DISTRIBUTION OF 1-HEXYLCARBAMOYL-5-FLUOROURACIL AND 5-FLUOROURACIL BY ORAL ADMINISTRATION IN MICE*

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The distribution of 1-hexylcarbamoyl-5-fluorouracil-6-¹⁴C (HCFU) and 5-fluorouracil-6-¹⁴C (5FU) was studied in mice following a single oral administration. When HCFU and 5FU were given orally to mice, they were readily absorbed from the gastro-intestinal tract and the radioactivity was detected in various tissues and organs. Highest radioactivity after administration of HCFU was shown in the liver, kidneys, stomach wall and plasma, followed by the lungs, and adrenals. On the other hand, highest radioactivity after administration of 5FU was exhibited in the liver, myocardium, lungs, pancreas, spleen, kidneys, adrenals and gastro-intestinal wall. Distribution pattern and disappearance of HCFU were similar to those of 5FU. Marked difference in the distribution between HCFU and 5FU was detected only in the gastro-intestinal wall, namely, HCFU was retained for a long period in the stomach wall while 5FU did in the intestinal wall.

Keywords—HCFU-6-¹⁴C; 1-hexylcarbamoyl-5-fluorouracil-6-¹⁴C; 5-fluorouracil-6-¹⁴C; autoradiography; distribution; oral administration; antitumor agents; antimetabolites

1-Hexylcarbamoyl-5-fluorouracil (HCFU) was synthesized by Ozaki, *et al.*, as one of the "masked form" derivatives of 5-fluorouracil (5FU) aimed for use by oral administration for maintenance therapy,¹⁾ and was selected as a candidate for oral antitumor agent because of its high activity against various mice tumors including L1210 and Lewis lung carcinoma and its low toxicity to the host.²⁻⁴⁾ Maximum effect of HCFU on tumor growth inhibition in adenocarcinoma 755 and ascites sarcoma 180 system was greater than those of 5FU and 1-(2-tetrahydrofuryl)-5-fluorouracil (FT).²⁾ In this paper, the tissue distribution pattern of HCFU and 5FU in mice after oral administration was examined by whole-body autoradiographic technique and changes in concentration of radioactivity in tissues as a function of

time were quantitatively examined.

MATERIALS AND METHODS

Labeled Compounds—1-Hexylcarbamoyl-5-fluorouracil-6-¹⁴C and 5-fluorouracil-6-¹⁴C were supplied from Mitsui Pharmaceuticals, Inc., Tokyo. The specific activity of HCFU and 5FU were 2.5 and 2.1 μ Ci/mg, respectively.

Animals—Female mice of ddN strain weighing 20—22 g were used without fasting. The animals used were 2 and 4 mice in each group for the autoradiography and distribution study, respectively.

Autoradiography—Radioactive HCFU or 5FU was suspended in 0.5% carboxymethyl cellulose solution at the concentration of 1 mg/0.2 ml, and administered orally using stomach tube at

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50 mg/kg (2.5 and 2.1 $\mu\text{Ci}/\text{mouse}$ of HCFU and 5FU, respectively). Mice were lightly anesthetized with ether and were frozen by immersion in a dry ice-acetone mixture of about -70° at 1/4, 1, 3, and 24 hr after oral administration. After a frozen animal was embedded with aqueous carboxymethyl cellulose gel on a microtome stage, sagittal 40μ sections were cut with a microtome (Yamato Koki) at -15° and freeze dried for more than 3 days. The dried sections were exposed to Fuji N-150 X-ray film for a constant period of 60 days. The films were developed in a Rendol-I developer for 5 min and fixed in Renfix-I for 10 min.

Quantitative Measurement of Radioactivity—HCFU or 5FU was administered orally to mice using a stomach tube at 50 mg/kg.

Blood samples were collected from the axillary artery under light anesthesia with ether at specified time intervals, 5, 15 and 30 min, and 1, 3, 6, 12, and 24 hr after the administration of HCFU or 5FU, and followed by excising various organs. The plasma was rapidly separated out. The excised organs were washed with physiological saline and weighed. Each of 100 mg of those tissues or whole organs was dissolved in 1 ml of Soluene-350 (Packard), and to the resulting solution were added 9 ml of scintillator (PPO 10g, POPOP 1g, ethylcellosolve 800 ml and toluene 1200 ml). A Tri-Carb liquid scintillation spectrometer (Packard, Model 3320) was used for the measurement of radioactivity.

RESULTS

Distribution of HCFU and 5FU

Whole-body autoradiograms obtained from mice after oral administration of HCFU and 5FU are shown in Fig. 1 and 2, respectively. Fifteen minutes after the administration of HCFU, the highest uptake was shown in the liver, blood, gastric mucosa, kidneys and bone marrow, followed by the lungs, myocardium, intestinal mucosa, adrenals and skin. The thymus, spleen and skeletal muscle showed lower uptake of radioactivity. Only a slight radioactivity was detected in the brain (Fig. 1A). In the adrenal glands, radioactivity in the zone between the cortex and

FIG. 1. Autoradiograms of 1-Hexylcarbamoyl-5-fluorouracil 15 min (A, B) and 3 hr (C) after Oral Administration

medulla was lower (Fig. 1B). One hour after administration of HCFU, an appreciable radioactivity remained in the circulating blood and a higher radioactivity was shown in the liver, kidneys, gastric mucosa and a part of small intestinal mucosa. Three hours after administration of HCFU, a considerable amount of radioactivity was retained in the liver, gastro-intestinal mucosa, and kidneys (Fig. 1C). Radioactivity in tissues disappeared within 24 hr except that in the gastric

FIG. 2. Autoradiograms of 5-Fluorouracil 15 min (A) and 3 hr (B) after Oral Administration

mucosa.

On the other hand, fifteen minutes after the administration of 5FU, a high uptake of radioactivity was shown in the liver gastro-intestinal mucosa, pancreas and kidneys, followed by the lymph node, thymus, myocardium, blood, lungs, spleen, adrenals, bone marrow, and skin (Fig. 2A). One hour after administration of 5FU, high concentration was shown in the liver, gastro-intestinal mucosa and kidneys, followed by the thymus, pancreas, spleen, adrenals and skin. Three hours after administration, high radioactivity remained in the liver, pancreas, spleen, gastro-intestinal mucosa, thymus, adrenals, kidneys and skin (Fig. 2B). Most of the radioactivity disappeared within 24 hr. From the result, HCFU was found to be absorbed easily by oral administration and retained for longer period of time than 5FU in most of the tissues. Distribution pattern of HCFU in tissues was essentially the same as that of 5FU. Results obtained by

the autoradiographic studies are qualitatively summarized in Table I.

Changes in Concentration of Radioactivity in Blood and Plasma

As shown in Table II and III, the highest concentrations of radioactivity in the plasma or blood were observed 15 min after administration of either HCFU or 5FU. The plasma concentrations of radioactivity 15 min after administration were 47.5 $\mu\text{g/ml}$ (as HCFU) or 23.0 $\mu\text{g/ml}$ (as 5FU). Thereafter, the activities decreased with time and reached 10% of the maximum values within 3 hr. Only a small amount of radioactivity was detected 12 hr after HCFU administration, but no activity was detectable with 5FU. It indicates that both compounds were rapidly absorbed through the gastro-intestinal tract and were slowly eliminated from the plasma. The ratio of plasma level to whole blood level of the compound was approximately 1.5 for HCFU and 1.0 for 5FU, indicating that unlike 5FU, HCFU did not enter the red blood cells. Half-lives of radioactivity derived from HCFU and 5FU in the plasma were about 57 and 50 min, respectively.

Changes of Distribution in Tissues

As shown in Table II and III, radioactivity in the tissues after oral administration of HCFU reached a peak at 15 min and declined with time-course similar to that in the plasma. Levels of radioactivity derived from HCFU were higher in the liver, kidneys and stomach wall than in the plasma 15 min or later after administration. The level in the adrenals was similar to that in the plasma. The levels in the lungs, spleen and myocardium were comparatively low. The activity in the brain and skeletal muscle were lower than that in other tissues.

On the other hand, levels of radioactivity derived from 5FU were higher in the liver, myocardium, lungs, pancreas, spleen, kidneys, adrenals and gastro-intestinal wall than in the plasma. The activity in the thymus was similar to that in the plasma and those in the brain and skeletal muscle were lower than that in the plasma. Radioactivity in the stomach wall after 5FU administration was as high as 10 fold of that in the plasma during initial 1

TABLE I. *Radioactivity appeared on Autoradiograms*

Tissues	15 min		1 hr		3 hr		24 hr	
	HCFU	5FU	HCFU	5FU	HCFU	5FU	HCFU	5FU
Brain	+	±	—	—	—	—	—	—
Lymph node	+	++	+	+	+	+	—	—
Brown fat	+	+	+	+	—	—	—	—
Thymus	+	++	+	++	+	++	±	+
Myocardium	++	+	++	+	+	—	—	—
Heart blood	+++	++	++	+	+	—	—	—
Hepatic blood	+++	+++	+++	+	±	—	—	—
Lung	++	++	++	+	+	—	—	—
Liver	+++	+++	+++	+++	++	++	—	+
Pancreas	+	+++	+	++	+	++	—	±
Spleen	+	++	+	++	+	++	±	±
Gastric mucosa	+++	+++	+++	+++	+++	+++	++	±
Small intestinal mucosa	++	+++	++	+++	++	+++	±	+
Large intestinal mucosa	+	++	+	++	+	++	—	—
Adrenal	++	++	++	++	+	++	—	—
Kidney	+++	+++	+++	+++	++	++	±	+
Bone marrow	+++	++	+	+	+	+	±	±
Skeletal muscle	+	+	+	+	+	—	—	—
Skin	++	++	++	++	+	++	—	±

+++ :highest radioactivity, ++ :high activity, + :moderate activity, ± :low activity and - :no activity.

hr and that in the wall of intestinal tract, especially in the duodenum, was also higher than that in the plasma. 5FU was more readily absorbed into the wall of gastro-intestinal tract than HCFU and declined faster than the latter in the stomach wall but *vice versa* in the intestinal wall. The time-course of decline in concentration in most tissues was similar to that in the plasma, and there was no particular accumulation in any specific organs or tissues observed with these compounds.

DISCUSSION

1-Hexylcarbamoyl-5-fluorouracil is a "masked form" of 5FU and its lethal toxicity in one-third of that of the latter by oral administration in mice.²⁾ Contrary to FT,²⁾ HCFU was markedly active against L5178Y culture cells *in vitro*. The present results revealed that HCFU was rapidly absorbed through the gastro-intestinal tract comparable to 5FU. Absorption of 5FU through the gastro-intestinal tract was reported to be rapid and retention time of radioactivity after oral administration

was longer than that after intravenous route.^{5,6)} Lower concentration of HCFU than 5FU in the small intestinal wall 12 or 24 hr after administration indicated that HCFU had a lesser tendency to accumulate in the intestinal tract than 5FU. The plasma concentration of HCFU was very high and maintained for a long period of time. Distribution pattern of HCFU was similar to that of 5FU, though solubility in water of the two compounds was different from each other, namely, HCFU is insoluble in water but 5FU is very soluble. Disappearance of radioactivity derived from HCFU in most tissues was similar to that from 5FU. However, unlike 5FU, HCFU was retained in the stomach wall rather than in the intestinal wall for a long period of time. Severe gastro-intestinal toxicity by oral 5FU administration was considered to be due to the long retention time of the drug in the intestinal wall.⁷⁾ In this sense, lower concentration of HCFU in the small intestinal wall suggests lower gastro-intestinal toxicity of the compound than 5FU by oral administration. Similar lower con-

TABLE II. Concentration of 1-Hexylcarbamoyl-5-fluorouracil in Tissues after Oral Administration

Tissues	Concentrations in tissues (as HCFU) ^{a)} ($\mu\text{g}/\text{ml}$ or wet weight)			
	5 min	15 min	30 min	1 hr
Blood	18.1 $\pm$ 0.8	30.8 $\pm$ 0.4	15.2 $\pm$ 0.1	12.1 $\pm$ 1.1
Plasma	27.2 $\pm$ 1.9	47.5 $\pm$ 2.8	23.4 $\pm$ 0.8	19.7 $\pm$ 1.6
Brain	4.3 $\pm$ 0.7	5.1 $\pm$ 0.3	4.2 $\pm$ 0.2	2.6 $\pm$ 0.2
Myocardium	12.3 $\pm$ 1.1	16.9 $\pm$ 0.7	12.0 $\pm$ 0.4	6.8 $\pm$ 0.5
Lung	14.8 $\pm$ 2.3	23.6 $\pm$ 1.6	16.4 $\pm$ 0.7	8.1 $\pm$ 0.5
Liver	61.9 $\pm$ 10.6	98.0 $\pm$ 12.1	74.4 $\pm$ 4.0	52.7 $\pm$ 1.7
Pancreas	27.3 $\pm$ 3.1	14.4 $\pm$ 0.6	13.4 $\pm$ 1.3	15.8 $\pm$ 1.9
Spleen	10.9 $\pm$ 1.0	9.8 $\pm$ 0.9	10.3 $\pm$ 1.2	10.5 $\pm$ 1.6
Kidney	19.6 $\pm$ 3.5	58.6 $\pm$ 2.0	48.9 $\pm$ 3.8	43.3 $\pm$ 2.0
Skeletal muscle	6.3 $\pm$ 0.4	9.2 $\pm$ 0.1	6.3 $\pm$ 0.3	3.5 $\pm$ 0.2
Adrenal	18.9 $\pm$ 1.0	36.0 $\pm$ 0.1	30.5 $\pm$ 2.8	18.9 $\pm$ 1.1
Thymus	9.3 $\pm$ 1.8	10.1 $\pm$ 1.4	7.7 $\pm$ 0.2	4.0 $\pm$ 0.3
Forestomach wall	127.8 $\pm$ 13.3	244.0 $\pm$ 79.1	231.0 $\pm$ 22.7	145.4 $\pm$ 19.7
Glandularstomach wall	121.1 $\pm$ 28.7	230.2 $\pm$ 4.3	126.6 $\pm$ 15.3	165.0 $\pm$ 14.8
Duodenum wall	27.3 $\pm$ 5.5	40.7 $\pm$ 8.3	20.7 $\pm$ 1.9	14.5 $\pm$ 1.7
Jejunum wall	12.3 $\pm$ 0.2	19.0 $\pm$ 0.1	8.6 $\pm$ 0.8	7.8 $\pm$ 0.5
Ileum wall	13.5 $\pm$ 2.7	13.5 $\pm$ 0.2	11.8 $\pm$ 0.8	11.3 $\pm$ 0.6
Large intestinal wall	10.7 $\pm$ 2.4	20.3 $\pm$ 3.2	13.6 $\pm$ 3.0	6.8 $\pm$ 1.1
Caecum wall	7.4 $\pm$ 0.9	11.6 $\pm$ 2.0	8.3 $\pm$ 0.3	7.2 $\pm$ 0.6

a) Values represent the mean $\pm$ SE of four mice in a group. The dose of HCFU-6- ^{14}C was administered orally at 50 mg/kg.

Concentration was calculated as HCFU.

	3 hr	6 hr	12 hr	24 hr
Blood	2.6 $\pm$ 0.3	1.7 $\pm$ 0.5	0.5 $\pm$ 0.2	<0.1
Plasma	3.7 $\pm$ 0.5	2.3 $\pm$ 0.7	0.7 $\pm$ 0.1	<0.1
Brain	1.4 $\pm$ 0.2	0.8 $\pm$ 0.1	0.4 $\pm$ 0.0	0.2 $\pm$ 0.0
Myocardium	3.6 $\pm$ 0.4	2.7 $\pm$ 0.5	1.1 $\pm$ 0.1	0.6 $\pm$ 0.1
Lung	3.9 $\pm$ 0.7	2.6 $\pm$ 0.5	1.2 $\pm$ 0.1	0.5 $\pm$ 0.0
Liver	11.9 $\pm$ 0.8	7.5 $\pm$ 0.1	4.3 $\pm$ 0.7	2.0 $\pm$ 0.4
Pancreas	4.7 $\pm$ 0.7	6.0 $\pm$ 0.6	2.2 $\pm$ 0.1	1.3 $\pm$ 0.2
Spleen	5.3 $\pm$ 0.8	5.0 $\pm$ 0.4	1.8 $\pm$ 0.1	1.1 $\pm$ 0.1
Kidney	9.2 $\pm$ 0.1	7.9 $\pm$ 2.1	3.1 $\pm$ 0.1	1.0 $\pm$ 0.1
Skeletal muscle	1.4 $\pm$ 0.1	1.2 $\pm$ 0.2	0.5 $\pm$ 0.1	0.6 $\pm$ 0.2
Adrenal	3.5 $\pm$ 0.4	4.9 $\pm$ 0.6	1.8 $\pm$ 0.2	0.4 $\pm$ 0.1
Thymus	3.6 $\pm$ 1.6	—	—	—
Forestomach wall	50.1 $\pm$ 3.9	32.2 $\pm$ 4.1	20.4 $\pm$ 2.7	5.0 $\pm$ 0.9
Glandularstomach wall	10.2 $\pm$ 2.7	29.6 $\pm$ 7.1	5.3 $\pm$ 1.0	1.7 $\pm$ 0.2
Duodenum wall	4.4 $\pm$ 0.3	3.4 $\pm$ 0.9	2.0 $\pm$ 0.1	0.7 $\pm$ 0.1
Jejunum wall	3.1 $\pm$ 0.3	3.3 $\pm$ 0.7	1.5 $\pm$ 0.0	0.8 $\pm$ 0.1
Ileum wall	3.6 $\pm$ 0.5	1.9 $\pm$ 0.1	1.2 $\pm$ 0.1	0.5 $\pm$ 0.0
Large intestinal wall	5.5 $\pm$ 1.7	1.5 $\pm$ 0.3	0.8 $\pm$ 0.1	0.4 $\pm$ 0.1
Caecum wall	3.3 $\pm$ 0.4	3.2 $\pm$ 0.7	1.4 $\pm$ 0.1	0.8 $\pm$ 0.0

TABLE III. *Concentration of 5-Fluorouracil in Tissues after Oral Administration*

Tissues	Concentration in tissues (as 5FU) ^{a)} ($\mu\text{g}/\text{ml}$ or g wet weight)			
	5 min	15 min	30 min	1 hr
Blood	17.1 $\pm$ 1.0	18.4 $\pm$ 1.5	14.7 $\pm$ 0.3	9.1 $\pm$ 0.7
Plasma	19.7 $\pm$ 0.7	23.0 $\pm$ 1.4	15.5 $\pm$ 0.7	10.6 $\pm$ 0.8
Brain	6.8 $\pm$ 0.7	5.6 $\pm$ 0.2	3.6 $\pm$ 0.1	2.6 $\pm$ 0.2
Myocardium	34.0 $\pm$ 1.6	38.9 $\pm$ 2.0	25.3 $\pm$ 1.0	14.6 $\pm$ 2.1
Lung	37.2 $\pm$ 3.4	53.8 $\pm$ 1.1	32.7 $\pm$ 0.3	12.7 $\pm$ 2.3
Liver	155.2 $\pm$ 10.6	241.0 $\pm$ 6.4	141.5 $\pm$ 4.6	60.7 $\pm$ 4.0
Pancreas	91.6 $\pm$ 7.9	120.1 $\pm$ 8.9	90.6 $\pm$ 6.3	36.4 $\pm$ 4.2
Spleen	37.4 $\pm$ 5.3	71.8 $\pm$ 6.5	84.6 $\pm$ 9.3	20.6 $\pm$ 2.5
Kidney	59.7 $\pm$ 5.4	107.1 $\pm$ 4.0	26.3 $\pm$ 0.3	69.8 $\pm$ 1.2
Skeletal muscle	12.7 $\pm$ 0.4	10.7 $\pm$ 0.6	8.9 $\pm$ 0.3	4.8 $\pm$ 0.3
Adrenal	27.2 $\pm$ 2.0	44.8 $\pm$ 5.8	13.6 $\pm$ 0.2	16.7 $\pm$ 1.0
Thymus	17.7 $\pm$ 1.4	17.1 $\pm$ 1.0	12.6 $\pm$ 0.2	8.4 $\pm$ 0.9
Forestomach wall	167.2 $\pm$ 16.6	211.9 $\pm$ 12.8	132.7 $\pm$ 9.4	79.8 $\pm$ 8.1
Glandularstomach wall	297.7 $\pm$ 7.1	281.7 $\pm$ 12.9	170.5 $\pm$ 7.8	90.9 $\pm$ 5.5
Duodenum wall	89.4 $\pm$ 17.9	40.5 $\pm$ 3.3	17.2 $\pm$ 4.3	7.2 $\pm$ 1.0
Jejunum wall	40.3 $\pm$ 3.7	15.2 $\pm$ 2.3	8.8 $\pm$ 0.7	5.5 $\pm$ 0.6
Ileum wall	9.8 $\pm$ 0.1	11.7 $\pm$ 1.7	8.8 $\pm$ 1.0	5.6 $\pm$ 0.7
Large intestinal wall	23.9 $\pm$ 4.5	15.9 $\pm$ 2.2	6.8 $\pm$ 1.4	6.8 $\pm$ 0.9
Caecum wall	10.9 $\pm$ 0.4	16.2 $\pm$ 3.7	7.8 $\pm$ 0.8	4.1 $\pm$ 0.3

a) Values represent the mean $\pm$ SE of four mice in a group. The dose of 5FU-6-¹⁴C was administered orally at 50 mg/kg. Concentration was calculated as 5FU.

	3 hr	6 hr	12 hr	24 hr
Blood	1.5 $\pm$ 0.1	0.1 $\pm$ 0.1	<0.1	<0.1
Plasma	1.9 $\pm$ 0.1	0.2 $\pm$ 0.1	<0.1	<0.1
Brain	1.1 $\pm$ 0.1	0.6 $\pm$ 0.1	0.5 $\pm$ 0.1	0.2 $\pm$ 0.0
Myocardium	3.6 $\pm$ 0.3	1.3 $\pm$ 0.2	1.2 $\pm$ 0.0	0.7 $\pm$ 0.1
Lung	4.1 $\pm$ 0.3	2.2 $\pm$ 0.3	1.0 $\pm$ 0.1	0.7 $\pm$ 0.1
Liver	27.3 $\pm$ 2.7	10.2 $\pm$ 1.7	5.4 $\pm$ 0.1	2.7 $\pm$ 0.1
Pancreas	12.5 $\pm$ 0.8	4.8 $\pm$ 1.0	3.5 $\pm$ 0.2	2.1 $\pm$ 0.2
Spleen	5.1 $\pm$ 0.0	3.0 $\pm$ 0.2	1.9 $\pm$ 0.2	1.9 $\pm$ 0.0
Kidney	24.1 $\pm$ 2.5	7.1 $\pm$ 0.8	2.8 $\pm$ 0.1	2.6 $\pm$ 0.1
Skeletal muscle	1.7 $\pm$ 0.1	0.7 $\pm$ 0.1	1.0 $\pm$ 0.2	0.4 $\pm$ 0.1
Adrenal	8.2 $\pm$ 1.1	2.7 $\pm$ 0.7	3.4 $\pm$ 0.8	3.4 $\pm$ 0.1
Thymus	3.5 $\pm$ 0.2	2.2 $\pm$ 0.5	—	—
Forestomach wall	51.9 $\pm$ 7.7	10.4 $\pm$ 0.4	5.8 $\pm$ 0.3	3.1 $\pm$ 0.4
Glandularstomach wall	41.8 $\pm$ 6.2	6.6 $\pm$ 0.6	4.9 $\pm$ 0.4	2.5 $\pm$ 0.2
Duodenum wall	6.5 $\pm$ 0.6	5.7 $\pm$ 0.4	4.7 $\pm$ 0.1	2.6 $\pm$ 0.1
Jejunum wall	3.4 $\pm$ 0.1	5.0 $\pm$ 0.1	3.8 $\pm$ 0.6	2.8 $\pm$ 0.5
Ileum wall	2.0 $\pm$ 0.3	2.3 $\pm$ 0.1	1.7 $\pm$ 0.1	1.6 $\pm$ 0.1
Large intestinal wall	4.2 $\pm$ 0.7	3.5 $\pm$ 0.2	2.3 $\pm$ 0.3	1.4 $\pm$ 0.1
Caecum wall	2.1 $\pm$ 0.2	2.5 $\pm$ 0.3	1.9 $\pm$ 0.2	1.6 $\pm$ 0.2

centration of FT than 5FU in the organ of rat was also reported.⁸⁾ FT shows also lower gastrointestinal toxicity. In conclusion, HCFU and 5FU were found to be well absorbed through the gastrointestinal tract, distributed into various tissues or organs and disappeared from tissues within 24 hr. In order to clarify the strict difference between HCFU and 5FU in toxicity and activity, distribution of HCFU, 5FU and its metabolites in tissues must be further investigated. Studies on metabolites of HCFU and 5FU in tissues are currently in progress.

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