5-FU Monitoring by 19F MRI: A Quantitative Study by Liquid Chromatography / Tandem Mass Spectrometry

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Introduction

5-Fluorouracil (5-FU) and its many clinical analogs have been widely used in cancer chemotherapy on various solid tumors. These drugs show significant individual differences in pharmacokinetics of metabolites, so some patients who received 5-FU and its analogs often suffer a critical adverse reaction. For personalized medicine, a therapeutic drug monitoring (TDM) system for monitoring 5-FU and metabolites in each patient is therefore essential. As a new TDM system for 5-FU and its metabolites, fluorine magnetic resonance imaging (^{19}F MRI) has many potential advantages in regard to measuring ^{19}F nuclei-containing drug distribution and metabolism. Two such advantages are higher MR signal of ^{19}F than MR signal of ^{13}C, ^{31}P and other nuclei (except ^{1}H) and no background signal because of less natural existence in plasma and tissues. In the present study, the efficiency of detecting the distribution of 5-FU and metabolites by a ^{19}F/^{1}H MRI system was evaluated. The ^{19}F/^{1}H MRI system is based on a 7T animal scanner with a ^{19}F-^{1}H double-tuned RF coil for studying small animals [1]. To determine the tissue concentrations of 5-FU and its metabolites, quantitative analysis using a liquid chromatography / tandem mass spectrometry (LC/MS/MS) was performed.

Methods

We used a 7T MRI system (Varian, Inc.) with in-house ^{19}F-^{1}H double-tuned solenoid RF coil. ^{19}F and ^{1}H MRI datasets were acquired by *iv* bolus injection of 250mg/kg 5-FU into rats bearing Walker256 tumor xenografts. ^{19}F MR images were obtained using a fast-spin echo with FOV of 400x100mm^2, matrix size of 64x16 without slicing, TR/TE/ETL =1000ms/7ms/4. ^{1}H MR images were obtained using a spin echo with FOV of 200x200mm^2, matrix size of 256x256, 2mm slicing, TR/TE/ETL =1000ms/12ms. The time course of 5-FU, FBAL images and signal intensity was obtained for 120min after 5-FU administration in both tumor and liver (n=3). Quantitative concentrations of 5-FU and fluoro-β-alanine (FBAL) of both tumor and liver were acquired by using a LC/MS/MS system (Waters Corp.) (n=3 to 5). The relation between the ^{19}F-signal intensity and tissue concentration of 5-FU and FBAL at point of 10, 30, 60, 120min was evaluated, respectively. All animal studies were conducted in accordance with guidelines with for the care and use of laboratory animals (Hitachi, Ltd.).

Results and Discussion

Fig. 1 showed a *in vivo* ^{19}F-^{1}H MR image. The region of interest (ROI) for obtaining the time course of ^{19}F-signals derived from 5-FU and FBAL was set in tumor and liver. ^{1}H MR image was used to guide setting ROI.

Fig. 2 showed the time course of tissue concentration of 5-FU and FBAL by LC/MS/MS, and of ^{19}F-signal intensity in tumor. The time course of signal intensity of 5-FU and FBAL fit to the concentration obtained by LC/MS/MS. Fig. 3 showed that it was observed in liver that the relationship between signal intensity and tissue level was the as the tumor data, as well as it was shown in Fig. 2.

The relationship between valid concentration and signal intensity for a tumor and liver was evaluated (Fig. 4). Clearly, well relationship coefficients were obtained (5FU in tumor: 0.82, FBAL in tumor: 0.96, 5-FU in liver: 0.94, FBAL in liver: 0.99).

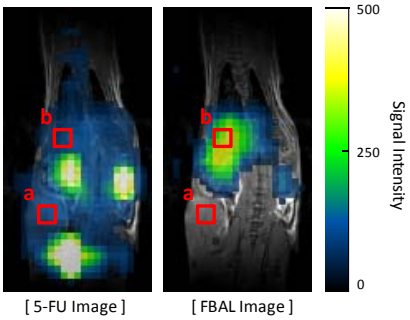

Fig. 1. In vivo MRI (^{19}F-^{1}H image merged)
(ROI-a: Tumor, ROI-b: Liver)

Conclusion

It was demonstrated that ^{19}F MRI can detect tissue distribution of 5-FU and FBAL in Walker256 tumor-bearing rats. To the best of our knowledge, this is the first report that ^{19}F MRI study can be evaluated by pharmacokinetics data obtained by quantitative LC/MS/MS *in vivo*. Accordingly, it is concluded that ^{19}F MRI is useful in noninvasive TDM system for tissue distributions of ^{19}F-containing drugs and metabolites.

Reference

[1] Otake et al. ISMRM 2009:2966.

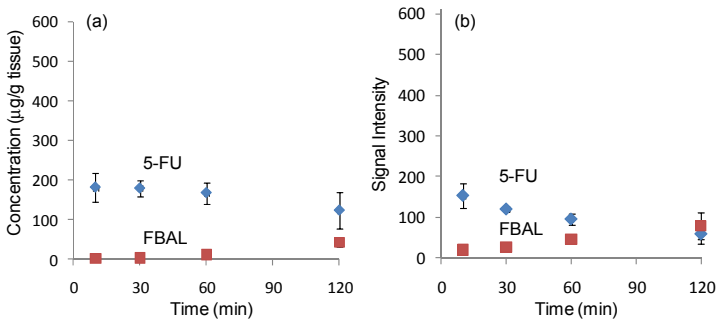

Fig. 2. In vivo dynamics of 5-FU and FBAL in tumor. ((a) LC/MS/MS, (b) ^{19}F MRI)

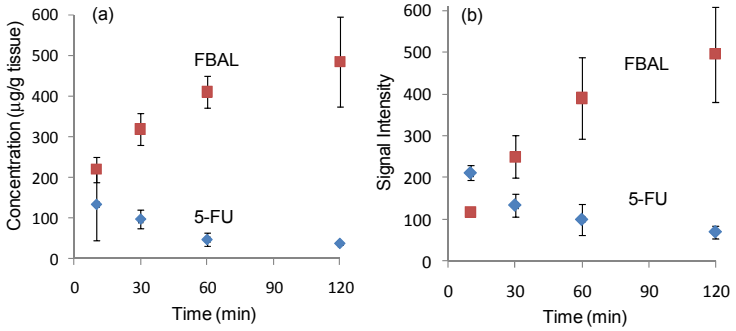

Fig. 3. In vivo dynamics of 5-FU and FBAL in liver. ((a) LC/MS/MS, (b) ^{19}F MRI)

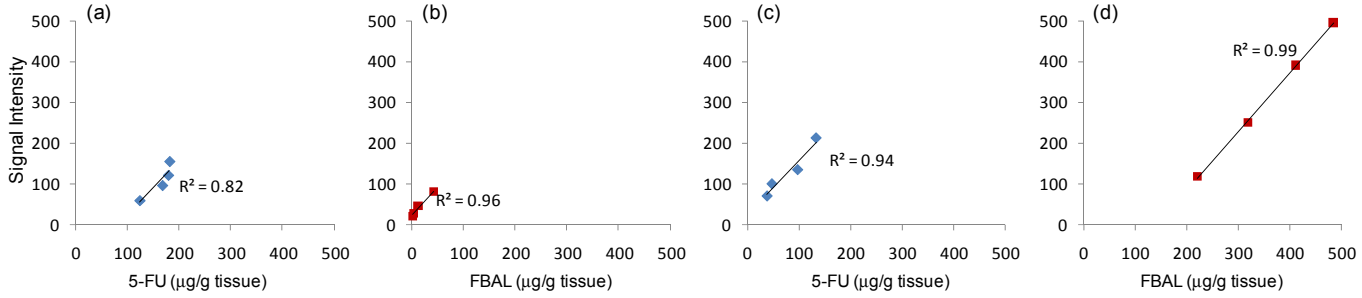

Fig. 4. Relationship between signal intensity and concentration. ((a) 5-FU in tumor, (b) FBAL in tumor, (c) 5-FU in liver, (d) FBAL in liver)