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Antitumor effects of IST-622, a novel synthetic derivative of chartreusin, against murine and human tumor lines following oral administration

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Abstract. The antitumor effects of 6-*O*-(3-ethoxypropionyl)-3′,4′-*O*-exo-benzylidenechartreusin (IST-622), a new synthetic derivative of chartreusin (CT), were investigated. Following oral administration, IST-622 showed marked antitumor effects against various mouse tumors such as P388 and L1210 leukemias, B16 melanoma, Lewis lung carcinoma, Colon 26 and Colon 38 adenocarcinomas, and M5076 reticulum-cell sarcoma. The best antitumor effects were obtained by five intermittent treatments given every 4 days. In addition, IST-622 showed a significant growth-inhibitory effect against two human tumor xenografts, a large-cell lung cancer (Lu-116) and a gastric adenocarcinoma (St-4), among the seven lines tested. IST-622, which was rapidly metabolized into 3′,4′-*O*-exo-benzylidenechartreusin (A-132) and not into CT in vivo or in culture medium, exhibited remarkable growth-inhibitory activity against P388 leukemia in vitro, its 50% growth-inhibitory concentration (IC_{50}) being over 20-fold lower than that of CT. IST-622 showed an in vivo antitumor effect superior to that of authentic A-132, possibly resulting from a higher absorption ratio of IST-622 through the gastrointestinal tract. IST-622 is now under clinical phase I study in Japan.

Key words: IST-622 – Chartreusin derivative – Orally active antitumor agent

Introduction

Chartreusin (CT, Fig. 1), a *Streptomyces chartreusis*-produced antibiotic, has been reported to have significant antitumor activity against several mouse tumors in vivo in the i.p.-i.p. system [2]. However, because of its unfavorable pharmacokinetics such as very rapid biliary excretion after i.v. administration as well as quite slow gastrointestinal absorption, chartreusin was not selected for clinical trials [2].

A series of 3′,4′-*O*-substituted derivatives of chartreusin were synthesized and their antitumor effects were tested [1]. Among them, 3′,4′-*O*-exo-benzylidenechartreusin (A-132, NSC-639831; Fig. 1) was found to be active against i.p.-implanted B16 melanoma following both i.p. and i.v. administration. By further chemical modification of A-132 on its 6-phenol position, more promising derivatives such as 6-*O*-(*N*,*N*-dimethylglycyl)-3′-4′-*O*-exo-benzylidenechartreusin (A-610) and 6-*O*-(3-ethoxypropionyl)-3′,4′-*O*-exo-benzylidenechartreusin (IST-622, NSC-639830; Fig. 1) were obtained. The former showed activity higher than that of A-132 following i.v. administration, whereas the latter exhibited a more prominent effect than did A-132 after oral administration [1].

Herein we describe the antitumor activity of IST-622 against various murine tumors as well as several human tumor xenografts and discuss the schedule dependency of these antitumor effects.

Materials and methods

Compounds. CT was obtained by fermentation of *Streptomyces chartreusis*. The 3′,4′-*O*-exo-benzylidenechartreusins A-132 and IST-622 were synthesized from CT by methods previously described elsewhere [1]. A-132M, a 3′-demethyl metabolite of A-132, was isolated from the feces of mice that had been treated with IST-622. IST-622 and A-132 were suspended in distilled water containing 0.5% (w/v) sodium carboxymethylcellulose using a Teflon homogenizer for in vivo experiments. For in vitro experiments, all compounds were dissolved in dimethyl sulfoxide and diluted with medium before their use.

Animals and tumor cells. Male DBA/2, C57BL/6, BALB/c, BALB/c × DBA/2 F_1 (hereafter called $CD2F_1$), C57BL/6 × DBA/2 F_1 (hereafter called $B6D2F_1$), and C57BL/6 × C3H/He F_1 (hereafter called $B6C3F_1$) mice were purchased from Charles River Japan, Inc. (Kanagawa, Japan) or SLC Japan, Inc. (Shizuoka, Japan), and female athymic BALB/c-nu/nu mice were obtained from CLEA Japan, Inc.

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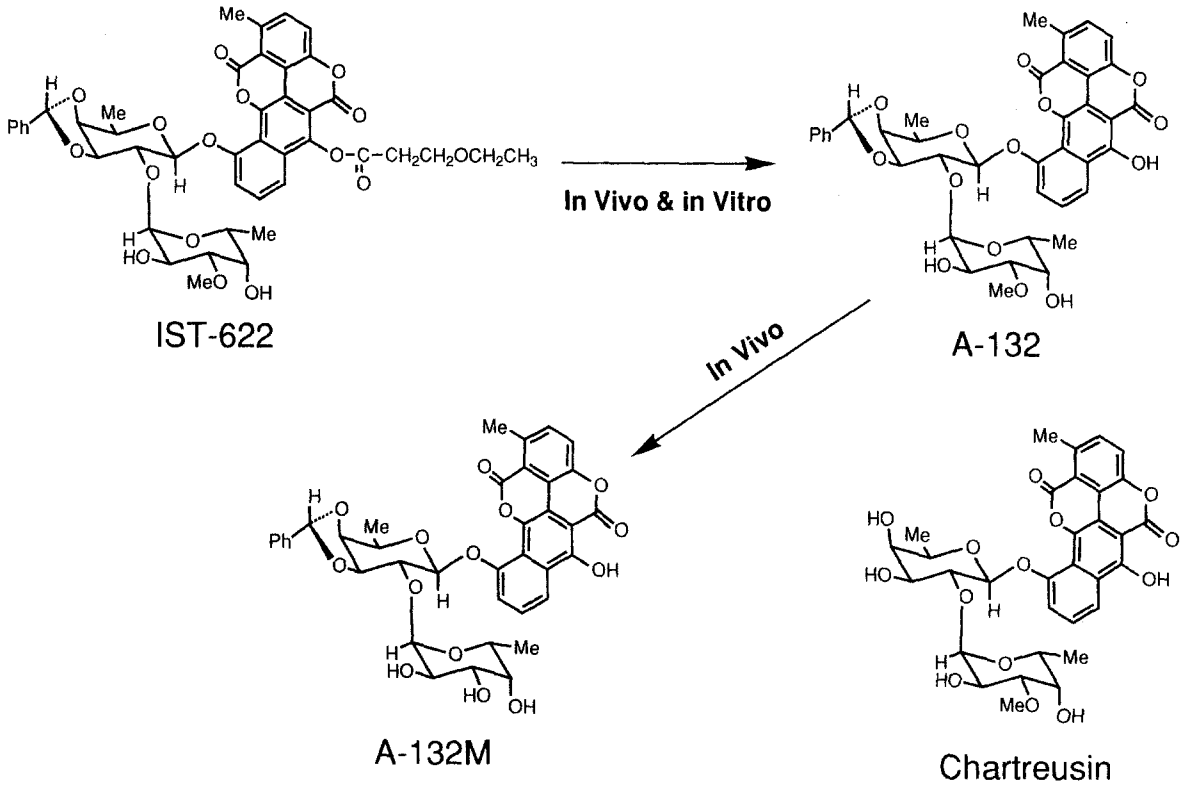

Fig. 1. Chemical structures of chartreusin and IST-622 and its metabolites

(Tokyo, Japan). P388 leukemia, L-1210 leukemia, B16 melanoma, Lewis lung carcinoma (LL), Colon 26 and Colon 38 adenocarcinomas, and M5076 reticulum-cell sarcoma were kindly provided by the National Cancer Institute, National Institutes of Health (Bethesda, Md.). These tumors were maintained in the respective syngeneic mice according to the protocols of the National Cancer Institute. The human tumor xenografts used in the experiments included three gastric adenocarcinomas (SC-6, St-4, and St-40), one small-cell lung carcinoma (LX-1), one non-small-cell lung carcinoma (Lu-116), and two mammary adenocarcinomas (MX-1 and H-31). MX-1 and LX-1 were kindly supplied by the National Cancer Institute; SC-6, by the Central Institute for Experimental Animals (Kawasaki, Japan); St-4 and St-40, by Dr. T. Kubota, Keio University (Tokyo, Japan); Lu-116, by Dr. Y. Shimosato, National Cancer Center Research Institute (Tokyo, Japan); and H-31, by Prof. T. Taguchi, Osaka University (Osaka, Japan). These human tumor xenografts were maintained in female BALB/c-nu/nu mice.

Evaluation of antitumor effects against mouse tumors. Each experimental group generally consisted of six mice. P388 (10^6) and L-1210 (10^5) cells were implanted i.p. into $CD2F_1$ mice. B16 (0.5 ml of 10% homogenate in 0.9% saline) and M5076 (10^6) and Colon 26 cells (5×10^5 viable cells) were implanted i.p. or s.c. into $B6D2F_1$, $B6C3F_1$, and $CD2F_1$ mice, respectively. LL (5×10^5 viable cells) and Colon 38 (a tumor fragment of 2-mm^3) were implanted s.c. into $B6D2F_1$ mice. Drug treatment was generally begun 1 day after tumor inoculation. To examine the effect of IST-622 on advanced tumors, the start of the treatment was postponed to 5 or 7 days after inoculation.

Antitumor activity against i.p.-implanted tumors was evaluated by the percentage of increase in life span (%ILS) based on the median survival time observed in the treatment group as compared with the control group. The perpendicular diameters of the s.c.-implanted tumors were measured with a caliper once or twice a week, and the tumor volume (V) was calculated as follows: $V = {}^1/_2 \times a \times b^2$, a and b being the long and short diameters of the tumor mass, respectively, as expressed in millimeters. The antitumor effect was determined by the percentage of mean tumor volume determined in the treatment group as compared with the control group as well as the %ILS.

Evaluation of antitumor effects against human tumor xenografts. The antitumor effects against human tumor xenografts were evaluated by methods previously reported elsewhere [5]. Briefly, a tumor fragment (2-mm^3) was inoculated s.c. and drug administration was started when the tumor volume reached 100–300 mm^3. IST-622 was given p.o. five times at 4-day intervals. Antitumor evaluation was based on the tumor growth rate calculated for each group.

In vitro growth-inhibition assays. P388 cells (5×10^4 cells/ml) were suspended in RPMI 1640 medium supplemented with 10% fetal bovine serum, penicillin (100 units/ml) and streptomycin (100 μg/ml) and cultured at 37° C in a humidified atmosphere containing 5% CO_2. Cells were exposed to various concentrations of CT derivatives in triplicate for 1 or 48 h, and after a 48-h culture period the number of cells were counted by a Coulter counter (model ZBI). Growth inhibition was expressed as the percentage of the mean number of cells counted in the drug-treated tubes as compared with the control tubes.

Measurement of areas under the plasma concentration-time curve for A-132 and A-132M in mice after oral administration of IST-622 and A-132. CD-1 (ICR) mice (three mice/group) were given IST-622 or A-132 orally. At 1, 3, 5, 8, and 24 h after drug administration, blood was aspirated from the right ventricles of mice under anesthesia with Nembutal and the plasma was separated by centrifugation (10,000 rpm at 4° C). Plasma concentrations of IST-622, A-132, and A-132M were assayed by high-performance liquid chromatography (HPLC). Mouse plasma was injected onto an ODS L-column, and metabolites were eluted isocratically using 20 m*M* acetate buffer (pH 4.0)/CH_3CN (4:6 v/v) at a flow rate of 1.2 ml/min. Detection was carried out by fluorescence with excitation at a 265-nm filter and emission at a 450-nm filter. Plasma AUCs were calculated from plasma concentration versus time curves with an extrapolation.

Results

Life-prolongation effect of IST-622 against P388 leukemia

Nine daily i.p. injections of IST-622 given beginning on day 1 had a marked life-prolongation effect on mice bearing P388 leukemia. In addition, the drug was similarly effective when given p.o., although twice the dose was necessary for an i.p.-equivalent effect (Fig. 2).

Schedule dependency of the antitumor effect of IST-622 on P388 leukemia: i.p.-p.o. system

In Table 1, the antitumor effects of IST-622 given at various intervals are compared for the same total dose. The optimal dose as well as the %ILS rose with the increase in the interval. The best %ILS was obtained by treatment at 4-day intervals; that is, a 184% (3-fold increase) and a 250% (5-fold increase) ILS was noted at a total dose of 1,000 mg/kg. The antitumor effect of a single treatment given on day 1 was lower than that of several intermittent doses.

Life-prolongation effect of IST-622 on mouse tumors: i.p.-p.o. system

Table 2 shows the life-prolongation effects of IST-622 on mice implanted i.p. with mouse tumors B16, Colon 26, and M5076 and treated five times at 4-day intervals. Oral administration of IST-622 significantly prolonged the median survival time (MST) of these tumor-bearing mice, especially those bearing B16 and M5076 tumors, whose MST showed over 2-fold increase at the optimal dose (240 mg/kg), although none of the mice was cured. Three intermittent treatments with IST-622 also proved quite effective against L1210 leukemia.

Tumor-inhibitory effect of IST-622 on mouse solid tumors: s.c.-p.o. system

IST-622 also demonstrated marked antitumor effects on various s.c.-implanted mouse tumors when it was given orally. As Table 3 shows, during five intermittent treatments with IST-622, the growth of each tumor strain was almost completely inhibited, at least at the optimal dose. In addition, life-prolongation effects were observed even at lower doses. Many of the mice implanted with Colon 38 or LL cells survived for more than 90 days without bearing any tumor mass.

Effect of IST-622 on advanced stages of P388 leukemia and B16 melanoma

Mice bearing P388 (i.p.) and B16 (s.c.) tumors were given IST-622 orally (q4d × 5) starting 5 and 7 days after inoculation, respectively (Tables 1, 3). IST-622 was quite effective against both tumors, even at advanced stages, although the %ILS was lower than that observed for tumors treated at the early stages and none of the mice was cured.

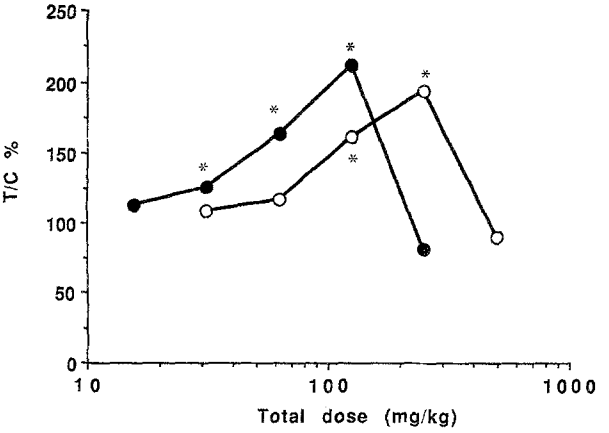

Fig. 2. Life-prolongation effect of IST-622 against P388 leukemia. P388 cells were inoculated i.p. into male CD2F$_1$ mice (6 mice/group). IST-622 was given i.p. (●) or p.o. (○) daily for 9 days beginning on day 1. T/C% exhibits the relative median life span of the treated group as compared with the control group. * $P < 0.01$ versus the control group (Mann-Whitney's U-test)

Table 1. Schedule dependency of the antitumor effect of IST-622 on P388 leukemia: i.p.-p.o. system

Total dose (mg/kg)	Life-prolongation effect (%ILS)					
	Q1d×9	Q2d×5	Q4d×3	Q4d×5	Q1d×1	Q4d×5[a]
2,000	–	–	Toxic	–	Toxic	
1,000	–	Toxic	184	250	80	160
500	Toxic	121	121	190	94	42
250	94	103	100	143	49	43
125	62	58	94	113	46	43
62.5	17	17	49	43	37	
31.3	–	17	–	–	31	

P388 (10^6) cells were implanted i.p. into male CD2F$_1$ mice (6 mice/group). Beginning on day 1, IST-622 was given orally on the schedules indicated. Effects are expressed as %ILS based on the MST, i.e. [(MST of the treated group – MST of the control)/MST of the control] ×100

[a] IST-622 was given beginning on day 5

Table 2. Life-prolongation effects of IST-622 on various mouse tumors: i.p.-p.o. system

Dose (mg/kg)	Life-prolongation effect (%ILS)			
	B16	M5076	Colon 26	L-1210[a]
240	129	145	91	206
160	96	113	86	164
80	57	84	70	124
40	39	80	41	81

Mouse tumor cells were implanted i.p. into male B6D2F$_1$ (B16) and B6C3F$_1$ (M5076) or CD2F$_1$ (Colon 26 and L-1210) mice (6 mice/group). IST-622 was given p.o. on days 1, 5, 9, 13, and 17. Effects are expressed as indicated in the footnote to Table 1

[a] Treated 3 times on days 1, 5, and 9

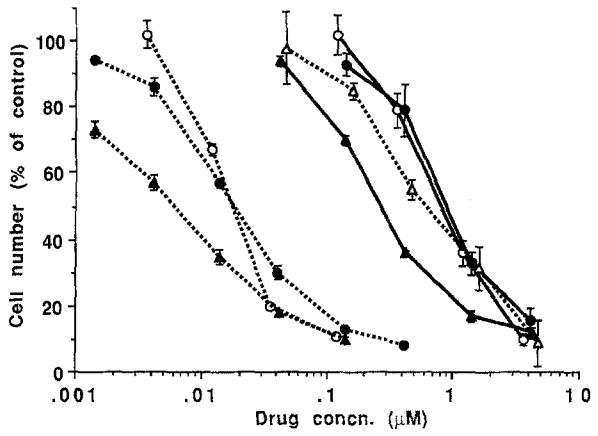

Fig. 3. In vitro sensitivity of P388 cells to IST-622 and its related compounds. P388 cells were exposed to various concentrations (*concn.*) of the compounds for 1 (—) or 48 h (···). After a 48-h culture period the number of cells were counted. ○, IST-622; ●, A-132; ▲, A-132M; △, chartreusin. *Vertical bars* represent standard deviations of each point

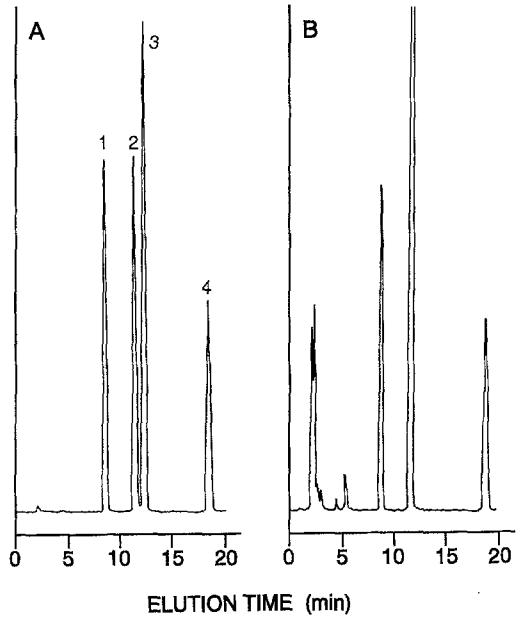

Fig. 4A, B. HPLC elution profiles of IST-622 and its metabolites. **A** Authentic samples: *peak 1*, A-132M (8.4 min); *peak 2*, A-132 (11.3 min); *peak 3*, IST-622 (12.1 min); *peak 4*, internal standard (18.4 min). **B** Mouse plasma at 1 h after oral administration of IST-622 (100 mg/kg)

Antitumor effect of IST-622 against human tumor xenografts

Table 4 shows the antitumor effects of oral IST-622 against several human tumors implanted into BALB/c-nu/nu mice. IST-622 showed a prominent growth-inhibitory effect on a large-cell lung carcinoma (Lu-116) and a significant effect on a gastric cancer (St-4) at a dose of 240 mg/kg. These effects were almost equivalent to those obtained with i.v. Adriamycin.

Table 3. Inhibitory effect of IST-622 on the growth of mouse solid tumors: s.c.-p.o. system

Tumor	Dose (mg/kg)	Tumor growth (T/C%)		Increase in life span	
		(day)[a]	(day)[a]	%ILS	Survivors[b]
		(19)	(21)		
B16	200	4	5	67	
	100	37	40	34	1
	50	46	47	19	1
B16[c]	200	13	10	7	
	100	27	29	42	
	50	79	96	13	
		(20)	(35)		
M5076	200	0	2	80	
	100	0	18	49	
	50	5.2	45	43	
	25	5.6	51	38	
		(20)	(29)		
LL	240	0	0	>200	6
	160	0	0	>200	5
	80	0	2.3	>200	5
	40	1.1	20	85	1
		(20)	(26)		
C38	240	0	0	Toxic	
	160	0	0	>42	2
	80	0	6.1	>42	4
	40	5.4	14	>42	3
		(10)	(12)		
C26	240	0	0.7	171	
	160	0.7	1.4	164	
	80	8	16	156	
	40	21	38	109	
	20	52	64	63	

Mouse tumor cells were implanted s.c. into male B6D2F$_1$ (B16, LL, and Colon 38), B6C3F$_1$, or CD2F$_1$ (Colon 26) mice (6 mice/group). IST-622 was given p.o. on days 1, 5, 9, 13, and 17. The tumor volume was calculated from perpendicular diameters, and growth inhibition was expressed as T/C%, T and C being the mean tumor volume determined in treated and control groups, respectively

[a] Days after implantation

[b] Number of mice surviving for more than 90 days without a tumor mass

[c] IST-622 was given beginning on day 7

Table 4. Inhibitory effect of IST-622 on the growth of human tumor xenografts: s.c.-p.o. system

Drug	Dose (mg/kg)	T/C (%)						
		MX-1	H-31	LX-1	Lu-116	SC-6	St-4	St-40
IST-622	240	47	58	107	6	72	33	77
	120	61	70	96	24	95	59	72
Adria-mycin	5	25	26	25	11	43	31	73

A tumor fragment (2-mm^3) was inoculated s.c. into a female BALB/c-nu/nu mouse (6 mice/group). When the tumor volume reached 100–300 mm^3, IST-622 was given p.o. five times at 4-day intervals. T and C represent the mean relative tumor growth observed in treated and control groups, respectively

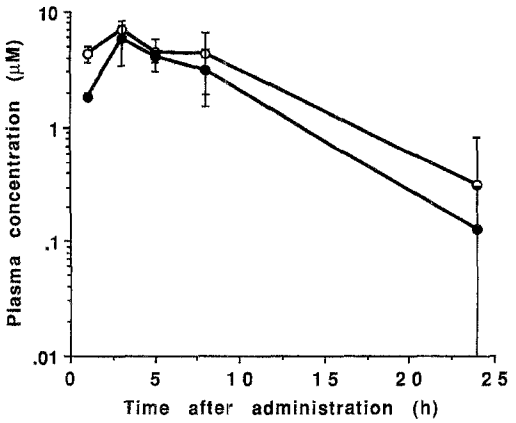

Fig. 5. Plasma concentrations of A-132 and A-132M measured in mice after oral administration of IST-622. ICR mice were given IST-622 orally (100 mg/kg). Blood was collected at 1, 3, 5, 8, and 24 h, and plasma concentrations of A-132 and A-132M were measured by HPLC. ○, A-132; ●, A-132M. *Vertical bars* represent standard deviations of each point

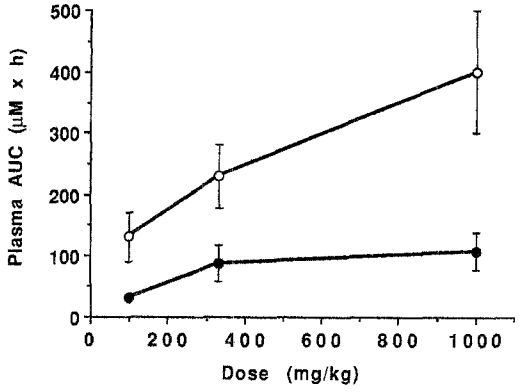

Fig. 6. Plasma AUC of IST-622 metabolites after oral administration of IST-622 and A-132. ICR mice were given IST-622 or A-132 orally. Blood was collected at 1, 3, 5, 8, and 24 h, and plasma concentrations of A-132 and A-132M were measured by HPLC. Plasma AUCs of A-132 plus A-132M calculated from plasma concentration versus time curves were plotted. ○, IST-622; ●, A-132. *Vertical bars* represent standard deviations of each point

Growth-inhibitory activity of IST-622 and related compounds against P388 cells in vitro

Cultured P388 cells were exposed to various concentrations of IST-622, CT, A-132, and A-132M (3′-demethylated A-132) for 1 or 48 h. Figure 3 shows the growth-inhibition curves generated for the compounds. IST-622 and its 6-deacylated metabolite A-132 showed similar activity and A-132M was the most active, whereas CT was over 20-fold less active than IST-622. The differences observed in 50% growth-inhibitory concentration (IC_{50}) values between a 1-h and a 48-h exposure to the drugs corresponded to a factor of approximately 40.

Comparison of the antitumor effects of IST-622 and A-132 on mouse tumors

Table 5 shows the antitumor effects of IST-622 and A-132 on P388, M5076, Colon 38, and LL tumors. Against i.p.-implanted P388 and M5076 tumors, IST-622 showed life-prolongation effects superior to those of A-132. Against s.c.-implanted Colon 38 and LL tumors, IST-622 exhibited greater inhibitory effects on tumor growth than did A-132, although the difference in survival time observed after treatment with the two drugs was not significant. Mice showed more tolerance for A-132 than for IST-622, but the %ILS values remained virtually unchanged at higher doses of A-132.

Metabolites of IST-622 detected in mice after oral administration

Plasma from mice given IST-622 orally (100 mg/kg) was analyzed by HPLC. No IST-622 was detectable in plasma even 30 min after treatment. Figure 4 shows the HPLC elution profiles obtained for authentic IST-622, A-132, and A-132M (Fig. 4A) and mouse plasma at 1 h after oral administration of IST-622 (Fig. 4B). The elution times for authentic IST-622, A-132, and A-132M were 12.1, 11.3, and 8.4 min, respectively. No peak was detectable at

Table 5. Comparison of the antitumor effect of IST-622 and A-132 against mouse tumors

Dose (mg/kg)	Antitumor effect (%ILS)							
	P388		M5076		LL		Colon 38	
	IST	A-132	IST	A-132	IST	A-132	IST	A-132
640	Toxic	164	–	93	–	>200 (0)	–	(0)
320	197	145	146	82	Toxic	>200 (0)	(0)	(0)
240	197	148	145	84	>200 (0)	>200 (0)	(0)	(0.6)
160	141	130	113	71	>200 (0)	>200 (0)	(0)	(0.6)
80	115	120	84	84	>200 (0.3)	117 (3.5)	(2.6)	(2.0)
40	92	98	80	61	85 (7.7)	56 (15)	(19)	(57)
20	58	61	–	–	–	–	–	–
10	26	21	–	–	–	–	–	–

P388 and M5076 cells were implanted i.p., and LL and Colon 38 cells were implanted s.c. Beginning on day 1, IST-622 or A-132 was given p.o. five times (three times only for P388) every 4 days. IST, IST-622.

Numbers in parentheses are T/C% values based on the tumor volume determined on day 23 (Colon 38) or 24 (LL)

12.1 min in mouse plasma (Fig. 4B). The time courses of plasma concentrations of A-132 and A-132M observed after oral administration of IST-622 are demonstrated in Fig. 5. At 1 h the level of A-132 was 2.4-fold that of A-132M, and subsequent plasma levels of both metabolites remained almost the same until 24 h.

AUCs of A-132 and A-132M in mouse plasma after oral administration of IST-622 and A-132

Figure 6 shows the plasma total AUCs of the metabolites A-132 and A-132M as determined at each dose. IST-622 gave 3- to 4-fold higher AUCs than did A-132 at any dose. Furthermore, the AUCs for IST-622 increased with the dose up to 1,000 mg/kg, whereas those for A-132 approached a plateau even at 333 mg/kg. The A-132 ratios were 50%–60% of the total AUC (data not shown).

Discussion

IST-622, a synthetic derivative of CT, showed marked antitumor activity against a broad spectrum of mouse tumor lines in vivo following oral administration. Studies on the schedule dependency of IST-622 revealed that five intermittent treatments given every 4 days resulted in the best antitumor effects. Furthermore, the drug showed significant antitumor effects on P388 leukemia and B16 melanoma even when the start of treatment was delayed for 5 and 7 days, respectively. IST-622 was also significantly effective against two human tumor xenograft lines, Lu-116 and St-4, among the seven lines tested. This effect was comparable with that of Adriamycin simultaneously given i.v. in the same experiment.

CT was reported at the first antitumor compound of this type of structure [2], but it was not selected as a candidate for clinical study because of its undesirable pharmacokinetics. Another antibiotic, elsamitrucin, is closely related to CT in structure. Only a small modification involving the replacement of a hydroxyl group of a sugar with an amino group greatly enhanced its antitumor activity against both solid and hematological tumor models [4]. Elsamitrucin is currently under clinical study [3].

In the in vitro experiment using P388 leukemia, IST-622 and its metabolites were over 20-fold more active than CT, whose IC_{50} as determined after a 48-h exposure was almost the same as that determined for IST-622 after a 1-h exposure. The IC_{50} value found for IST-622 after a 48-h treatment was approximately 40-fold lower than that observed after a 1-h treatment, which would mean that the cytotoxicity of this drug might be regulated with the product of the concentration of the drug and the exposure time. In in vivo experiments, intermittent treatments gave the best therapeutic results as compared with single or consecutive treatments, although IST-622 was effective on any treatment schedule, possibly due to differences in its toxic effects on host tissues.

IST-622 was so rapidly deacylated in plasma, resulting in A-132, that 30 min after oral administration, only A-132 and A-132M, a further demethylated metabolite, could be detected (Figs. 4, 5). We consider that IST-622 is a prodrug of the active metabolites A-132 and A-132M. Similarly, rapid deacylation of IST-622 would occur in the culture medium, and the growth-inhibitory curves generated for IST-622 and A-132 against P388 cells in vitro were similar even after a 1-h exposure to the drugs. No CT was detectable in the plasma throughout the experiment, suggesting that IST-622 is not a prodrug of CT and that the 3′,4′-*O*-exo-benzylidene group would be quite important for the superior antitumor activity of IST-622.

Although IST-622 was rapidly metabolized into A-132 in mouse plasma, higher doses of IST-622 had antitumor effects greater than those of A-132, as is shown in Table 5. The absorption of A-132 through the gastrointestinal tract might have been 3- to 4-fold lower than that of IST-622 at an equal dose and was saturated at a lower dose than that of IST-622 (Fig. 6), resulting in a saturation of %ILS value at higher doses. Therefore, IST-622 was selected as a candidate for clinical study.

In conclusion, in spite of its weak water solubility, following oral administration, IST-622 showed marked antitumor activity against a wide spectrum of murine hematologic and solid tumors as well as human tumor xenografts. Although IST-622 was not metabolized into CT, its antitumor mechanism would be similar to that of CT, mainly involving topoisomerase II inhibition, which will be reported separately. The phase I study of IST-622 has been started in Japan.

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