

Pharmacodynamics of Co-Administration of Uracil and 1-(2-Tetrahydrofuryl)-5-Fluorouracil (FT-207) for Malignant Brain Tumors*

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(Received August 18, 1983)

Key words: Pharmacodynamics, Futrafur, Uracil, UFT, Brain tumor

ABSTRACT

UFT, a mixture of FT-207 and uracil in a molar ratio 1 : 4, has been noticed to have the higher antitumor activity to various tumors other than FT-207. We studied the pharmacodynamics of UFT (900 mg for FT-207) after oral administration on 3 cases of malignant glioma and 4 cases of metastatic brain tumor by using high performance liquid chromatography, and the following results obtained;

1. Most of unchanged FT-207, 5-FU and uracil were excreted in the urine within 24 hours.
2. The $t^{1/2}$ of α -phase of FT-207 was 4.59 hours and that of β -phase was 9.99 hours. The $t^{1/2}$ of α -phase of 5-FU was 0.75 hours, and that of β -phase was 11.04 hours. The AUC of 5-FU was 12.434 $\mu\text{g}\cdot\text{hrs}/\text{ml}$. This drug was found to stay in the plasma over a long period, followed by a slow elimination. In CSF, the higher concentration of 5-FU stayed over a longer period.
3. The concentration of FT-207 in the brain tumor tissues was 17.11 $\mu\text{g}/\text{g}$ on the average in malignant glioma and 17.61 $\mu\text{g}/\text{g}$ on the average in metastatic brain tumor. The concentration of 5-FU was 0.02 $\mu\text{g}/\text{g}$ on the average in the former, and 0.47 $\mu\text{g}/\text{g}$ on the average in the latter, which indicating an efficient transfer to the tissues of metastatic brain tumor. The concentration of FT-207 and 5-FU in the brain tissues adjacent to the tumor was approximately the same as that in the brain tumor tissues, indicating an effective transfer to the brain tissues adjacent to the tumor.
4. On the basis of the results of this study, uracil seems to inhibit the degradation of 5-FU in the liver and/or in the tumor tissues themselves, and to enhance the concentration of 5-FU in the brain tumor tissues and the brain tissues adjacent to the tumor. UFT would be useful as a chemotherapeutic agent for malignant brain tumors.

INTRODUCTION

The treatment of malignant brain tumors has been made with the multimodality treatment such as surgery, chemotherapy and immunotherapy. Chemotherapy, especially, plays an important role for the adjuvant therapy. Ni-

trosoreas such as BCNU, CCNU, Methyl-CCNU and ACNU have been recognized to be useful as chemotherapeutic agents for malignant brain tumors with or without radiotherapy^{10-12, 21, 23, 24}. In particular, BCNU was available for extensive clinical trials^{11, 23, 24}.

FT-207, 1-(2-tetrahydrofuryl)-5-fluorouracil,

*) 原田 廉, 岡本博文, 藤岡敬己, 木失克造, 魚住 徹: 悪性脳腫瘍におけるUFTのpharmacodynamics

masked compound for 5-FU⁶⁾, is a lipid-soluble antimetabolic antitumor agent. It is one of the chemotherapeutic agent for primary or metastatic brain tumors either alone or in combination with nitrosoureas or radiotherapy^{1,4,5,9)}.

However, it was recognized to produce rather little effect on malignant gliomas. It was apparently because the higher concentration of 5-FU did not maintain in the tumor tissues of malignant gliomas and other neoplasmas. Several augmentations of the antitumor activity have been made.

The co-administration of uracil and FT-207 in a molar ratio of 1 : 4 (abbreviated as UFT) was synthesized by Fujii et al.^{2,3)} in 1978. This combination was shown to have an augmented antitumor effect against various tumors compared with FT-207 alone. Phase study has been carried out with UFT for gastrointestinal and breast cancer in Japan^{8,15,16,19,20)}.

In order to define further possibility of clinical application of UFT on malignant brain tumors, the pharmacodynamics of UFT in vivo was studied in patients with malignant brain tumors in this report.

MATERIALS AND METHODS

A total of seven patients with malignant brain tumors, three with malignant gliomas and for with metastatic brain tumors, were examined in this study. The patients had a nasogastric tube inserted prior to craniotomy and UFT containing 900 mg of FT-207 was dissolved in physiological saline solution and administered into the stomach. Urine, plasma, CSF (via ventricular drainage), brain tumor tissues and brain tissues adjacent to the tumor were collected at interval and immediately frozen. The concentration of FT-207, 5-FU and uracil in these samples were measured after dissolution and extraction by high performance liquid chromatography¹³⁾. UFT contained 100 mg of FT-207 per capsule.

RESULTS

1) Urinary excretion dynamics (Fig. 1)

The concentration of unchanged FT-207 in urine was 48.5 $\mu\text{g/ml}$ after 4 hours and 22.4 $\mu\text{g/ml}$ after 6 hours. There was a tendency of gradual reduction, reaching 16.1 $\mu\text{g/ml}$ after 12 hours and 15.9 $\mu\text{g/ml}$ after 24 hours. The concentration of unchanged 5-FU in urine was

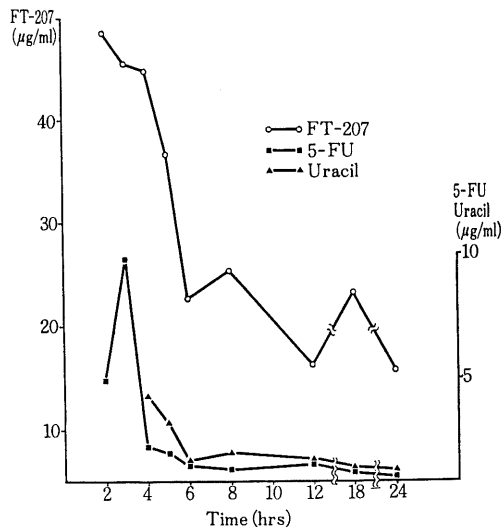


Fig. 1. Mean concentration of FT-207, 5-FU and Uracil in urine

9.7 $\mu\text{g/ml}$ after 2 hours, 4.92 $\mu\text{g/ml}$ after 3 hours and 1.57 $\mu\text{g/ml}$ after 4 hours, followed by a marked reduction hereafter, reaching 0.23 $\mu\text{g/ml}$ after 24 hours. The concentration of unchanged uracil in urine was 41.2 $\mu\text{g/ml}$ after 2 hours and 28.1 $\mu\text{g/ml}$ after 3 hours indicating a rapid excretion. After 4 hours this concentration reached 4.2 $\mu\text{g/ml}$ with a subsequent pattern of excretion similar to that of 5-FU.

2) Dynamics in plasma (Fig. 2)

The concentration of FT-207 in plasma was

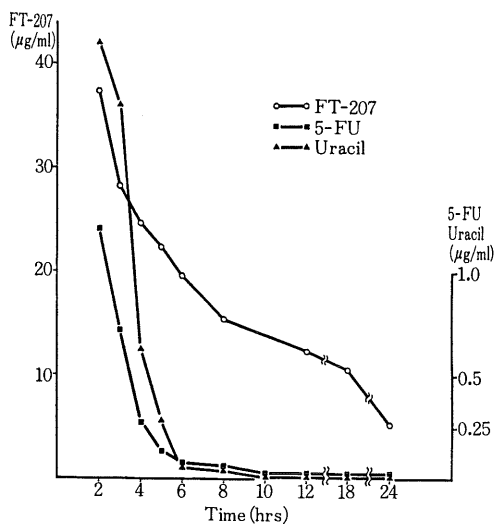


Fig. 2. Mean concentration of FT-207, 5-FU and Uracil in plasma

37.1 $\mu\text{g/ml}$ after 2 hours, 19.6 $\mu\text{g/ml}$ after 5 hours and 5.3 $\mu\text{g/ml}$ after 24 hours. The concentration of 5-FU was 1.2 $\mu\text{g/ml}$ after 2 hours, followed by a decrease to 0.27 $\mu\text{g/ml}$ after 4 hours and a marked decrease to 0.06-0.02 $\mu\text{g/ml}$ after 6 hours and subsequently. The concentration of uracil in plasma was 2.3 $\mu\text{g/ml}$ after 2 hours, 1.6 $\mu\text{g/ml}$ after 3 hours, 0.28 $\mu\text{g/ml}$ after 5 hours and 0.07-0.02 $\mu\text{g/ml}$ after 6 hours.

3) Dynamics in cerebrospinal fluid (CSF) (Fig. 3)

In these patients with metastatic brain tumor, the concentration of FT-207, 5-FU and uracil in the cerebrospinal fluid was measured. The concentration of FT-207 in CFS was 20.2 $\mu\text{g/ml}$ after 3 hours, 15.6 $\mu\text{g/ml}$ after 6 hours, 4.9 $\mu\text{g/ml}$ after 12 hours and 1.8 $\mu\text{g/ml}$ after

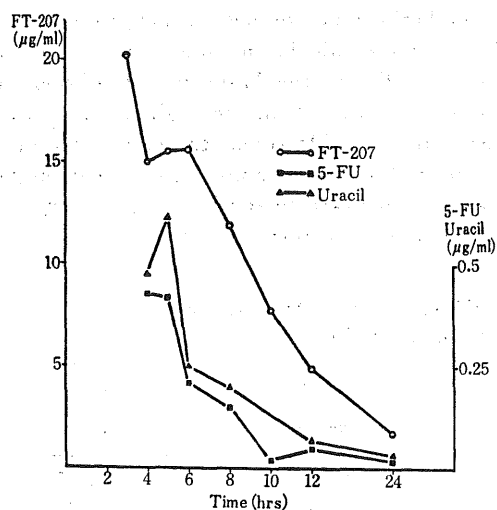


Fig. 3. Mean concentration of FT-207, 5-FU and Uracil in CSF

24 hours. The concentration of 5-FU was 0.4 $\mu\text{g/ml}$ after 4 hours and 0.21 $\mu\text{g/ml}$ after 6 hours, followed by a gradual decrease, reaching a low level of 0.02 $\mu\text{g/ml}$ after 24 hours. The concentration of uracil was 0.5 $\mu\text{g/ml}$ after 4 hours and 0.25 $\mu\text{g/ml}$ after 6 hours.

4) Pharmacokinetical analysis (Table 1)

The half life ($t^{1/2}$) of the distribution (α -phase) and that of the elimination (β -phase) for the concentration of FT-207 and 5-FU were calculated by the least square method. It was possible to measure the $t^{1/2}$ of α -phase of FT-207 in only two patients. The $t^{1/2}$ of β -phase was 4.59 hours, and that of β -phase, 9.99 hours. The $t^{1/2}$ of α -phase of 5-FU was 0.75 hours, and that of β -phase was 11.04 hours. The α -phase of 5-FU indicated absorption into the plasma within a short time after oral administration. The β -phase of 5-FU was slightly prolonged compared with FT-207. Area Under Drug Concentration-Curve (AUC) for the concentration of 5-FU up to 24 hours was averaged 12.434 $\mu\text{g}\cdot\text{hr/ml}$ in malignant gliomas.

5) The concentration in the brain tumor tissues and the brain tissues adjacent to the tumor (Fig. 4, Table 2)

The tumors were removed 4 to 6 hours after the administration of UFT. The concentration of FT-207 was 15.90-19.54 $\mu\text{g/g}$ in the tissues of malignant glioma, with 17.11 $\mu\text{g/g}$ on the average. The concentration in the metastatic brain tumor was 10.04-21.60 $\mu\text{g/g}$, with 16.71 $\mu\text{g/g}$ on the average. No difference in the concentration of FT-207 was noted between these different types of tumor tissues. The concentration of 5-FU was 0.07-0.29 $\mu\text{g/g}$ in the tissues of malignant glioma, with 0.02 $\mu\text{g/g}$

Table 1. Half life of FT-207 and 5-FU in plasma on brain tumor patients

| Case | Age | Sex | | FT-207 | | 5-FU | |
|------|-----|-----|------------------------|---------------|--------------|---------------|--------------|
| | | | | α (hr) | β (hr) | α (hr) | β (hr) |
| Y.O. | 46 | M | Metastatic Brain Tumor | | 9.44 | 0.91 | 8.48 |
| Y.O. | 46 | M | Metastatic Brain Tumor | | 9.32 | 0.72 | 14.29 |
| Y.O. | 34 | F | Metastatic Brain Tumor | 4.12 | 8.67 | 0.61 | 6.75 |
| M.O. | 71 | M | Malignant Glioma | | 15.60 | 0.75 | 10.07 |
| S.O. | 72 | F | Malignant Glioma | 5.06 | 6.90 | 0.76 | 15.60 |
| Mean | | | | 4.59 | 9.99 | 0.75 | 11.04 |

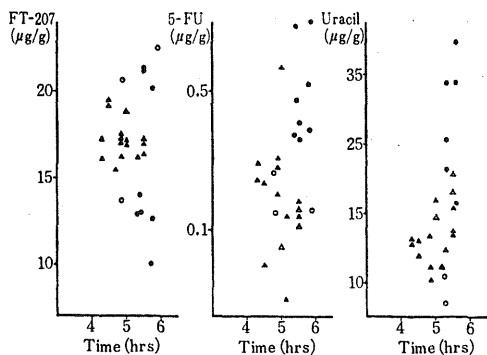


Fig. 4. The concentration of FT-207, 5-FU and Uracil in the brain tumor tissues (BT) and the brain tissues adjacent to the tumor (BAT)

- metastatic brain tumor (BT)
- Metastatic brain tumor (BAT)
- ▲ Malignant glioma (BT)
- △ Malignant glioma (BAT)

on the average, and that in metastatic brain tumor was 0.36–0.76 $\mu\text{g/g}$, with 0.47 $\mu\text{g/g}$ on the average, indicating an efficient transfer of 5-FU to metastatic brain tumor. The concentration of uracil was 4.77–20.71 $\mu\text{g/g}$ in malignant glioma, with 10.12 $\mu\text{g/g}$ on the average and 16.47–60.58 $\mu\text{g/g}$ in the metastatic brain

tumor, with 33.57 $\mu\text{g/g}$ on the average. The concentration of uracil in the tumor was especially higher in metastatic brain tumor.

As to the concentration of the brain tissues adjacent to the tumor, the concentration of FT-207 was 16.23–18.91 $\mu\text{g/g}$ in malignant glioma, with 17.38 $\mu\text{g/g}$ on the average. In metastatic brain tumor, it was 13.60–22.74 $\mu\text{g/g}$, with 19.10 $\mu\text{g/g}$ on the average. The concentration of 5-FU was 0.09–0.57 $\mu\text{g/g}$ in malignant glioma with 0.27 $\mu\text{g/g}$ on the average, and 0.15–0.26 $\mu\text{g/g}$ in metastatic brain tumor with 0.21 $\mu\text{g/g}$ on the average. The concentration of uracil was 14.56–20.71 $\mu\text{g/g}$ in malignant glioma with 17.96 $\mu\text{g/g}$ on the average, and 1.91–4.75 $\mu\text{g/g}$ in metastatic brain tumor with 3.13 $\mu\text{g/g}$ on the average. The concentration of 5-FU in the brain tissues adjacent to the tumor was slightly higher than in the brain tumor tissues on malignant glioma. But on metastatic brain tumor, the concentration of 5-FU in the brain tissues adjacent to the tumor was about one-half in the brain tumor tissues. Moreover, the concentration of uracil in the brain tumor tissues was higher than that of uracil in the brain tissues adjacent to the tumor, on metastatic brain tumor.

Table 2. The concentration of FT-207, 5-FU and Uracil in the brain tumor tissues (BT) and the brain tissues adjacent to the tumor (BAT)

| | | | FT-207 ($\mu\text{g/g}$) | 5-FU ($\mu\text{g/g}$) | Uracil ($\mu\text{g/g}$) |
|------------------------|-----|---------|-------------------------------|-----------------------------|-------------------------------|
| Malignant Glioma | BT | Minimum | 15.90 | 0.07 | 4.77 |
| | | Maximum | 19.47 | 0.29 | 15.27 |
| | | Mean | 17.11 | 0.20 | 10.12 |
| | BAT | Minimum | 16.23 | 0.09 | 14.56 |
| | | Maximum | 18.91 | 0.57 | 20.71 |
| | | Mean | 17.38 | 0.27 | 17.96 |
| Metastatic Brain Tumor | BT | Minimum | 10.04 | 2.36 | 16.47 |
| | | Maximum | 21.60 | 0.70 | 60.58 |
| | | Mean | 16.71 | 0.47 | 33.57 |
| | BAT | Minimum | 13.60 | 0.15 | 1.91 |
| | | Maximum | 22.74 | 0.26 | 4.75 |
| | | Mean | 19.10 | 0.21 | 3.13 |

DISCUSSION

Chemotherapy for malignant brain tumors has made great progress due to the development and/or pharmacokinetics of various nitrosoureas such as BCNU, CCNU, Methyl-CCNU and ACNU. A cooperative clinical trial by the Brain Tumor Study Group²³⁾ has clearly defined the effectiveness of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. Median survival time of BCNU only was 25.0 weeks; radiotherapy: 37.5 weeks; and BCNU plus radiotherapy: 40.5 weeks. Furthermore, Walker²⁴⁾ reported the randomized comparisons of radiotherapy and nitrosoureas for the treatment of 358 cases of malignant gliomas after surgery. Median survival time of radiotherapy was 36 weeks; Methyl-CCNU: 24 weeks; BCNU plus radiotherapy: 51 weeks; and Methyl-CCNU plus radiotherapy: 42 weeks. Malignant brain tumors were treated by other combined chemotherapy such as Procarbazine, CCNU and vincristine (PCV) or BCNU and 5-FU¹⁰⁻¹²⁾.

Fujita^{4,9)} and Bloklia¹⁾ reported the effectiveness of FT-207 for malignant brain tumors. Because of the effectiveness of FT-207 for various adenocarcinomas, it has been used for metastatic brain tumors rather than for primary malignant brain tumors^{5,9)}. The lipid-soluble FT-207 is absorbed from the digestive tract by simple diffusion and stays in the organism for several hours at a higher concentration. It is metabolized to 5-FU, an active substance, in the liver, so as to exert an antitumor effect. Such transformation and degradation from FT-207 to 5-FU is mainly accomplished by the metabolizing enzyme P-450 in the microsomal fraction of the liver, with the requirement of NADPH as the coenzyme²²⁾. However, the mechanism of the transformation of 5-FU is still unknown.

Mukherjer and Heidelberger¹⁴⁾ reported on the augmentation of the antitumor effect by the combined use of 5-FU and thymidine, along with the increase of the toxicity of 5-FU. Schumacher¹⁸⁾ reported on an inhibition of degradation of 5-FU in vitro by addition of uracil or thymidine. Fujii et al.^{2,3,7)} further studied the combined use of 5-FU with a pyrimidine compound. Simultaneous administration of FT-207 and uracil resulted in a rise of concentration of 5-FU in the tumors, because of the inhibition

of degradation of 5-FU by uracil, resulting in a marked augmentation of the antitumor effect of FT-207. UFT, containing uracil and FT-207 in a molar ratio 1 : 4, was reported to be more effective on experimental tumors, gastrointestinal, and breast cancer^{3,15,16,19,20)}. However, UFT has never been clinically used for malignant brain tumors.

In the present study, in order to evaluate the possibility of clinical application of UFT on malignant brain tumors, the pharmacodynamics of UFT was analyzed in patients with malignant brain tumor in vivo. Unchanged FT-207, 5-FU and uracil were gradually excreted in the urine, and no retention in vivo appeared to take place. The concentration of FT-207 in plasma showed the peak value of 37.1 $\mu\text{g/ml}$ at 2 hours after the administration. The concentration of 5-FU also reached the peak value of 1.2 $\mu\text{g/ml}$ at one hour after the administration, followed by a gradual decrease with time to 0.27-0.06 $\mu\text{g/ml}$ up to 6 hours. For a certain periods, nevertheless, the concentrations were found to be maintained above 0.005 $\mu\text{g/ml}$ which is sufficient for an antitumor effect. Fujita and Kohno⁴⁾ measured the concentrations of FT-207 and 5-FU in plasma by bioassay after an oral administration of 1600 mg of FT-207 in a patient with malignant brain tumor. They reported the maximum concentration of FT-207 as 22.0 $\mu\text{g/ml}$ at 3 hours after the administration. In this study, we administered UFT containing 900 mg of FT-207 and we obtained a concentration of 5-FU higher than Fujita and Kohono's result¹⁰⁾. The co-administration of FT-207 and uracil corroborates the fact that the concentration of 5-FU was increased through the inhibition of the catabolic process of 5-FU. Moreover, after the administration of UFT, the concentration of 5-FU in CSF was 0.4 $\mu\text{g/ml}$ at 4 hours later and 0.2 $\mu\text{g/ml}$ at 6 hours later. With the use of FT-207 alone, the transfer of 5-FU to CSF appear to be favorable.

From the results of pharmacological analysis, the $t^{1/2}$ of α -phase of FT-207 was about 5 hours, and the $t^{1/2}$ of β -phase was about 10 hours. The $t^{1/2}$ of α -phase of 5-FU was 0.75 hours and the $t^{1/2}$ of β -phase about 11 hours. Thus, FT-207 appears to be gradually transformed to 5-FU, so that the time dependent antitumor effect of 5-FU is re-enforced.

As to the concentration of 5-FU in the brain

tumor tissues, Fujiwara et al.⁵⁾ found 24.3 $\mu\text{g/g}$ of the concentration of FT-207 on the average, and 0.12 $\mu\text{g/g}$ of 5-FU on the administration of a 1500 mg of FT-207 suppository. In our study, the concentration of FT-207 was lower in both malignant glioma and metastatic brain tumor, but the concentration of 5-FU was higher than with the administration of FT-207 alone. Moreover, the concentration of 5-FU was slightly higher in the brain tissues adjacent to the tumor than in the brain tumor tissues on malignant glioma. But, on metastatic brain tumor, the concentration of 5-FU was higher in the brain tumor tissues than in the brain tissues adjacent to the tumor. Higher concentration of 5-FU in brain tumor tissues was apparently in accord with higher concentration of 5-FU in other malignant tumor tissues with the administration of UFT. As to the mechanism of such changes, it was suggested that the degradation of 5-FU would be inhibited by uracil in the brain tumor tissues, as previously noted. It is due to the major participation of uracil that the concentration of uracil in the brain tumor tissues was higher than that in the brain tissues adjacent to the tumor on metastatic brain tumor. Nogaki¹⁷⁾ also reported the corelationship between the concentration of 5-FU and uracil in the tumor tissues on malignant brain tumors. The concentration of FT-207 and 5-FU in the brain tissues adjacent to the tumor was similar to that within the tumor itself.

Thus, uracil in UFT shows a satisfactory transfer to the brain tissues adjacent to the tumor without changing the property of FT-207, and also, the enhancement of 5-FU in the malignant brain tumor tissues. Compared with FT-207 alone, the higher concentration of 5-FU may be achieved with a lower dose of 5-FU on the administration of UFT. These results seem to suggest a superior effect of UFT as a chemotherapeutic agent for malignant brain tumors.

ACKNOWLEDGMENT

We wish to thank Messrs. Teruyoshi Marunaka, Yukihiro Umeno and Masato Sano of Taiho Pharmaco. L. T. D. for their measurement of samples and technical assistance.

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