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SHORT COMMUNICATION

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Superiority of hepatic arterial infusion in preventing catabolism of 5-FU compared with portal vein infusion revealed by an in vivo ^{19}F NMR study

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Abstract *Purpose*: The aim of this study was to identify the route of administration of 5-FU with the greatest pharmacological advantage in a rat model using non-invasive in vivo ^{19}F nuclear magnetic resonance (NMR) spectroscopy. *Methods*: 5-FU (50 mg/kg) was administered to anesthetized Wistar rats cannulated into the hepatic artery, portal vein or tail vein and 11 NMR spectra were acquired from the liver region to 60.5 min every 5.5 min. *Results*: With systemic i.v. (tail vein) infusion, the ^{19}F-NMR signal for 5-FU from the liver region peaked in the first spectrum (0–5.5 min), and then gradually decreased. The signal for the 5-FU catabolite α-fluoro-β-alanine (FBAL) gradually increased to the sixth spectrum (0–33.0 min) and then plateaued. Following portal vein infusion the intensity of the first 5-FU spectrum was twice as high as that following i.v. infusion, but the intensity decreased and the FBAL signal increased gradually in the sixth spectrum as systemic i.v. infusion. In contrast, the intensity of the 5-FU signal following hepatic artery infusion was the same as that following portal vein infusion in the first spectrum, and maintained a strong intensity to the final spectrum (60.5 min). The FBAL signal was detected from the second spectrum following hepatic artery infusion, but its intensity was significantly weaker than that following i.v. or portal vein infusion. *Conclusions*: Hepatic arterial infusion resulted in the active form of 5-FU being present for a longer time and its degradation in the liver being suppressed compared with the results following portal vein infusion. This catabolic advantage of hepatic areterial infusion could lead to a more potent anti-tumor activity against liver metastases, but could also lead to significant host toxicity including biliary toxicity. We recommend that the dose/schedule of 5-FU administered via the hepatic artery should be adjusted carefully.

Key words 5-FU · FBAL · ^{19}F-NMR · Hepatic arterial infusion · Portal vein infusion

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Introduction

The antineoplastic agent 5-fluorouracil (5-FU) is widely used in the therapy of head, neck, breast, and colorectal tumors. Anabolism converts 5-FU into nucleosides and nucleotides (5-FUranuc) such as 5-fluorouridine-5′-monophosphate (FUMP), FUDP, FUTP, 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), FdUDP, and FdUTP. The cytotoxic effect of fluoropyrimidine chemotherapy is attributed to FdUMP, which inhibits thymidylate synthase and subsequently DNA synthesis, and also to FUTP, which interferes with the maturation of ribosomal RNA. Enzymatic catabolism of 5-FU leads to 5-fluoro-5,6-dihydrouracil (DHFU), and α-fluoro-β-alanine (FBAL). The major catabolite, FBAL, is excreted via the kidneys.

Regional chemotherapy using 5-FU or 5-fluorodeoxyuridine (FUDR) has been well established in the treatment of colorectal liver metastases [7]. The rationale for regional chemotherapy is based on the hypothesis that increased local drug concentration may improve the tumor response rate [2]. Whereas normal liver parenchyma and early micrometastases are mainly fed by the portal vein, established hepatic metastases are believed to receive most of their blood supply from the hepatic artery. Moreover, metabolism of agents, including fluoropyrimidines, delivered via the hepatic arterial

route results in the clearance of roughly 95% of the administered dose [3]. This results in less exposure of normal extrahepatic tissues to the drug, resulting in less systemic toxicity. Based on this theoretical rationale, regional chemotherapy using the hepatic artery or portal vein for drug delivery is believed to be better than systemic administration. However, the pharmaceutical advantage of regional administration in terms of drug metabolism has not been clearly demonstrated.

In the present study, we carried out a real-time follow-up of the concentrations of 5-FU and its major catabolite, FBAL, in the liver using noninvasive ^{19}F nuclear magnetic resonance (NMR) spectroscopy in a rat model.

Materials and methods

Experimental model

Inbred male Wistar rats weighing 250 to 280 g were obtained from Japan Company (Shizuoka, Japan). Under pentobarbital sodium anesthesia, the abdomen was opened through a midline incision and an additional small transverse incision. Portal vein cannulation was carried out by introducing a 3-Fr tube into the portal trunk. Hepatic artery cannulation was accomplished by introducing a tube into the gastroduodenal artery [5]. A 3-Fr polyethylene tube was stretched over a flame and served as a cannulation tube. The use of a bonding agent (Aron Alpha; Konishi Company, Osaka) at the cannulation site was of great help in preventing dislodgement of the tube. Systemic infusion was carried out through the tail vein. Each rat received a bolus infusion of 5-FU (50 mg/kg) in 0.5 ml saline via the hepatic artery, portal vein or tail vein. There were three animals in each group.

NMR spectroscopy

^{19}F-NMR spectra were obtained on a SISCO spectrometer (Spectroscopy Imaging System Corporation) operating at 80.442 MHz for fluorine. Spectra were obtained with a two-turn surface coil 2.5 cm in diameter of wound 14-gauge copper wire. Spectral acquisition parameters included a spectral width of 20 kHz, a pulse interval of 0.5 s, and 512 acquisitions. A 100-μs pulse width and a repetition time of 2.5 s were used for all experiments. Measurements were continued for up to 60.5 min after injection of 5-FU. For the liver measurements, the rats were immobilized by 0.5% halothane anesthesia.

Prior to the acquisition of the ^{19}F-NMR spectra, the B_0 field was shimmed onto the H_2O signal. Spectra were Fourier transformed with an exponential multiplication giving a line broadening of 80 Hz. Peak areas were estimated using programs available on the spectrometer. The various fluorouracil nucleotide phosphates could not be resolved by in vivo ^{19}F-NMR; therefore, the nucledotide peak reflects the total concentration of the unbound fluorouracil nucleotide species. The ^{19}F chemical shifts were arbitrarily referred to 5-FU at 0 ppm. The metabolite, FBAL, was observed at −19 ppm from the chemical shift value of 5-FU [4, 11, 12].

Results

Sequential ^{19}F-MR spectra of the liver region of rats after 5-FU infusion via the hepatic artery, portal vein, and intravenous route

The complete series of in vivo ^{19}F NMR spectra taken with the surface coil placed over the rat liver after the infusion of 5-FU is illustrated in Fig. 1. Each of the spectra measured at 5.5 through 60.5 min after infusion via the hepatic artery (left), the portal vein (center), and the tail vein (right) shows the reference peak of 5-FU at 0 ppm and that of FBAL (−19 ppm). After systemic i.v. (tail vein) administration of 5-FU, the 5-FU peak was observed in the first spectrum (0–5.5 min) and its signal intensity decreased gradually, and no more 5-FU resonance was detected after the ninth spectrum (49.5–55.0 min). The FBAL signal was detected in the second spectrum and increased rapidly. In the case of portal vein infusion, the kinetics of 5-FU and FBAL showed basically the same pattern as that of systemic i.v. infusion. In contrast, the 5-FU signal in the rats receiving 5-FU via the hepatic artery continued at a high level throughout the study.

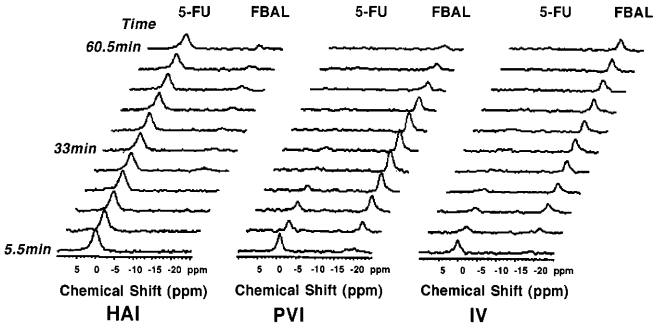

Fig. 1 Sequential ^{19}F-MR spectra of the liver region of a rat during the first 60.5 min after hepatic artery (*left*), portal vein (center), and intravenous (*right*) infusion of 5-FU. The time after injection of 5-FU when the specific spectral acquisition began is noted on the left side

Time courses of 5-FU and FBAL signal intensities of rat liver after 5-FU infusion via the hepatic artery, portal vein, and intravenous route

The corresponding time courses of the normalized peak integrals of 5-FU are shown in Fig. 2. With regional

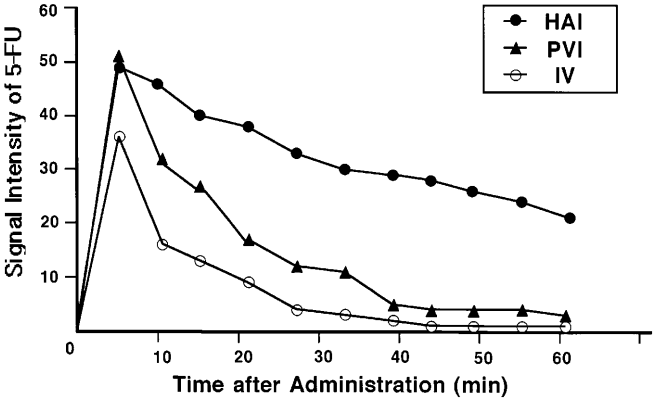

Fig. 2 Time courses of 5-FU signal intensity of ^{19}F-MR of a rat liver after hepatic artery, portal vein, and intravenous infusion of 5-FU. Data points are the mean values from three rats

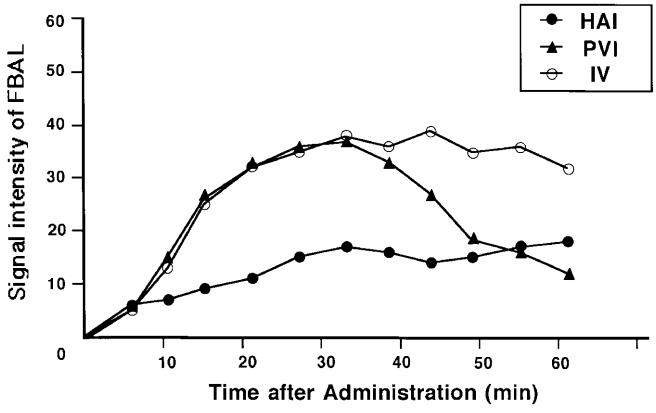

Fig. 3 Time courses of FBAL signal intensity of ^{19}F-MR of a rat liver after hepatic artery, portal vein, and intravenous infusion of 5-FU. Data points are the mean values from three rats

administration (portal vein and hepatic artery infusion), the 5-FU peaks of the first spectrum were both more intense (about 1.5 times stronger) than that for animals receiving 5-FU via systemic i.v. injection. The rates of decrease were similar for portal vein and for systemic i.v. infusion. Interestingly, the rate of decrease in the liver 5-FU signal was much slower with hepatic artery infusion. The strong intensity of 5-FU persisted up to the final spectrum (55–60.5 min) in animals receiving 5-FU via the hepatic artery.

The changes in the level of the FBAL signal in each group are shown in Fig. 3. The NMR signal of FBAL was detected from the first spectrum and showed a faster increase in both the portal vein and the systemic i.v. infusion groups. In contrast, the rate of increase of the FBAL signal was significantly suppressed through the final spectrum in the hepatic artery infusion group.

Discussion

Regional chemotherapy using 5-FU or FUDR is well established in the treatment of colorectal liver metastases [6, 7]. The rationale for regional chemotherapy including hepatic artery infusion and portal infusion is based on the hypothesis that increased local drug concentrations may improve the tumor response rate.

On the basis of the concept that hepatic metastases obtain most of their blood supply from the hepatic artery, hepatic arterial chemotherapy has been used in the treatment of unresectable liver metastases [6]. Several randomized studies have indeed demonstrated higher response rates (50–60%) with hepatic arterial chemotherapy than with systemic chemotherapy (20–30%). However, a survival advantage has not been clearly demonstrated in these trials [10].

As some hepatic recurrence may be attributed to the seeding of tumor cells into portal venous blood during and after surgical manipulation of the primary lesion, postoperative portal vein chemotherapy has been advocated for the prevention of liver metastases. Taylor et al. [13] have demonstrated a significant survival advantage for patients with stage B or C colonic carcinoma receiving 7 days of portal vein 5-FU. The survival advantage from portal vein chemotherapy primarily stems from a reduction in the incidence of liver metastases. However, not all patients with clinically normal livers at the time of resection will benefit from this form of treatment. In this trial, approximately 20% of liver recurrence occurred in the portal vein infusion group.

In spite of an appealing pharmacological rationale of regional administration of 5-FU, clinical efficacy varies widely. To understand this disparity in the results of regional chemotherapy with 5-FU, more must be discovered about 5-FU metabolism in the liver. In vivo magnetic resonance spectroscopy (MRS) may help to elucidate the reasons for the efficacy of 5-FU treatment. The anabolic conversion of 5-FU into cytotoxic nucleotides can be monitored by MRS. MRS allows the differentiation between 5-FU and its metabolites and, in principle, provides a means of determining in vivo metabolic rates and the distribution of 5-FU into anabolic versus catabolic pathways [4, 11, 12].

Regional infusion including portal vein infusion and hepatic arterial infusion have been considered to have the advantage of increasing the local concentration of the drugs in the liver. However, the present study using NMR demonstrated that 5-FU metabolism in the liver showed significantly different patterns with hepatic arterial and with portal vein infusions. The level of 5-FU in the liver was sustained and the anabolic pathway was depressed with administration via the hepatic artery. This catabolic advantage with the hepatic artery route may contribute to the therapeutic efficacy of hepatic artery infusion of 5-FU in the treatment of liver metastases.

Hepatic blood flow comprises approximately 70% of portal blood flow and 30% of hepatic arterial flow. Anatomically, the portal vein spreads out in branches and directly drains into sinusoids. In contrast, hepatic arteries are connected exclusively to the peribiliary plexuses (PBP) and finally drain into sinusoids [1]. The interaction between the two inflows is not precisely understood, but it is clear that there is at least one interaction, the hepatic arterial buffer response that regulates arterial inflow in order to maintain total hepatic flow constant. That is, a decrease in portal flow results in an increased arterial flow independent of hepatic metabolic requirement. Changes in hepatic blood flow directly alter hepatic clearance of many compounds whose levels are regulated by hepatic catabolism [9].

Our present data indicate that 5-FU given via the hepatic artery tends to stay longer in the PBP, and is released slowly into the hepatic sinusoids. This is a favorable feature in treating metastatic liver tumors nourished by the hepatic artery. We have confirmed that the administration of 5-FU through the hepatic artery induces significantly higher concentrations of 5-FU in tumors compared to that in surrounding normal liver

tissue utilizing a rat liver metastasis model (Okuno et al.; manuscript in preparation).

However, this implies that 5-FU given via the hepatic artery may cause a greater adverse effect on the bile duct than we have estimated. Indeed, many investigators have found severe biliary toxicity associated with hepatic artery infusion of 5-FU/FUDR. The most serious toxic effect, sclerosing cholangitis, occurs in 5% to 29% of patients [7]. This necessitates both dose reductions and treatment delays. Therefore, decreasing the hepatic toxicity of hepatic artery infusion may improve the therapeutic efficacy in treating liver metastases. Kemeny et al. [8] have reported that the use of dexamethasone with FUDR decreases hepatic toxicity and increases response rate.

Although the precise difference in the metabolic mechanism between the portal venous route and the hepatic arterial route cannot be explained clearly at present, these results may be of relevance to investigators considering the administration route/dose of 5-FU. We are now carrying out a study to attempt to elucidate the appropriate dose timing/schedule of hepatic artery infusion of 5-FU for avoiding excess 5-FU levels in the PBP using this experimental system.

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