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A protein-bound polysaccharide immunomodulator, PSK, does not suppress the conversion from 1-(2-tetrahydrofuryl)-5-fluorouracil to 5-fluorouracil in patients with gastric cancer

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Effects of the immunomodulator PSK on the metabolism of 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) to 5-fluorouracil (5-FU) were examined in 10 patients with advanced gastric cancer and who had undergone curative resection. PSK is a protein-bound preparation, extracted from *Coriolus versicolor* and belongs to *Basidiomycetes*. The 5-FU concentration in the plasma was 0.024 μg/ml at 15 min after the intravenous injection of 400 mg of tegafur and the area under the curve of 5-FU was 0.58 μg·h/ml. Following administration of PSK, 3 g/day for 8–14 months, there was no change in the plasma level of 5-FU, in any patient. As the clinical dose of PSK had no apparent influence on the metabolism of tegafur to 5-FU, the combination of PSK and tegafur can be prescribed to treat patients with advanced gastric cancer.

Key words: Gastric carcinoma, 5-fluorouracil, PSK, 1-(2-tetrahydrofuryl)-5-fluorouracil.

Introduction

Immunotherapy added to chemotherapy plays an important role in the management of extended malignancies.[1] Nevertheless, the incidence of hepatic dysfunction was found to be high, in experimental[2,3] and in clinical situations,[4–6] when the treatment included immunomodulators. Alteration in hepatic function assumes paramount significance in patients receiving chemotherapy because biological properties of drugs can be greatly modified by hepatic enzymes. The NADPH-dependent mixed-function oxidase system located in the endoplasmic reticulum plays a major role in the metabolism of various anticancer drugs.[2] Adjuvant-induced changes in mixed-function oxidase activity can affect the rate of metabolism of such drugs and, conceivably, alter their duration of action and toxicity.

In the treatment of gastric cancers, the use of various immunomodulators, including the protein-bound preparation, PSK, combined with 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) has significantly enhanced the survival rate.[7–9] Tegafur is transformed to 5-fluorouracil (5-FU) primarily by hepatic drug-metabolizing enzymes which exhibit anti-neoplastic effects.[10] As PSK was found to have an inhibitory effect on these enzymes,[11] the effects of the combined use of tegafur and PSK should be given attention. We determined the influence of the clinical dose of PSK on the conversion from tegafur to 5-FU. When intravenously administered, tegafur is transferred to the liver and is metabolized to 5-FU, therefore, 5-FU levels in the plasma should reflect the hepatic metabolism of the drug. We examined 5-FU concentrations in blood samples following the intravenous administration of 400 mg of tegafur to patients with advanced gastric cancer, pre- and post-operatively following the administration of PSK.

Materials and methods

Drugs

Tegafur was obtained from Taiho Pharmaceutical Co. (Japan) and PSK from Sankyo Co. (Japan).

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Patients

The 10 patients included in this trial had undergone a macroscopic curative gastric resection.[12] PSK is a protein-bound preparation, extracted from *Coriolus versicolor* and belongs to *Basidiomycetes*.[13] The criteria for patient selection were as follows: (1) histological diagnosis of gastric cancer; (2) macroscopic diagnosis as a curative case on completion of surgical procedures; (3) under 76 years of age; (4) grade of 0–3 in performance status; (5) no evident synchronous or metachronous double cancer; (6) adequate organ system function (leukocytes > 4000/mm^3, platelets > 100 000/mm^3, GOT and GPT < 100 U).

Influence of the administration of PSK on the metabolism of tegafur to 5-FU

Patients with gastric cancer were given PSK 3 g/day and tegafur 600 mg/day orally for 8–14 months from post-operative day 14. Blood samples were collected pre-operatively at 15 min, 30 min, 1 h, 2 h, 3 h and 6 h after the intravenous injection of 400 mg of tegafur to determine the concentrations of tegafur and 5-FU. In these patients, the same test was performed after tegafur administration was withdrawn for 2 weeks to eliminate 5-FU from the bloodstream.

Assay of drug concentration

The concentrations of tegafur and 5-FU (Figure 1) in plasma were determined using the gas chromatographic–mass fragmentographic method.[14] A plasma volume of 1 ml was adjusted to pH 2.0 with 5 N HCl, chloroform was added and the preparation was shaken vigorously. The aqueous layer was used to determine the level of 5-FU and the chloroform layer was used to determine the level of tegafur.

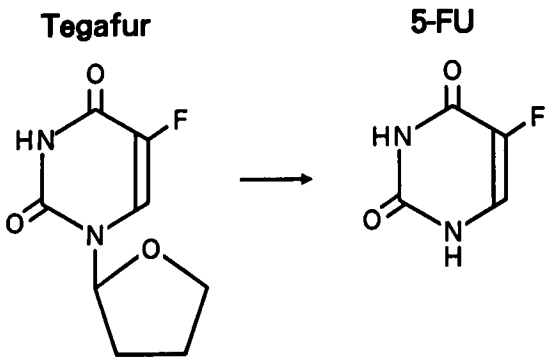

Figure 1. The conversion of tegafur to 5-FU by hepatic microsomal enzymes.

Pharmacokinetic analysis

The area under the curve (AUC) was calculated using the logarithmic trapezoidal method.[15]

Statistical analysis

The data were analysed using the paired *t*-test. A p value of less than 0.05 was considered to be statistically significant.

Results

The clinicopathological features of the 10 patients are shown in Table 1. These patients were prescribed 180.7 ± 65.3 g of tegafur and 945.0 ± 264.6 g of PSK, as out-patients.

The plasma levels of tegafur and 5-FU were determined twice. The peak levels of tegafur and 5-FU were noted at 15 min (Table 2). The levels decreased gradually for up to 6 h. With the administration of PSK, there were no differences between pre- and post-operative concentrations.

Table 1. Clinicopathological characteristics of patients surgically treated for gastric cancer

Variable	Patients
Age (years)	55.3 ± 6.8
Sex	
Male	6
Female	4
Location of tumor	
Upper	2
Middle	4
Lower	4
Histology	
Differentiated	4
Undifferentiated	6
Depth of penetration	
No serosal invasion	3
With serosal invasion	6
Lymph node metastasis	
Negative	2
Positive	8
Operative procedure	
Partial gastrectomy	7
Total gastrectomy	3

Table 2. Drug pharmacokinetics

Drug	Plasma concentration at 15 min (μg/ml)		Plasma drug AUC (μg·h/ml)	
	Pre	Post	Pre	Post
Tegafur	25.6 ± 4.2	26.8 ± 6.3	65.3 ± 7.8	61.7 ± 10.4
5-FU	0.024 ± 0.015	0.022 ± 0.01	0.58 ± 0.3	0.55 ± 0.16

Pre, pre-treatment period; Post, post-treatment period.

The AUC of tegafur and 5-FU obtained after the long-term administration of PSK was similar to that prior to its administration. PSK had no apparent influence on the activity of conversion from tegafur to 5-FU.

Discussion

The *in vitro* degradation of tegafur to 5-FU was noted in the microsomal fraction of the liver, in the presence of NADPH.[10] Although some of the tegafur is converted to 5-FU, within the tumor cells, it is primarily converted to 5-FU by an enzymatic pathway in the liver.[16,17] Immunomodulators including PSK, BCG and anaerobic *Corynebacterium* have been reported to decrease the activity of the drug-metabolizing enzymes of the liver.[2,3] A plausible mechanism for inhibition of the drug-metabolizing enzyme system involves elaboration of components of the immune effector arm.[2] The macrophage response damages some component of the electron-transport chain of drug-metabolizing enzymes. In clinical studies, a high incidence of hepatic dysfunction was seen in cancer patients treated with BCG.[4–6]

PSK is a widely prescribed immunomodulator in Japan[13] and is effective for experimental and clinical tumors alone or in combination with antitumor drugs.[18] A post-operative regimen consisting of intermittent administration of mitomycin C and long-term continuous administration of tegafur and PSK lengthened the survival time of patients with advanced gastric cancer.[7,8] As PSK inhibits hepatic microsomal enzyme activities, under experimental conditions, it is of great importance to determine the possible therapeutic effectiveness of concomitantly administered drugs in a clinical situation. Regarding effects of PSK administered for long periods, there were no marked changes related to PSK administration in the plasma concentrations of 5-FU. When PSK is administered concomitantly with tegafur to patients with gastric cancer, the clinical dose of PSK does not alter the pharmacokinetics of tegafur.

Conclusion

We determined the influence of the clinical dose of PSK on the conversion from tegafur to 5-FU in 10 patients with advanced gastric cancer. When intravenously administered, tegafur is transferred to the liver and is metabolized to 5-FU; therefore, 5-FU levels in the plasma should reflect the hepatic metabolism of the drug. Following administration of PSK, 3 g/day for 8–14 months, there was no change in the plasma level of 5-FU. The clinical dose of PSK does not alter the pharmacokinetics of tegafur.

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