III. 10  Distribution and Enterohepatic Circulation of $^{18}$F-5-Fluorouracil in Tumor-Bearing and Normal Rats


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Introduction

Although chemotherapeutic efficacy of anticancer drugs is evaluated by the disparity between cytotoxic effects of drugs on tumor and normal tissues, no absolute difference of sensitivity to chemotherapeutic agents have been proved between tumors and normal tissues. Therefore, the distribution of chemotherapeutic agents in tumors and normal tissues plays an important role in cancer chemotherapy.

Short-lived positron emitting radioisotopes have much lower irradiation dose than those of conventional nuclear medicines. They decay by a positron emission and the resulting annihilation radiation can be detected externally. These facts suggest the clinical availability of chemotherapeutic agents labelled with short-lived positron emitting radioisotopes.1)

5-Fluorouracil (5-FU) is an effective and widely used chemotherapeutic agents for the treatment of a variety of solid tumors. Thus, at the present study, the distribution of 5-FU in both tumor-bearing and normal rats were investigated with $^{18}$F-5-FU which is one of short-lived positron emitting radioisotopes.

Materials and Methods

Male Donryu rats, weighing 110-180g were used. Cells ($2 \times 10^6$) of Yoshida sarcoma (YS) which is sensitive to 5-FU and ascites hepatoma AH109A insensitive to 5-FU were respectively implanted subcutaneously at the left thigh 10 days prior to the experiment.

$^{18}$F-5-Fluorouracil ($^{18}$F-5-FU) provided by Cyclotron and Radioisotope Center, Tohoku University immediately before the experiment, was injected into the tail veins of the normal and tumor-bearing rats at the dose of 15, 30 or 35 μCi/body. The rats were sacrificed by cervical dislocation at the specified intervals of 5, 30, 60 and 120 min. following the injection of $^{18}$F-5-FU. The tissues and the contents of the digestive tract as presented in fig. 1-3 were removed and counted. The small intestine was divided into 8 equal parts from the duodenum to the ileum, and the large intestine into quarters from the ascending colon to the rectum.

The tissue uptake and radioactivity of contents of the digestive tract were
expressed as per cent of injected dose per g of tissue and content, and were stated regardless of the chemical form of the $^{18}\text{F}$ in them.

Results and Discussion

As presented in fig. 1, in YS bearing rats the uptake of $^{18}\text{F}$ by the tumor is low and that by the liver and that by the kidney are extremely high. The uptake by the small intestine is slightly higher than that by the tumor. The radioactivity of the blood and the uptake of the lung, the heart, the spleen, the pancreas, the muscle and the bone (inclusive of the marrow) are approximately equal to that of the tumor uptake. The testis and brain uptake is lower than the tumor uptake. Figure 2 presents a similar result in AH109A bearing rats to that in YS bearing rats.

In YS bearing rats tumor-to-blood ratios are 0.32, 0.83 and 1.16 respectively at 5, 30 and 60 min. after $^{18}\text{F}$-5-FU administration, and in AH109A bearing rats 0.68, 1.45 and 1.39 respectively at 5, 30 and 60 min. Thus no appreciable difference between the two tumor types is observed. It is not possible at any time studied to obtain satisfactory images of these tumors. One can speculate that no correlation in respect of tumor uptake of $^{18}\text{F}$ may exist between 5-FU sensitivity differences and its arrival.

A high excretion of most of anticancer drugs into the bile and urine was observed after the intravenous injection, and anticancer drugs excreted into the bile are reabsorbed from the small intestine by way of enterohepatic circulation and return to the general circulation.\textsuperscript{2,3} Therefore, anticancer drug arrival at the bile, enterohepatic circulation influence on the tissue distribution of anticancer drugs and the digestive tract injury which is one of the damages caused by anticancer drugs to the host should be investigated.

Anticancer drug distribution in the whole esophagus, the whole stomach, the small intestine and the large intestine as well as contents of the digestive tract were studied. Then the $^{18}\text{F}$ distribution in the respective segments of the intestine was observed. In order to study the distribution, exclusive of influence of the enterohepatic circulation, the total $^{18}\text{F}$ was investigated at 60 and 120 min. after $^{18}\text{F}$-5-FU injection in the respective tissues and contents of the digestive tract of rats with the ligated bile duct for 3-5 hr. prior to the administration. The distribution data of $^{18}\text{F}$-5-FU in each tissue from the esophagus to the rectum does not show any appreciable differences both in normal rats and bile duct ligated rats and is less than 1% injected dose/g. Regarding the contents of the digestive tract of normal rats, gastric contents radioactivity is low, whereas in the contents from the first to eighth segment (the end of the ileum) of the small intestine to which the bile is excreted, high activity of $^{18}\text{F}$ is found. The activity of $^{18}\text{F}$ of the contents of the large intestine (faces) was considerably low. It is suspected that the contents of the intestinal tract have not yet moved to the large intestine. In another experiment the low activity
of $^{18}$F of the contents of the large intestine at sacrificed times of 2, 3, 4 and 6 hr. was observed. This suggests that almost all the $^{18}$F excreted into the bile is absorbed from the small intestine. The activity of $^{18}$F of contents of the digestive tract in the bile ligated rats is much lower than in untreated rats. In case of the blood, the liver, and the kidney the activity and the uptake of $^{18}$F in the rats with the ligated bile duct are higher than in the untreated rats. These findings led us to a conclusion that $^{18}$F which was not excreted into the bile caused a high activity of the blood and the rest of the tissues in the rats with the ligated bile duct.

Conclusion

1. As for the tumor-bearing rats, the tumor uptake of $^{18}$F is low both with YS which is sensitive to 5-FU and with AH109A tumor which resists 5-FU.
2. The intestinal tract injury by anticancer drugs may be due to their arrival at the small intestine via the blood stream, however, our data indicates a possibility that intestinal absorption of anticancer drugs excreted into the bile in the process of the enterohepatic circulation may also cause the intestinal tract injury.

References

Fig. 1. Tissue distribution in rats bearing YS tumors following IV administration of 30 μci/body of $^{18}$F-5-FU.

Fig. 2. Tissue distribution in rats bearing AH109A tumors following IV administration of 30 μci/body of $^{18}$F-5-FU.
Fig. 3. Distribution of total $^{18}$F in tissue and contents of the digestive tract following IV administration of $^{18}$F-5-FU to normal rats.