper hepatic artery came to more than 40mcg/ml.

ROCHLIN, BURROWS and CLARKSON also observed the effect of 5-FU by the long-term injection⁶⁾⁷⁾²³⁾.

For the therapy of liver tumor, the interception of blood flow of the hepatic artery is carried out, and this way came to be used since BENGMARK, NILSON, and others reported that the ligation of the branch of inflow hepatic artery was effective for liver tumor³⁾²⁰⁾.

MURRAY-LYON and others try to inject 5-FU through the portal vein after ligating the hepatic artery for metastatic liver tumor¹⁸⁾.

According to the author's experimental results, when MMC or 5-FU was injected into the mesenteric vein by drip infusion, the influence of the ligation of the hepatic artery upon the concentration in the hepatic vein was scarcely observed.

As for the side effect of anticancer drugs in the case of local medication we must take every possible precaution not to inject a large amount of drugs.

Especially regarding the influence upon the bone marrow, after 10mg of MMC in 500ml of the physiological saline solution were injected into the mesenteric vein by drip infusion within 100 minutes, MMC could not be observed at all in the bone marrow of the long bones.

As to the prevention of side effect, there are many countermeasures and it became clear that a premedication of V. B₆ decreased remarkably the concentration of MMC in the peripheral blood.

FUJITA and others also reported that in a test with a mouse an acute and a chronic toxicity of MMC was reduced and the maximum concentration in blood dropped by the premedication of V. B₆⁹⁾.

From the viewpoint of prevention of side effects, it would be a better way to medicate V. B₆ one or two hours after giving an anticancer drug in order to extinguish the anticancer

drug of low concentration which has no antitumor effect and brings only side effects.

Besides V.C and glutathione are said to quicken the inactivation of drugs by the liver.

As for the concentration in the liver tissue of MMC and 5-FU, 5 minutes after the injection of 250mg of 5-FU into the hepatic artery by one shot, 38mcg/g of 5-FU were detected, but MMC was not observed at all.

This showed that the liver played an important role in the inactivation of MMC.

FUJITA and others reported that MMC and 5-FU showed a tendency to distribute in tumor tissue in a large quantity, but MMC was not found in the liver, and 5-FU was found in a relatively great amount⁹⁾. When MMC was injected into the celiac artery of a patient by one shot clinically and the concentration in the peripheral blood was measured, a very low concentration was observed in comparison with the injected amount of 10mg, that is, drug level was 0.14mcg/ml 10 minutes later, and 0.06mcg/ml 80 minutes later, and the peak concentration in the blood was 0.25mcg/ml.

When 10mg of MMC was injected into the hepatic artery by one shot in dogs, the peak concentration in the hepatic vein blood showed 2 mcg/ml and the concentration in the peripheral blood was 1.6mcg/ml. Therefore, if 20~30mg of MMC were injected into the hepatic artery by one shot clinically, it is presumed that the blood can keep the concentration to a certain degree by which a sufficient antitumor effect can be obtained.

ITO described that the maximum concentration in the hepatic vein blood showed 6.3 mcg/ml when 20mg of MMC were injected into the hepatic artery by one shot¹⁴⁾.

Conclusion

MMC or 5-FU was injected into the blood vessels which flow into the liver by various types of administration and drug levels in various body fluids and tissues were measured.

The inactivation of these drugs by such tissues, as the normal liver, liver tumor, etc., was also investigated. And the following results were obtained.

- 1) The tissue homogenates of the normal liver of men and dogs inactivated MMC and 5-FU remarkably.
- 2) When MMC or 5-FU was injected into the mesenteric vein or into the hepatic artery by one shot, MMC was excreted into the thoracic duct lymph, and 5-FU into the bile in high concentration, respectively.
- 3) The inactivation of MMC in the liver occurred markedly when it was injected into the hepatic artery while that of 5-FU occurred in the same manner when injected into the mesenteric vein.
- 4) The mass injection of MMC into the hepatic artery by one shot showed that it keeps a sufficient concentration by which we can expect an antitumor effect judging from its concentration in the hepatic vein blood, and it was verified that the injection of MMC in a small amount on the systemic route was quite ineffective and only brought side effects.
- 5) When MMC was injected continuously into the portal vein in dogs, the distribution of

MMC in the bone marrow was not observed.

- 6) Premedication of V.B₆ reduced MMC levels in the hepatic vein when MMC was injected into the mesenteric vein by drip infusion.
- 7) It is hard to obtain an effective drug concentration in the peripheral blood during continuous injections of MMC with the infusion pump, and its effect can not be expected.
- 8) Even when 10mg of MMC was injected into the celiac artery by one shot, the concentration in the peripheral blood was comparatively low.
- 9) When MMC was injected into the hepatic artery by one shot, drug level in the normal liver was not observed and 5 minutes after 250mg of 5-FU was injected, similarly, 38mcg/g of 5-FU was detected in the normal liver.

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和文抄録

肝癌の局所性化学療法に関する基礎的検討

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肝臓は悪性腫瘍の転移の好発臓器であり、あらゆる部位の悪性腫瘍が肝に転移をきたす。この肝癌はこれが原発性であれ、転移性であれ、これを切除しうる症例はかぎられており、その切除率は他臓器の癌のそれと比較して全く不良であり、しかも放射線療法の効果も限られているので、局所性化学療法の効果に期待がよせられている。肝癌に対する局所性化学療法を行うさいに各種体液および肝組織をはじめとする各種臓器内の制癌剤濃度、あるいは正常肝または肝癌組織による制癌剤の不活性化に関する問題はこの療法の奏効機転と副作用防止の解明に重大である。イヌについて帯培養法 (大久保) を用いて、MMC または 5-FU を各種方法で肝臓に流入する脈管内へ投与し、これらの薬剤がいかに不活性化されるか、またどのように排泄されるかを明らかにするために、MMC および 5-FU の各種体液中の濃度を測定し、次のような結果を得た。

1) 人および犬の正常肝エマルジョンは強力なMMC および 5-FU の不活性化作用を示した。

2) 門脈系静脈内投与または肝動脈内ワンショット投与の場合にMMCは胸管リンパ中に、また5-FUは胆汁中に高濃度に排泄された。MMCの門脈内投与による効果が示唆された。

3) 肝臓における制癌剤の不活性化はMMCでは経肝動脈性投与、一方5-FUでは経門脈性投与の場合に

最も著明にみられた。

4) MMCの肝動脈内ワンショット大量投与は肝静脈血中濃度から判定すると、抗腫瘍効果を期待できるに十分な濃度を保つことが証明された。また少量の全身投与は全く無意味であり、副作用のみをきたすと考えられた。

5) 犬におけるMMCの門脈内持続注入のさいには骨髓におけるMMCの分布は証明できなかった。

6) V.B₆の前投与は経門脈性投与のさいのMMCの肝後性漏出を減少せしめた。従って副作用防止の点からいえば、V.B₆は前投与よりも抗腫瘍効果のない、副作用のみをきたすような低濃度の制癌剤を消失せしめる目的で、制癌剤投与後1~2時間後に投与するのがよいと考えられた。

7) 持続注入ポンプによるMMCの投与は有効血中濃度が得がたく、その効果は期待できないと考えられた。

8) 腹腔動脈内へMMC 10mgを投与した場合には末梢血中濃度は比較的低値に止まった。

9) ワンショット肝動脈内投与では正常肝ではMMCは検出されなかったが、5-FUは250mg投与5分後に肝組織1gについて38mcgが検出された。肝によるMMCの不活性化作用が強いことが示唆された。