STUDIES ON DISTRIBUTION OF ORAL 5-FLUOROURACIL FOR TREATING GASTRIC CANCER

1) COMPARISON OF ORAL ADMINISTRATION AND INTRAVENOUS ADMINISTRATION

KEIICHI MIYASAKA
Dept. of Radiology
Showa University
(Director : Prof. TOYOHIKO HISHIDA)

(Received September 24, 1983)

When antineoplastic agent is administered to patients with advanced gastric cancer, two modes of administration i. e., oral administration and intravenous administration, will be thought. In order to investigate the metabolism *in vivo* of antineoplastic agent, the study has been conducted by using 5-fluorouracil (5-FU).

i) A peak level of the 5-FU concentration in blood of the peripheral vein in humans and normal dogs was lower in oral administration than in intravenous administration, but 5-FU was maintained in blood for a longer time in case of oral administration.

ii) It was demonstrated that 5-FU was excreted from the gastric juice in humans and normal dogs.

iii) It was confirmed that the 5-FU concentration in the gastric mucosa of normal dogs was maintained for a long time, adsorbed and remained well to the tissues.

iv) It was confirmed that 5-FU was rapidly transferred into the portal vein when administered from the serous membrane to the stomach of the normal dog in which the cardia and pylorus were ligated. This suggested that 5-FU was absorbed from the gastric wall.

v) The 5-FU concentration in blood of the portal vein in the normal dogs was maintained at higher level than that of the peripheral vein when administered by oral route, whereas the 5-FU concentration in blood of both the portal and the peripheral veins demonstrated nearly the same pattern when administered by intravenous route. From the above, it was confirmed that oral administration showed the different *in vivo* kinetics from that of intravenous administration because 5-FU adsorbed and absorbed directly to cancer lesion of the stomach when administered orally.

INTRODUCTION

In recent year, it has become clear that oral preparations of fluorinated pyrimidines, 5-FU or its derivative, Tegafur alone or in combination with Mitomycin C or Adriamycin were effective for advanced gastric cancer[1,2]. Especially, oral preparation of 5-FU is expected as an effective antineoplastic agent because 5-FU is directly contacted with cancer lesion of the stomach in active form. In fact, there have been several reports describing that marked improvement on macroscopic morphologic findings was observed[1,3-13].

Accordingly, in this paper, the comparative study of two modes of administration, by oral route and by intravenous route was conducted in order to elucidate the kinetics *in vivo* of 5-FU when administered by oral route, that is, how 5-FU is distributed, remained, absorbed in the stomach and transferred into the peripheral or portal vein.

I. MATERIALS AND METHODS

1. Determination of 5-FU concentration in blood of the peripheral vein and in gastric juice

in patients with malignant tumor

a. Blood in the peripheral vein

In oral administration, 200 mg of 5-FU dry syrup which was dissolved in 100 ml of tap water was administered at 30 minutes after breakfast to 8 in-patients with gastrointestinal cancer without passage disturbance, metastasis to the liver, renal diseases or cardiac diseases, and the blood was collected from the peripheral vein at hourly intervals.

In intravenous administration, 200 mg of 5-FU solution was given by a bolus intravenous injection to 6 in-patients with gastrointestinal cancer who satisfied the conditions mentioned above, and the venous blood was collected.

b. Gastric juice

4 μg/kg of tetragastrin was intramuscularly administered to 6 patients with gastrointestinal cancer and simultaneously 200 mg of 5-FU was administered intravenously, and afterwards, the gastric juice was collected.

2. Determination of 5-FU concentration in blood, gastric juice and several organs of normal dogs

In oral administration, 10 mg/kg or 20 mg/kg of 5-FU dry syrup which was dissolved in tap water was infused through a fibersigmoidscope (FSS-L Machida Co., Ltd.) into the stomach of anesthetized 6 mongrel dogs (11±2 kg, B.W.). Then, the posture of the dogs was intensely rolled right and left. However, when the 5-FU concentration in blood of the portal vein was determined by ligature of the stomach, the esophagous-gastric junctions and the pyloric canal were ligated after the blood vessels were exposed and removed.

After the pulsation of the artery was confirmed, 10 mg/kg of 5-FU dry syrup dissolved in tap water was infused into the stomach through a needle which pierced the stomach wall from the serous membrane side.

a. Collection of blood of the peripheral vein

About 3 ml of blood of the peripheral vein was collected from the femoral vein at hourly intervals.

b. Collection of blood of the portal vein

After abdominal incision, about 3 ml of blood of the portal vein was collected at hourly intervals through a catheter which was inserted into the portal vein from the splenic vein.

c. Collection of the tissue specimen of the gastric mucosa and various organs

The tissue specimens of the gastric mucosa were collected from 8 regions of the stomach according to the procedure of gastric biopsy at 20~60 minutes intervals.

At 60, 180 and 360 minutes after 5-FU administration, each of 3 dogs was bled to death and received autopsy. The gastric wall which was divided into the superficial layer (mucosa and submucosa) and the deep layer (muscular layer and serosa) of the corpus and antrum, was collected. Further, the tissue specimens of the small intestine, large bowel, mesenteric lymph nodes, brain, lung, liver, pancreas, and kidneys were collected.

d. Collection of gastric juice

After the gastric tube was inserted into the stomach of the anesthetized dogs and tetragastrin was infused, the gastric juice was collected.

3. Method of determination of 5-FU concentration

The 5-FU concentration was determined according to the bioassay using *Staphylococcus aureus* 209 P described by FUJITA[10].

II. RESULTS

1. Changes of 5-FU concentration in blood of the peripheral vein and in gastric juice in humans

a. Concentration in blood of the peripheral vein

The results obtained from patients to whom 200 mg of oral administration of 5-FU dry syrup and 200 mg of intravenous administration of 5-FU were given were shown in Fig. 1.

In case of oral administration, the mean level (trace was calculated as 0) showed as high as 0.0176±0.0054 μg/ml after 5 minutes, 0.0231±0.0091 after 10 minutes and 0.145±0.051 after 15 minutes, and thereafter, tended to decrease:

Fig. 1 5-FU levels in peripheral plasma after administration of 5-FU in patients with gastrointestinal cancer

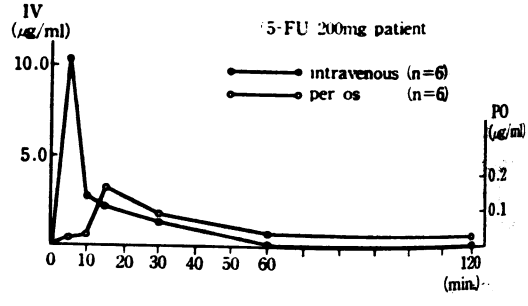


Fig. 2 5-FU levels in gastric juice after intravenous administration of 5-FU in patients with gastrointestinal cancer

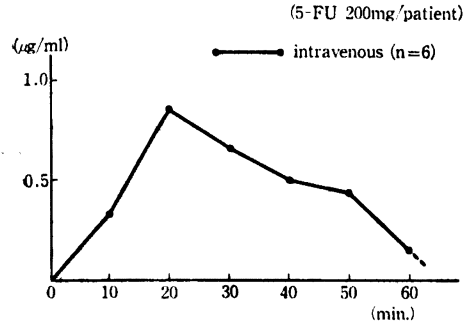
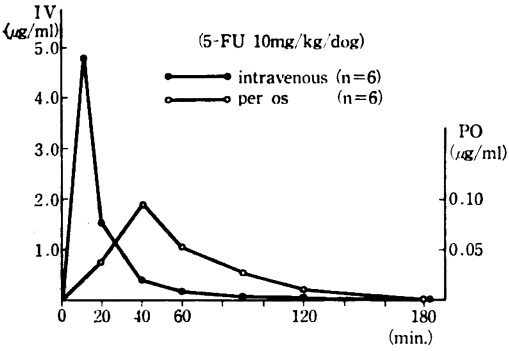


Fig. 3 5-FU levels in peripheral plasma after administration of 5-FU in dogs



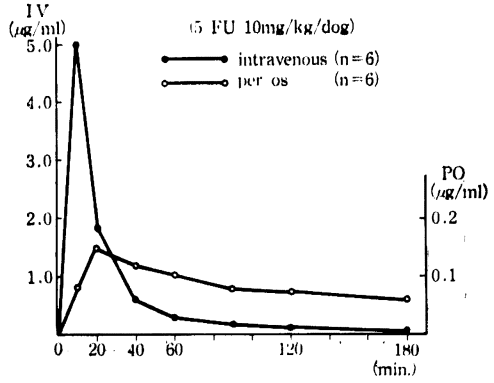
0.0914±0.0704 μg/ml after 30 minutes, 0.0369±0.0129 after 60 minutes and 0.0273±0.0253 after 120 minutes.

In case of intravenous administration, the mean highest level was 10.43±1.83 μg/ml after 5 minutes of administration and thereafter, decreased rapidly, i.e., 3.798±0.978 after 10 minutes, 2.173±1.153 after 15 minutes, 1.373±0.371 after 30 minutes, 0.005±0.002 after 60 minutes and trace after 120 minutes.

b. Concentration of gastric juice

Fig. 2 shows the time-course changes of 5-FU concentration in gastric juice following 200 mg of intravenous administration to patients. The mean level rose with time, i.e., 0.323±0.152 μg/ml after 10 minutes, and 0.857±0.261 after 20 minutes, and thereafter, tended to decrease gradually 0.650±0.275 after 30 minutes, 0.498±0.216 after 40 minutes, 0.430±0.142 after 50 minutes and 0.142±0.075 after 60 minutes.

Fig. 4 5-FU levels in portal plasma after administration of 5-FU in dogs



2. Changes of 5-FU concentration with time in normal dogs

a. Concentration in blood of the peripheral vein

The results were shown in Fig. 3. In oral administration group, the mean level was 0.0399±0.0129 μg/ml after 20 minutes, and 0.0959±0.0395 after 40 minutes, and thereafter, decreased to 0.052±0.023 after 60 minutes, 0.0291±0.0162 after 90 minutes, 0.0116±0.0090 after 120 minutes and trace after 180 minutes. In intravenous administration, the highest level was 4.833±1.833 μg/ml after 10 minutes, and thereafter decreased rapidly to 1.492±0.482 after 20 minutes, 0.392±0.122 after 40 minutes, 0.153±0.062 after 60 minutes, 0.042±0.023 after 90 minutes and 0.010±0.006 after 120 minutes, and trace after 180 minutes.

b. Concentration in blood of the portal vein

The results were shown in Fig. 4. In oral administration, the mean level was 0.0795±0.0461 μg/ml after 10 minutes and 0.1532±0.0075 after 20 minutes, and thereafter showed a tendency to gradually decrease, i.e., 0.1290±0.0452 after 40 minutes, 0.1167±0.0400 after 60 minutes, 0.0750±0.0405 after 90 minutes, 0.0725±0.0356 after 120 minutes and 0.0585±0.0247 after 180 minutes. In intravenous administration, the highest level was 5.00±1.50 μg/ml after 10 minutes, and thereafter decreased rapidly to 1.827±0.607 after 20 minutes, 0.617±0.367 after 40 minutes, 0.313±0.093 after 60 minutes, 0.107±0.009 after 90 minutes, 0.017±0.003 after 120 minutes, and trace after 180 minutes. Furthermore, in order to investigate the process of 5-FU adsorption and absorption to the

Fig. 5 5-FU levels in portal plasma after intragastric administration of 5-FU dry syrup in dogs

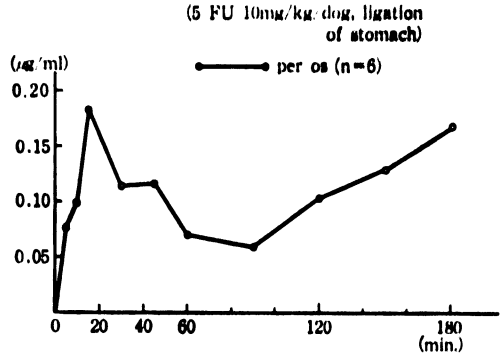


Fig. 6 5-FU levels in gastric juice after intravenous administration of 5-FU solution in dogs

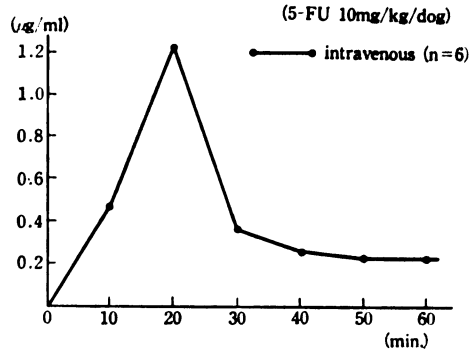
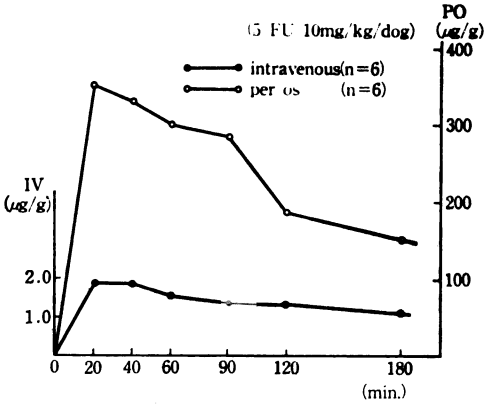


Fig. 7 Gastric mucosal 5-FU levels after administration of 5-FU in dogs



stomach, the stomach was ligated and the changes of 5-FU concentration in blood of the portal vein in normal dogs were measured with time.

The results were shown in Fig. 5. The mean highest level was 0.0534±0.0251 μg/ml after 5 minutes, 0.0798±0.0293 after 10 minutes and 0.1421±0.0411 after 15 minutes, and thereafter decreased to 0.1275±0.0327 after 30 minutes, 0.1144±0.0223 after 45 minutes, 0.0756±0.0165 after 60 minutes and 0.0674±0.0404 after 90 minutes. However, it showed a tendency to increase again thereafter, that is, 0.0764±0.0182 after 120 minutes, 0.0659±0.0254 after 150 minutes and 0.1105±0.0299 after 180 minutes.

c. Gastric juice

The results were shown in Fig. 6. The mean level was risen to 0.474±0.098 μg/ml after 10 minutes and 1.230±0.437 after 20 minutes, and thereafter showed a tendency to decrease, i.e., 0.363±0.121 after 30 minutes, 0.263±0.098 after 40 minutes, 0.233±0.064 after 50 minutes and 0.236±0.082 after 60 minutes.

d. 5-FU concentration in gastric mucosa

The results obtained were shown in Fig. 7. In oral administration, the mean highest level was 350.1±126.9 μg/g after 20 minutes and thereafter showed a tendency to decrease gradually, i.e., 335.0±82.4 after 40 minutes, 300.9±65.9 after 60 minutes, 286.3±71.3 after 90 minutes, 186.0±74.8 after 120 minutes and 155.7±29.8 after 180 minutes. In intravenous administration, the highest level was 1.860±0.450 μg/g after 20 minutes and 1.863±0.513 after 40 minutes, and thereafter tended to decrease gradually, i.e., 1.620±0.480 after 60 minutes, 1.430±0.750 after 90 minutes, 1.422±0.544 after 120 minutes and 1.110±0.480 after 180 minutes.

e. Concentration in various organs on autopsy

The results were shown in Table 1 and 2. In oral administration, the mean level in the superficial layer of the corpus of the stomach was 29.00±13.42 μg/g after 60 minutes, 9.93±6.15 after 180 minutes and 4.91±2.45 after 360 minutes, and that in the deep layer of the corpus was 4.87±1.96 μg/g after 60 minutes, 2.37±1.01 after 180 minutes and 0.82±0.57 after 360 minutes. In the superficial layer of the antrum, the mean level was 9.53±4.82 μg/g after 60 minutes, 5.58±3.17 after 180 minutes and 1.76±0.98 after 360 minutes,

Table 1 5-FU concentration in various organs after intragastric administration of 5-FU dry syrup in dogs. (5-FU 100mg/dog)

Viscera \ Time (min.)			60	180	360
Stomach	Corpus	superficial layer	29.00	9.93	4.91
		deep layer	4.87	2.37	0.82
	Antrum	superficial layer	9.53	5.58	1.76
		deep layer	1.28	1.10	0.13
Small intestine			28.00	1.45	1.10
Colon			0.69	0.28	t
MesenteriC lymph node			t	t	t
Brain			0.01	0.01	0.03
Lung			0.03	t	t
Liver			0.04	t	t
Pancreas			0.16	t	0.0007
Kidney			t	t	t

t : trace (μg/g)

Table 2 5-FU concentration in various organs after intravenous administration of 5-FU solution in dogs. (5-FU 100mg/dog)

Viscera \ Time (min.)			60	180	360
Stomach	Corpus	superficial layer	0.25	0.36	0.26
		deep layer	0.11	0.11	0.15
	Antrum	superficial layer	0.62	0.72	0.40
		deep layer	0.17	0.11	0.12
Small intestine			1.10	1.21	0.30
Colon			0.56	0.69	0.33
Mesenteric lymph node			0.57	0.50	0.12
Brain			t	t	t
Lung			0.14	0.26	0.17
Liver			0.81	0.68	0.14
Pancreas			0.11	0.15	0.01
Kidney			0.50	0.21	0.08

t : trace (μg/g)

and in the deep layer of the antrum, it was 1.28±0.74 μg/g after 60 minutes, 1.10±0.58 after 180 minutes and 0.13±0.07 after 360 minutes. In intravenous administration, the mean level was 0.25±0.18 μg/g after 60 minutes, 0.36±0.24 after 180 minutes and 0.26±0.18 after 360 minutes in the superficial layer of the corpus, and 0.11±0.07 μg/g after 60 minutes, 0.11±0.05 after 180 minutes and 0.15±0.08 after 360 minutes in the deep layer of the corpus. In the superficial layer of the antrum, the mean level was 0.62±0.41 μg/g after 60 minutes, 0.72±0.53 after 180 minutes and 0.40±0.29 after 360 minutes, and in the deep layer of the antrum, 0.17±0.05 after 60 minutes, 0.11±0.08 after 180 minutes and 0.12±0.06 after 360 minutes. In order to compare, 5-FU concentration in other organs (small intestine etc.) were showed in these Tables.

III. DISCUSSION

Studies on oral administration of 5-FU was tried for the first time by CHAUDURI et al. (1958)[15]. They reported that the peak level of 5-FU in blood of the peripheral vein was found at 20 minutes following administration when 15 mg/kg (138 μCi) of 5-FU-^{14}C dissolved in pine apple juice was orally administered to patients with recurrent fibroadenoma accompanied by mastectomy. Also, CURRERI et al. (1958)[16] administered 5-FU dissolved in orange juice by oral route, but there was no detail description on dosage, etc. in their paper. Therapeutic trials with oral 5-FU for malignant tumor were conducted by GOLD (1959)[17], and STARLEY (1962)[18], however there was no case in which antineoplastic effects of 5-FU on inoperable gastric cancer were observed. It seems to be the first report that KHUNG (1966)[19] orally administered 15 mg/kg of 5-FU injectable solution dissolved in tap water to 3 patients with gastric cancer and abdominal tumor, tumor successfully disappeared in one of those 3 cases with some side effects. Thereafter, BATEMAN et al. (1971)[20] reported the successful cases of I-A in 2 out of 6 cases of gastric cancer according to KARNOFSKY's criteria. And in Japan, NAKATSU et al. (1973)[21] reported that more than 25% of tumor was reduced in 2 out of 7 cases of IVth stage of gastric cancer. Following the development of 5-FU dry syrup, clinical application was positively made in Japan where there are a lot of gastric cancers, and a large number of effective cases have been reported [1~6,8~13,22,23].

It has been well known that when 5-FU was administered orally to the patients without antral stenosis, the 5-FU concentration curves in blood of the peripheral vein reached its peak within

10 to 30 minutes, and thereafter rapidly decreased, being unable to detect at 60 to 120 minutes[24-26]. It was considered to be practically difficult to follow up periodically the 5-FU concentration in the gastric mucosa if the patients were subjected to a long time endoscopic examination. In order to determine the 5-FU concentration in the tissue specimen obtained by a biopsy forceps according to bioassay method, at least more than 8 pieces of the tissue specimens were required, considering from the preliminary experiment. Therefore, the time course studies of 5-FU concentration in the gastric mucosa following 5-FU administration was conducted in dogs which had almost the same size of stomach as human, in which the endoscopic examination can be done. As a result, it has become clear that 5-FU remained in the gastric mucosa for a long time even under such non-physiological conditions as anesthesia.

Even in the 5-FU intravenous administration under the same conditions as mentioned above, 5-FU was detected in the gastric mucosa but remained at low level. It has been reported only by our group that when 5-FU was administered intravenously, 5-FU was detected in the gastric juice, and it will be suspected that the effects are obtained by also 5-FU dry syrup[27]. The 5-FU concentration was determined in the canine stomach which was divided into the superficial layer region (mucosa and submucosa) and the deep layer region (muscular layer and serosa) after the dogs were sacrificed. It was found that the 5-FU concentration maintained throughoutly higher level in the superficial layer region than in the deep layer region. In the cases of oral administration the 5-FU concentration of the stomach showed a higher level in both the superficial and deep layers of the stomach than in intravenous administration. And this suggested that oral preparation was more suitable for local therapy for the original lesion of gastric cancer. However, the transfer of 5-FU to the mesenteric lymph nodes in normal dogs was low level under measurable limit in oral administration. When examined in only the metastasis to the lymph nodes, the results showed that the more excellent effects were expected in intravenous administration. In order to examine whether 5-FU was absorbed from the gastric wall when 5-FU dry syrup was administered by oral route, the variation of the 5-FU concentration in blood of the portal vein was measured. There is a background in this problem, that is, whether 5-FU is absorbed from the gastric wall or not was discussed in the meeting of Japanese Cancer Chemotherapy Association from the facts that 5-FU is found in the blood at 3 minutes after oral administration of 5-FU dry syrup to the patients with cancer of the terminal stage, and that the drugs are generally absorbed from the small intestine. We manifested the absorption of 5-FU from the gastric mucosa from the evidence that 5-FU rapidly appeared in the blood of the portal vein with its peak after 20 minutes of administration when 5-FU dry syrup solution was infused into the stomach through the serous membrane of the canine stomach in which cardiac portion and pyloric canal were ligated under abdominal incision. However, there was a paper[28] describing that the drugs were absorbed from the stomach when the stomach becomes to be congested due to pyloric stenosis. Therefore, we should not make a hasty conclusion that this experiment expresses properly the stomach under physiological conditions without stenosis. However, KAIBARA et al.[29] also proved that the drugs are absorbed from the stomach from the fact that the drug was detected in the peripheral blood when administered to the rat of which stomach was ligated.

Also KUBO et al.[30] stated that the drug was absorbed from the gastric mucosa from the fact that the 5-FU concentration was extremely high in the gastric wall when orally administered, whereas the concentration was low in the small intestine like the concentration when intravenously administered. Moreover, in case of oral administration, the 5-FU concentration was higher in the portal vein than in the peripheral vein, whereas in case of intravenous administration, the 5-FU concentration curves showed the same pattern both in the portal vein and peripheral vein. Therefore, it seems that there is a difference in the kinetics *in vivo* between oral and intravenous administration. The similar results were reported from the experiments using humans[31] and rats[32]. From these facts, the oral antineoplastic agents which will contact and adsorb directly with the advanced gastric cancer seems to exert the effect due to the *in vivo* kinetics different from the intravenous

administration.

Acknowledgement

I wish to express my thanks to Prof. TOYOHIKO HISHIDA and Prof. MINORU KURIHARA, Showa University for their constant interest and guidance in this investigation, and Prof. HIKOO SHIRAKABE, Juntendo University for providing an opportunity of conducting the experiments.

REFERENCES

1) KURIHARA, M. & T. NAKAJIMA : Cancer Chemotherapy on gastric cancer. Shinko Igaku Shuppan, Tokyo pp. 85～158, 1981 (Japanese)
2) KURIHARA, M.; K. MIYASAKA, T. IZUMI, T. MARUYAMA, Y. SASAKI, H. SHIRAKABE & T. KAMANO : Gastrointestinal cancer-Gastric cancer. The Saishin-Igaku 36 : 1138～1145, 1981 (Japanese)
3) WATANABE, H.: Clinical trials of 5-FU oral administration. Cancer & Chemotherapy 1 : 669～675, 1974 (Japanese)
4) NAITO, T.; K. SATO, M. HARADA, A. SEKI, N. OKISHIO, K. IZUMI & K. HORIE : Clinical Report : Treatment of Advanced Stomach Cancer with Oral Administration of 5-Fluorouracil in Solution. Cancer & Chemotherapy 1 : 419～431, 1974 (Japanese)
5) TAMURA, M.; R. KOYAMA & M. FUKUDA : Clinical Trial of the Oral Carcinostatica, 5-Fluorouracil Dry Syrup, with Special Reference to Plasma and Tissue Concentrations of the Drug. Cancer & Chemotherapy 2 : 297～303, 1975 (Japanese)
6) KURIHARA, M.; T. IZUMI, K. MIYASAKA, H. SHIRAKABE, A. YASUI, Y. KARASAWA & H. OONUMA : Improvement of radiological, endoscopic and biopsied findings of gastric cancer by anticancer chemotherapy. Cancer & Chemotherapy 4 : 330～336, 1977 (Japanese)
7) TAKAHASHI, T.; K. KONO & T. YAMAGUCHI : Enhancement of the Cancer Chemotherapeutic Effect by Anticancer Agents in the Form of Fat Emulsion. Tohoku J. Exp. Med. 123 : 235～246, 1977
8) KURIHARA, M. et al.: Cancer Chemotherapy on Gastric Cancer. J. Jap. Soc. Cancer Ther. 13 : 700～711, 1978 (Japanese)
9) KURIHARA, M. et al.: Cytotoxic Chemotherapy for Advanced Gastric Cancer-Form the view point of macroscopic improvement on X-ray and gastroscopic views. Stomach and Intestine 14 : 1623～1637, 1979 (Japanese)
10) MIYASAKA, K.; M. KURIHARA, T. MARUYAMA, T. IZUMI & H. SHIRAKABE : A Case of Early Gastric Cancer (Type IIa) Disappeared During Anti-Cancer Chemotherapy. Stomach and Intestine 14 : 1663～1668, 1979 (Japanese)
11) IWANAGA, T.; I. FUKUDA, H. FURUKAWA, M. TATSUTA & H. TANIGUCHI : Histological Changes of Gastric Carcinoma by Oral Administration of Anticancer Drug. J. Jap. Soc. Cancer Ther. 16 : 1257～1262, 1981 (Japanese)
12) SAKATA, Y.; K. SUGAWARA, Y. KOMATSU, Y. TOSHIDA & S. NISHIMURA, K. KIKUCHI : Combination Chemotherapy of Mitomycin C, Carboquome, 5-Fluorouracil and OK-432 for Inoperable Gastric Cancer. J. Jap. Soc. Cancer Ther. 4 : 978～987, 1979 (Japanese)
13) KURIHARA, M.; I. IZUMI, K. MIYASAKA, T. MARUYAMA, F. YAMAYA, I. YAMAMOTO, T. YARITA, J. ARIYAMA & H. SHIRAKABE : Analysis of Improved X-ray Findings of Gastric Cancer by Anti-Cancer Chemotherapy. Jap. J. Clin. Radi. 24 : 817～822, 1979 (Japanese)
14) FUJITA, H.: *In vivo* distribution of anticancer agents-Methods of Assay (1)-. Cancer & Chemotherapy 1 : 497～503, 1974 (Japanese)
15) CHAUDHURI, N. K.; K. L. MUKHERJEE & C. HEIDELBERGER : Studies on Fluorinated Pyrimidines VII-The Degradative Pathway. Biochem. Pharmacol. I : 328～341, 1958
16) CURRERI, A. R.; F. J. ANSFIEID, F. A. MCLVER, H. A. WAISMAN & C. HEIDELBERGER : Clinical Studies with 5-Fluorouracil. Cancer Res. 18 : 478～484, 1958
17) GOLD, G. L.; T. C. HALL, B. I. SHINDER, O. SELAWRY, J. COLSKY, A. H. OWENS, M. M. DEDERICK, J. F. HOLLAND, C. O. BRINDLEY & R. JONES : A Clinical Study of 5-Fluorouracil. Cancer Res. 19 : 935～939, 1959
18) STARLEY, C. J.; J. T. HART, F. V. HAGEN & F. W. DRESTON : Various methods of administering 5-Fluorouracil. Cancer Chemother. Rep. 20 : 107～112, 1962
19) KHUNG, C. L.; T. C. HALL, A. J. PIRO & M. M. DEDERICK : A Clinical trial of oral 5-Fluorouracil. Clin. Pharmacol. & Therap. 7 : 527～533, 1966
20) BATEMAN, J. R.; R. P. PUGH, F. R. CASSIDY, G. J. MARSHALL & L. E. IRWIN : 5-Fluorouracil Given Once Weekly Comparison of Intravenous and Oral Administration. Cancer 28 : 907～913, 1971
21) NAKATSU, T.; J. SATOH, Y. USHIJIMA, T. TSUMURA, H. HISAMOTO, K. ISHIBIKI, M. YONEZAWA : Oral Administration of Injectable 5-Fluorouracil to Various Carcinomas. Jap. J. Cancer Clin. 19 : 986～990, 1973 (Japanese)
22) TAGUCHI, T. & Y. NAKANO : A Clinical trial of oral 5-Fluorouracil dry syrup. Cancer &

Chemotherapy 1 : 415～418, 1974 (Japanese)
23) NAKATSU, T.; Y. UEMATSU & Y. SUZUKI : Oral Administration of Powder Form of 5-Fluorouracil to Various Carcinomas. Cancer & Chemotherapy 2 : 131～135, 1975 (Japanese)
24) MIYASAKA, K.; M. KURIHARA, T. IZUMI & H. SHIRAKABE : 5-Fluorouracil level in the dog gastric mucus membrane after its oral administration. Cancer & Chemotherapy 3 : 143～147, 1976 (Japanese)
25) KANNO, H.; K. KIKUCHI, Y. ANEHA & Y. KUNII : Clinical studies on Tissue Level of 5-FU Dry Syrup. Cancer & Chemotherapy 5 : 155～161, 1978 (Japanese)
26) NAKATSU, T.: Dosing Conditions and Blood Level of Oral 5-Fluorouracil. Cancer & Chemotherapy 7 : 694～699, 1980 (Japanese)
27) YAMAYA, F.; K. MIYASAKA, M. KURIHARA, T. IZUMI, T. MARUYAMA, Y. SASAKI, T. KAMANO, H. SHIRAKABE & S. ITO : Excretion of 5-Fluorouracil into exocrine juice. J. Med. and Pharmacol. 5 : 767～770, 1981 (Japanese)
28) GIGON, A.; G. KATSCH, M. LUDIN & H. PICKERT : Resorption im Magen, Handbuch der Inneren Medisin, 4 Auflage Verdauungs Organe Springer Verlag. BERLIN pp. 234～244, 1968
29) KAIBARA, N.: Increased Concentration of 5-FU in lymph by oral administration of 5-FU fat emulsion. Cancer & Chemotherapy 4 : 131～134, 1977 (Japanese)
30) KUBO, K.; Z. TAMURA, H. USAMI, S. TAKEDA, T. SUZUKI, E. NINOMIYA & K. ISOBE : Distribution in tissues of 5-Fluorouracil and 5-Fluorouridylic acid after oral and intravenous administrations. Medicine and Biology 86 : 69～72, 1973 (Japanese)

胃癌治療を目的とした経口抗癌剤 (5-FU) の生体内動態に関する研究

1) 経口投与と静脈投与の比較検討

宮 坂 圭 一
昭和大学放射線医学教室
(主任：菱田豊彦教授)

進行胃癌に抗癌剤を投与する場合，経口投与，静脈投与がある。そこで，この薬剤の生体内動態をみるため，5-FU を用い検討した。

i) ヒトおよび正常犬の末梢静脈血中濃度は，経口投与をした場合，ピークは静脈投与より低値であるが，長時間血中に維持されている。

ii) ヒトおよび正常犬の胃に 5-FU が胃液中より排泄されることが証明された。

iii) 正常犬の胃粘膜内 5-FU 濃度は，長時間にわたり残存しており，組織への吸着，滞留がよいことを認めた。

iv) 正常犬の噴門，幽門部を結紮して漿膜側から胃内へ投与すると，門脈内へ速やかに 5-FU が移行することも確認し，胃壁から吸収されることを証明した。

v) 正常犬の門脈内 5-FU 血中濃度は，経口投与で末梢静脈血より高濃度をとって持続するが，静脈投与では，門脈血，末梢血とも殆ど同じ濃度パターンを示した。

以上のことから，経口投与は，直接胃癌に吸着し，吸収するため，静脈投与と異なる生体内動態をとることがわかった。