W-4 [11:20~11:50]

New Anti-Cancer Agent S-1: Metabolism Based Drug Combination

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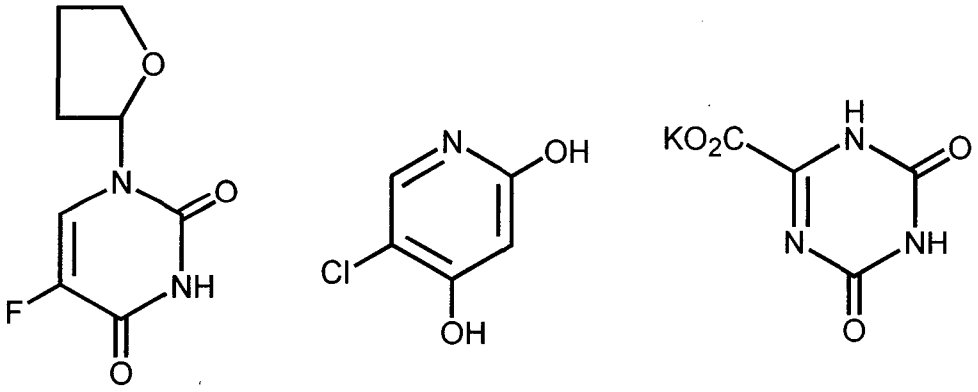
S-1 is a novel oral fluorinated antitumor drug that combines three pharmacological agents: tegafur (FT)(Fig. 1), which is a prodrug of 5-fluorouracil (5-FU); 5-chloro-2,4-dihydroxypyridine (CDHP)(Fig. 1), which inhibits dihydropyrimidine dehydrogenase (DPD) activity; and potassium oxonate (Oxo)(Fig. 1), which reduces gastrointestinal toxicity. FT is absorbed and then gradually converted into 5-FU, which has antitumor activity. CDHP potently and competitively inhibits degradation of 5-FU resulting prolonged high concentrations of 5-FU in blood and tumor tissue, thereby enhancing antitumor activity[1].



Tegafur	Gimeracil	Oteracil
(FT)	(CDHP)	(Oxo)

Fig.1 Chemical Structure of Each Compound

5-FU, discovered by Heidelberger[2] et al. in 1957, is a highly useful anticancer agent, which has been used alone or in combination to treat several classes of solid tumors for about 30 years up to the present. Furthermore, several methods of administration of 5-FU have been examined, and, in recent years, a long-term (4 weeks or more) persistent intravenous drip infusion method has drawn attention as the method of administration which allows maximal exertion of the effects of 5-FU. The dose-limiting toxicity in this method of administration involves mostly gastrointestinal mucosal disturbances, e.g., diarrhea and stomatitis, and bone marrow depression.

Complications accompanying catheter indwelling and decreased quality of life (QOL) of patient are also frequently reported. In addition, blood concentrations of 5-FU using intravenous drip infusion method have varied from report to report. The following reasons are considered to explain this finding: 1) there exists individual difference in the activity of the degrading enzyme of 5-FU and 2) there exist circadian variations in this enzyme. To solve these problems and utilize 5-FU effectively, it was considered necessary to potently inhibit the degrading enzyme of 5-FU.

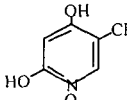
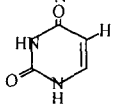
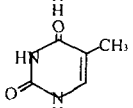
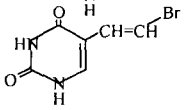
Oral agents of 5-FU and its derivatives have been developed, as well as the evaluation that oral administration is adequate for a long-term treatment. However, this method fails to obtain blood concentrations of 5-FU comparable to intravenous drip infusion; therefore, oral administration has not gained the therapeutic results equivalent to those of the persistent intravenous drip infusion method.

S-1 was developed to enhance the clinical advantage of 5-FU and ameliorate its disadvantage of gastrointestinal toxicity.

FT is a prodrug of 5-FU, with excellent oral bioavailability. It is gradually converted in 5-FU in the organism especially in the liver.

CDHP is a metabolic inhibitor of 5-FU[3](Table 1). CDHP allows to maintain blood and tumor concentrations of 5-FU for a long time by potently inhibiting the metabolism of 5-FU released from FT.

Table 1 Inhibitory Effect of CDHP Against to 5-FU Degradation

Compounds	Structure	IC_{50} [a] (μM)
5-Chloro-2, 4-dihydroxy-Pyridine(CDHP)		0.1
Uracil		18.0
Thymine		8.0
(E)-5-(2-bromovinyl) Uracil(BVU)		3.5

Enzyme :Supernatant of Rat Liver Homogenate
Substrate 5-FU :1 × 10-5M
a :50% Inhibition Concentration

A combination ratio between FT and CDHP required to inhibit the degradation of 5-FU generated from FT, to retain high concentrations in blood, and to enhance antitumor effect was investigated, and the optimal combination ratio was determined to be 1:0.4 [1](Fig. 2) .

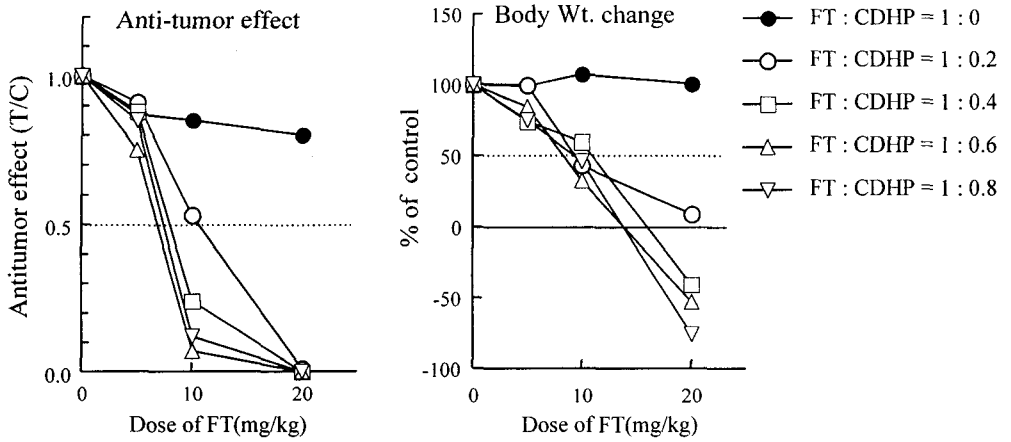


Fig. 2 Combination effect of FT and CDHP Against to Yoshida Sarcoma Bearing Rats

Oxo is a substance that blocks phosphorylation of 5-FU. Oxo shows a toxicity-reducing action on the 5-FU provoked gastrointestinal disturbances through its distribution in gastrointestinal tissues at high concentrations after oral administration.
A combination ratio of Oxo to suppress adverse effects, especially gastrointestinal toxicity, was investigated, and the ratio was determined to be 1 mol. Thus, the combination of FT, CDHP, and Oxo was set at 1:0.4:1.(Fig. 3)

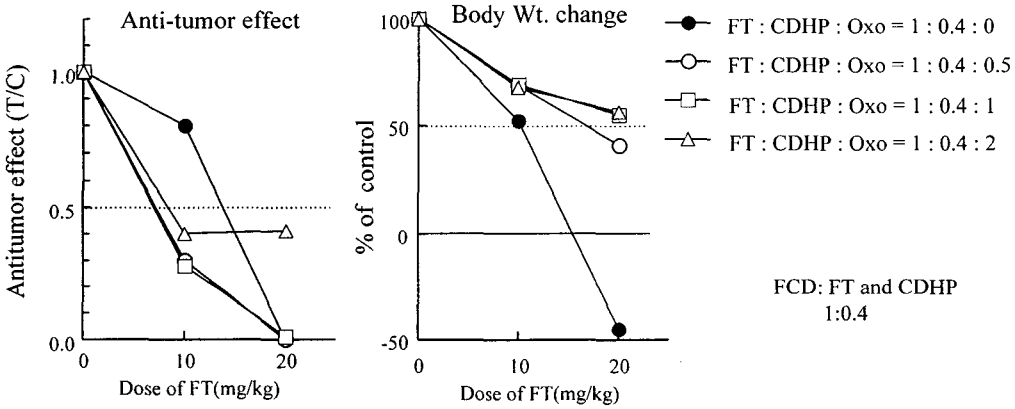


Fig. 3 Combination Effect of FCD and Oxo Against to Yoshida Sarcoma Bearing Rats

In the preclinical studies, S-1 showed a tumor proliferation-inhibitory action at lower doses than other conventional pyrimidine fluoride-derived anticancer agents, such as 5-FU. In the human tumor/nude rat system, S-1 was found to possess a tumor proliferation-inhibitory action on gastric cancer strain (1 strain), colon cancer strain (1 strain), and breast cancer strain (1 strain), which was superior to that of 5-FU.

In the 5-FU-provoked diarrhea model in Cynomolgus monkeys and Beagle dogs, S-1 showed a marked inhibitory action on the development of diarrhea (Table 2). In Beagle dogs especially, S-1 showed a marked inhibitory action on stomatitis, which was observed simultaneously, suggesting its clinical usefulness. (Table3)

Table 2 Combination Effect of Oxo to Diarrhea of Cynomolugus Monkeys

Drug	Dose (mg/kg)	Day of ad. (mean)	Animal (n)	Occurrence of Diarrhea
FCD	10	5.8	6	5
TS-1	10	6.3	6	1

Table 3 Combination effect of Oxo to Gastrointestinal Toxicity of Beagle Dog

Drug	Dose (mg/kg)	Period (day)	Animal n	Diarrhea (n)	Anorexia (n)	Stomatitis					B.W. change (kg, Mean)
						−	±	+	++	+++	
FCD(FT+CDHP)	5.0	7	5	5	5	0	0	0	1	4	- 0.91
TS-1(FCD+Oxo)	5.0	7	5	0	0	0	0	3	2	0	- 0.04

On the basis of the results of the preclinical studies, e.g., pharmacology, ADME, and safety, S-1 was expected to possess usefulness for several malignant tumors (solid tumors); Phase I and II clinical trials have been conducted in Japan.

Phase I study were conducted in Japan in patients with solid tumors as single-oral administration at doses of 25 mg(as FT)/body to 200 mg/body and 28 day administration, once or twice daily. The maximum tolerated dose was 200 mg/body/day, the dose limiting toxicity being bone marrow suppression.

Pharmacokinetic parameters obtained from the plasma concentrations of S-1 administered to 12 cancer patients in a single oral dose of 32-40 mg/m^2 after a meal are shown in the Table 4[4]. The amount excreted in the urine within 72 hours after

administration accounted for 52.8% of the CDHP, 7.8% of the FT, 2.2% of the Oxo, 11.4% of the metabolite cyanuric acid (CA;metabolite of Oxo) and 7.4% of the 5-FU.

Table 4 Pharmacokinetic Parameter of Each Analytes After Oral Administration of S-1 to Cancer Patients

	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0-48h)}$ (ng·hr/mL)	$T_{1/2}$ (hr)
FT	1971.0±269.0	2.4±1.2	28216.9±7771.4	13.1±3.1
5-FU	128.5± 41.5	3.5±1.7	723.9±272.7	1.9±0.4
CDHP	284.6±116.6	2.1±1.2	1372.2±573.7	3.0±0.5
Oxo	78.0± 58.2	2.3±1.1	365.7±248.6	3.0±1.4
CA	117.9±184.4	3.4±1.0	892.0±1711.7	3.8±1.6

(n=12, mean±S.D.)

When S-1 was orally administered at a dose of 25-200 mg/body, the AUC and C_{max} of FT, CDHP, Oxo and 5-FU increased in a dose-dependent manner. When the plasma concentration of S-1 was measured 1, 7, 14 and 28 days after administration of 32-40 mg/m^2 of S-1 twice a day for 28 consecutive days, it rapidly reached a constant level. Endogenous uracil rapidly decreased even after consecutive administration of S-1, and the CDHP-induced DPD inhibition was reversible, and no enhancing effect was observed.

Summarized were the results of clinical trials of S-1 (corresponding to 80-150 mg of FT/day) in two divided doses a day on the basis of oral administration. The response rate of gastric cancer and of head and neck cancer patients were 46.5%(60/129 patients) [5,6] and 34.1%(29/85 patients).

S-1 is approved in Japan for the treatment of stomach and head and neck cancer.

For the colorectal, breast, and lung cancer clinical developing are ongoing.

Biological action of S-1 is summarized in Fig. 4.

S-1 contains FT, CDHP and Oxo, and the antitumor activity of S-1 after oral administration is based on 5-FU that appears gradually in the body via the transformation of FT. CDHP increased the concentration of 5-FU, which is converted from FT, by selectively and reversibly inhibiting DPD, a catabolic enzyme of 5-FU, which is particularly distributed in the liver. 5-fluoronucleotides, phosphorylated

metabolites of 5-FU, are highly maintained in tumor tissues, thereby enhancing the antitumor activity in portion to the increase in the concentration of 5-FU in the body.

Oxo selectively inhibits the production of 5-fluoronucleotides from 5-FU by distributing in the gastrointestinal tissues as a result of oral administration and selectively and reversibly inhibiting orotate phosphoribosyltransferase(OPRT). Gastrointestinal toxicity appears to be relieved as a result, without interfering with the antitumor activity of 5-FU.

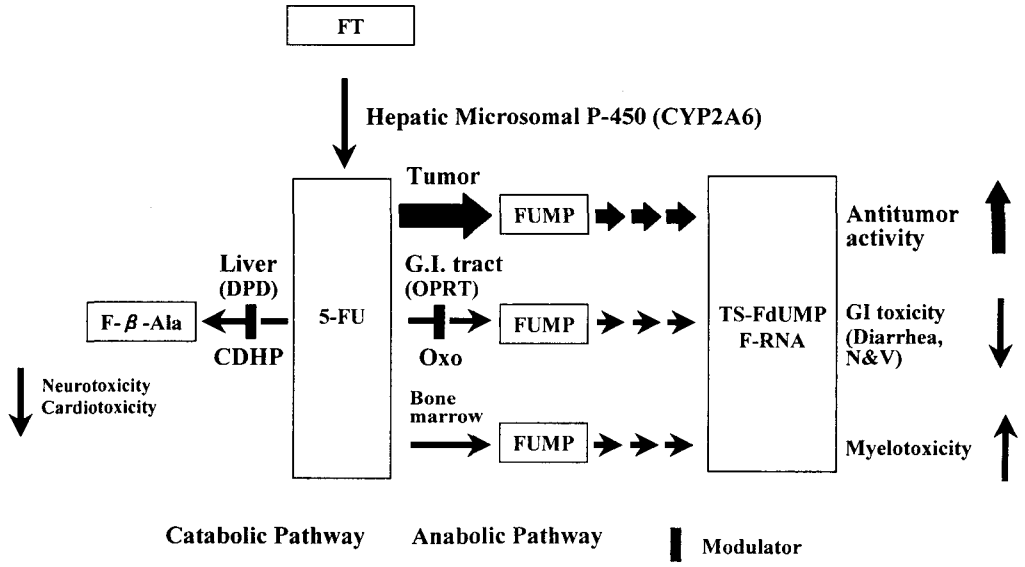


Fig. 4 Biological Action of S-1

Abbreviation

DPD: Dihydropyrimidine dehydrogenase, OPRT: Orotate Phosphorybosyl Transferase

TS: Thymidylate Synthase, G.I.: Gastro-Intestinal, N&V: Nausea and Vomitting

FUMP: Fluorouridine-monophosphate, FdUMP: Fluorodeoxyuridine-monophosphate

F-β-Ala: α-Fluoro-β-alanine

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