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In vivo Anti-tumor Activity of a Novel Indolocarbazole Compound, J-107088, on Murine and Human Tumors Transplanted into Mice

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J-107088 (6-*N*-(1-hydroxymethyl-2-hydroxy)ethylamino-12,13-dihydro-2,10-dihydroxy-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]-pyrrolo [3,4-*c*]carbazole-5,7(6*H*)-dione) is a derivative of NB-506, an indolocarbazole compound previously reported as an anti-tumor agent targeting topoisomerase I. The optimal administration schedule of J-107088 was found to be intermittent injections. The GID_{75} (75% growth inhibiting total dose) values of J-107088 against LX-1 lung cancer and PC-3 prostate cancer when given by intermittent injection (twice a week for 2 consecutive weeks) were 200 and 15 mg/m^2, respectively, whereas the 10% lethal dose (LD_{10}) values of J-107088 against LX-1- and PC-3-bearing mice were 578 and 1200 mg/m^2. The ratio of LD_{10}/GID_{75} indicates the therapeutic window of an anti-tumor agent. Although the ratios of doxorubicin, paclitaxel and cisplatin against PC-3 were <0.3, <0.5 and <0.2, J-107088 showed the widest therapeutic window among the anti-tumor drugs tested. J-107088 was also effective on cells that had acquired resistance related to P-glycoprotein. Furthermore, J-107088 was found to be highly effective in inhibiting proliferation of micro-metastases of tumors to the liver in mice. Therefore, J-107088 is considered to be a promising candidate as an anti-tumor drug for treatment of solid tumors in humans.

Key words: Anti-tumor — J-107088 — Indolocarbazole — Toxicity — Metastasis

The indolocarbazole compound NB-506 (Fig. 1A) was previously reported as a new selective topoisomerase I inhibitor.[1, 2] NB-506 has strong anti-tumor effects and less cumulative toxicity than presently available anti-tumor drugs in terms of lethality. NB-506 was effective at doses of 90 to 300 mg/m^2/day for 10 consecutive days against the human colon tumor LS180 xenografted into nude mice, and at 30 to 300 mg/m^2/day for 10 consecutive days against xenografted human lung tumor PC-13. But although it shows good anti-tumor activity, its effective dosage is higher than those of other anti-tumor drugs.

Therefore, many derivatives of NB-506 have been synthesized in attempts to obtain more effective and less toxic compounds than NB-506. Of these derivatives of NB-506, J-107088 (6-*N*-(1-hydroxymethyl-2-hydroxy)ethylamino-12,13-dihydro-2,10-dihydroxy-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione) (Fig. 1B) was found to be the most potent inhibitor of topoisomerase I.[3]

This paper reports studies on the anti-tumor efficacy of J-107088 against various human xenografts and murine tumors, including a P-glycoprotein-mediated multi-drug-resistant tumor, and its lethal toxicity in mice. In addition, the anti-metastatic effect of J-107088 is described. Biochemical studies on J-107088 have been reported by Yoshinari *et al*.[3]

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MATERIALS AND METHODS

Mice Female CDF_1 mice were purchased from Charles River Japan (Kanagawa), and Balb/c *nu*/*nu* mice from Japan CLEA (Tokyo). All mice were 5 or 6 weeks old at the start of experiments.

Tumors Murine P388/ADM leukemia cells were provided by Dr. T. Tsuruo of the Institute of Molecular and Cellular Biosciences, University of Tokyo. Murine liver metastatic tumor cells, IMC-HM cells, were established in our institute.[4] Human lung tumor LX-1 cells were provided by Dr. K. Komiyama of Kitasato Institute, Tokyo. Human stomach tumor MKN-45 cells were purchased from Immuno Biological Laboratories (Gunma). Human bladder tumor UM-UC-3 cells, human cervix tumor HeLaS3 cells, human melanoma C32 cells and human prostate tumor PC-3 cells were purchased from the American Type Culture Collection (Rockville, MD). Human colon tumor LS180 cells were provided by Dr. H. Fukazawa of the National Institute of Health, Tokyo. Human breast tumor MX-1 cells were provided by Dr. T. Tashiro of the Japanese Foundation for Cancer Research, Tokyo.

In *in vivo* anti-tumor tests, mice received transplants of these cells propagated *in vivo*.

J-107088 and other chemicals J-107088 was synthesized

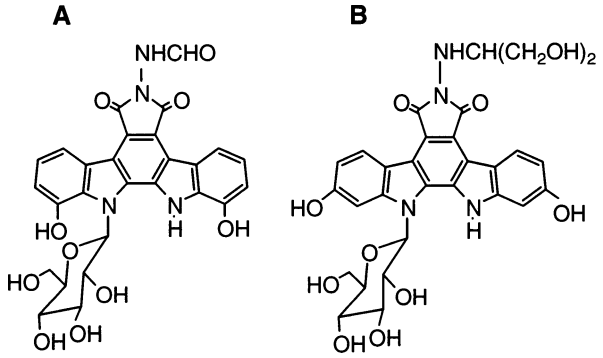

Fig. 1. Structures of indolocarbazole compounds.

in our institute by a procedure to be reported elsewhere. NB-506 was synthesized by a published method.[5] Doxorubicin was purchased from Kyowa Hakko Kogyo Co. (Tokyo), and etoposide and cisplatin from Nippon Kayaku Co. (Tokyo). Paclitaxel was purchased from Sigma Chemical Co. (St. Louis, MO).

***In vivo* anti-tumor evaluation** Growth-inhibitory effects on P388/ADM cells implanted into the peritoneal cavity of CDF_1 mice (control, n=10; test, n=5) at 1×10^6 cells/mouse on day 0 were evaluated by determination of survival days after tumor implantation. Effects on human tumors were examined by tumor regression assay as follows. A human tumor grown s.c. in nude mice was cut into 3 mm cubes and transplanted s.c. into the flank of mice. The i.v. injections of various concentrations of J-107088 were started when the tumor nodules reached 0.2 cm^3 or more according to the schedule for each experiment (control, n=12; test, n=6). The most frequently used administration schedule was injections twice a week for 2 consecutive weeks. In the case of NB-506, cisplatin, doxorubicin and paclitaxel were administered at their optimum schedules. Tumor volumes and body weights were recorded periodically. Tumor volumes were calculated according to the formula $(L\times W^2)/2$, where L is the length (longer diameter) and W is the width (shorter diameter) of the tumor.[6] In anti-metastatic assays, CDF_1 mice with a s.c. transplant of IMC-HM cells (5×10^4 cells/mouse) were treated with various doses of J-107088 from 4 days after the implantation. Anti-metastatic effects were evaluated by monitoring survival periods.

The doses of drugs are expressed in mg/m^2; a dose of 1 mg/kg approximately corresponds to that of 3 mg/m^2 in mice.[7] J-107088 and doxorubicin were dissolved in 5% glucose. Cisplatin and etoposide were diluted with 5% glucose when necessary. Paclitaxel dissolved in 50% ethanol-50% Cremophor EL was diluted 10-fold with saline.

Efficacy and lethality In human tumor xenograft experiments, values for GID_{75} (75% tumor growth inhibiting total dose) and LD_{10} (10% lethal dose in xenograft experiments) were calculated. Ratios of LD_{10} to GID_{75} were also calculated as an indicator of therapeutic windows.

Statistical analysis Statistical analysis by the Mann-

Table I. Anti-tumor Effects and Toxicities of J-107088 on Various Administration Schedules in Mice with a Human LX-1 Lung Tumor

Total dose (mg/m^2)	Treatment schedule					
	1/w×2		2/w×2		5/w×2	
	Anti-tumor (Inh.%)	BWC[a] (g)	Anti-tumor (Inh.%)	BWC (g)	Anti-tumor (Inh.%)	BWC (g)
0	0	+0.6	0	−0.4	0	−0.7
6.4	1	+0.3				
16			16	−0.3	23	−0.6
32	18	+1.2				
80			52*	−0.4	25	−0.8
160	80**	+0.7				
400			77**	−0.6	Toxic death	
800	70*	+1.7				
2000			89***	−1.1		

a) Body weight change in the period from day 26 to 39.
*, ** and ***: P<0.05, 0.01 and 0.001 by the U-test.
LX-1 cells were transplanted s.c. into nude mice on day 0. Tumor volumes were measured on day 43. J-107088 was injected i.v. according to the indicated schedules. 1/w×2 means once a week for 2 consecutive weeks (days 26 and 33). 2/w×2 means twice a week for 2 consecutive weeks (days 26, 29, 33 and 36), and 5/w×2 means five times a week for 2 consecutive weeks (days 26–30 and 33–37).

Whitney *U*-test was performed to compare each treatment group with the corresponding control group.

RESULTS

Treatment schedule-dependent anti-tumor effect of J-107088 *in vivo* J-107088 was injected i.v. into female nude mice with LX-1 human lung tumor once a week, twice a week or 5 times a week for 2 consecutive weeks to determine the appropriate administration schedule. As shown in Table I, injections once a week or twice a week significantly inhibited tumor growth, while consecutive injections caused toxic death at high doses and failed to inhibit tumor growth at sub-toxic doses.

The optimal administration schedule for J-107088 may vary with the tumor tested, depending upon the growth rate of the tumor and other factors, but the recommended administration schedule for J-107088 is probably once or twice a week because J-107088 is tightly bound to a DNA-protein complex in the cells.[3)]

Regressive effects on human solid tumor xenografts The anti-tumor effects of doxorubicin (5 times a week for 2 consecutive weeks), paclitaxel (5 times a week for 2 consecutive weeks) and cisplatin (twice a week for 2

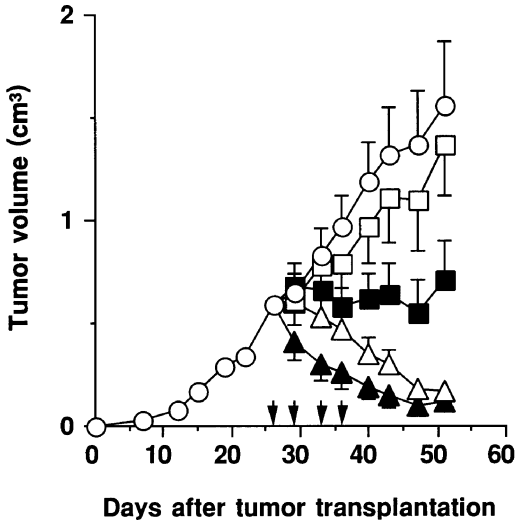

Fig. 2. Regressive effect of J-107088 on LX-1 human lung tumor in nude mice. LX-1 cells were transplanted s.c. into nude mice on day 0. J-107088 was administered i.v. twice a week for 2 consecutive weeks in the period shown by arrows in the figure. Control (○), J-107088 at 4 mg/m^2 (□), J-107088 at 20 mg/m^2 (■), J-107088 at 100 mg/m^2 (△), J-107088 at 500 mg/m^2 (▲). Bars, SE.

Table II. Comparison of Anti-tumor Activities of J-107088, Cisplatin, Doxorubicin and Paclitaxel in Mice with Xenografts of LX-1 Human Lung Tumor

Compound	Dose (mg/m^2/day)	Schedule	Tumor volume		Body weight change (g)[a)]
			cm^3±SE	Inh.%	
Control		2/w×2	1.32±0.23	0	−0.4
J-107088	4	2/w×2	1.11±0.22	16	−0.3
	20	2/w×2	0.64±0.15*	52	−0.4
	100	2/w×2	0.30±0.07**	77	−0.6
	500	2/w×2	0.15±0.06***	89	−1.1
Cisplatin	1.2	2/w×2	1.16±0.10	11	−1.2
	6	2/w×2	0.75±0.16*	43	−3.0
	30	2/w×2	Toxic death		—
Control		5/w×2	1.34±0.31	0	−0.7
Doxorubicin	1.2	5/w×2	1.02±0.20	24	−1.0
	6	5/w×2	1.17±0.29	13	−1.1
	30	5/w×2	Toxic death		—
Control		5/w×2	1.38±0.13	0	+0.3
Paclitaxel	5	5/w×2	1.26±0.34	9	−1.7
	15	5/w×2	1.50±0.12	−9	−1.1
	45	5/w×2	0.71±0.16**	49	−3.4

a) Body weight change in the period from day 26 to 39.
*, ** and ***: $P<0.05$, 0.01 and 0.001 by the *U*-test.
LX-1 cells were transplanted s.c. into nude mice on day 0. Tumor volumes were measured on day 43. J-107088 was injected i.v. according to the indicated schedules. 1/w×2 means injections on days 26 and 33. 2/w×2 means injections on days 26, 29, 33 and 36. 5/w×2 means injections on days 26–30 and 33–37.

Table III. Growth-inhibitory Effects of Various Anti-tumor Drugs on PC-3 Human Prostate Tumor in Nude Mice

Compound	Dose (mg/m^2/day)	Schedule	Tumor volume		Body weight change (g)[a)]
			cm^3±SE	Inh.%	
Control		2/w×2	2.40±0.36	0	−0.6
J-107088	0.8	2/w×2	1.89±0.35	21	−0.6
	4	2/w×2	0.54±0.24**	78	−1.3
	20	2/w×2	0.31±0.08***	87	−1.6
	100	2/w×2	0.30±0.08***	88	−1.5
	500	2/w×2	0.16±0.07**	93	−2.9
NB-506	30	5/w×2	0.96±0.31*	60	−1.1
	90	5/w×2	0.23±0.08***	90	−1.7
	300	5/w×2	0.16±0.06**	93	−4.4
Paclitaxel	15	5/w×2	1.22±0.40	49	−2.3
	45	5/w×2	0.70±0.23*	71	−4.0
Doxorubicin	1.2	5/w×2	2.21±0.48	8	−1.3
	6	5/w×2	2.71±0.70	−13	−2.1
Cisplatin	1.2	2/w×2	2.93±1.04	−22	−1.5
	6	2/w×2	1.46±0.60	39	−3.6

*, ** and ***: $P<0.05$, 0.01 and 0.001 by the *U*-test.
PC-3 cells were transplanted s.c. on day 0. Tumor volumes were measured on day 73. Body weight change from day 48 to 60 is shown.

Table IV. Comparison of Therapeutic Windows of J-107088, NB-506, Paclitaxel, Doxorubicin and Cisplatin in Mice with Xenografts of PC-3 Human Prostate Tumor

Compound	(mg/m^2, total dose)		Ratio (LD_{10}/GID_{75})
	LD_{10} [a)]	GID_{75} [b)]	
J-107088	578	15	38.5
NB-506	641	505	1.3
Paclitaxel	<150	>450	<0.3
Doxorubicin	32	>60	<0.5
Cisplatin	<4.8	>24	<0.2

a) LD_{10}: 10% killing dose on the treatment schedule.
b) GID_{75}: 75% growth inhibiting dose.

consecutive weeks) on an LX-1 xenograft model were compared with that of J-107088. Treatments were started when the tumor reached 0.59 cm^3 (day 26). J-107088 suppressed tumor growth at 20 mg/m^2/day and caused regression of tumors at 100 mg/m^2/day or more (Fig. 2). Cisplatin and paclitaxel also suppressed tumor growth, but did not cause tumor regression at their maximal tolerated doses (Table II).

The anti-tumor activity of J-107088 against PC-3 human prostate tumor cell xenografts in male nude mice was also investigated (Table III). The efficacy of J-107088 was compared with those of NB-506, paclitaxel, doxorubicin and cisplatin. The effective dose range of J-107088 was 4 to 500 mg/m^2/day. NB-506 also significantly inhibited the growth of PC-3 at 30 to 300 mg/m^2/day. Paclitaxel inhibited the growth of prostate tumor only at 45 mg/m^2/day. Its effective dose range was narrower than that of J-107088 (Table III). Doxorubicin and cisplatin did not inhibit the growth of prostate tumor PC-3 at their maximum tolerated doses of 6 mg/m^2/day. Therefore, the effective dose range and efficacy of J-107088 against the PC-3 human prostate tumor were superior to those of NB-506, paclitaxel, doxorubicin and cisplatin.

Therapeutic windows of J-107088 on various tumor cells *in vivo* To evaluate efficacy and toxicity, we calculated the GID_{75} and LD_{10} values. The GID_{75} value was defined as the dose that reduced the volume of solid tumors by 75% relative to that of control tumors. The LD_{10} value indicates the dose that killed 10% of the mice on the treatment schedule. The LD_{10} to GID_{75} ratio is a measure of the therapeutic window of a drug. If the ratio is less than 1.0, a drug cannot inhibit the growth of a solid tumor without causing severe toxicity. We thought that GID_{75} represents a sufficient dose for growth-inhibiting activity against solid tumors. On the other hand, LD_{10} on the treatment schedule is a good parameter for evaluating the toxicity of the tested compounds. Therefore, the LD_{10}/GID_{75} ratio represents the therapeutic window of a test compound.

The therapeutic window of J-107088 against PC-3 prostate cancer was 38.5, while those of NB-506, paclitaxel, doxorubicin and cisplatin were 1.3, less than 0.3, less than 0.5 and less than 0.2, respectively (Table IV and Fig. 3).

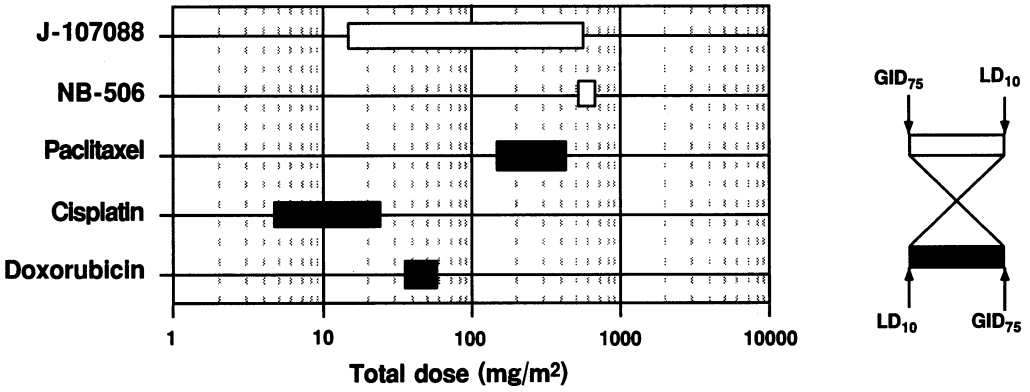

Fig. 3. Comparison of therapeutic windows in mice with xenografts of PC-3 human prostate cancer. Right and left edges of the open column indicate the LD_{10} and GID_{75}, respectively. The right and left edges of the closed column indicate the GID_{75} and LD_{10}, respectively. GID_{75}: dose that inhibited tumor growth by 75%. LD_{10}: dose on the treatment schedule that killed 10% of tumor-bearing mice. J-107088 and cisplatin were administered i.v. twice a week for 2 consecutive weeks and NB-506, paclitaxel and doxorubicin were administered i.v. 5 times a week for 2 consecutive weeks.

The therapeutic windows of J-107088 against various other tumor cells were also investigated. The ranges of therapeutic windows of J-107088 were 6 to 103, depending on the type of tumor (Fig. 4). J-107088 consistently showed a much wider therapeutic window than NB-506. The therapeutic window of J-107088 was more than 100 with UM-UC-3. This enormous safety margin has not been observed previously with other anti-tumor agents. These results show that J-107088 has much wider safety margins than other agents against various human tumors grown in mice.

Anti-tumor effect on multi drug-resistant leukemia The anti-tumor effects of J-107088 on the murine P388 multi drug-resistant leukemia cell line P388/ADM and the drug-sensitive line P388 were examined. It was expected that J-107088 would be highly effective against both drug-sensitive and drug-resistant leukemia cells, because there was no cross-resistance to J-107088 in multi drug-resistant MCF-7 AdrR cells *in vitro*.[3] As shown in Table V, doxorubicin, which is highly effective against P388 leukemia, was not effective against the resistant cells P388/ADM, even at a nearly toxic level. Paclitaxel was also found to be ineffective against the drug-resistant cells. Cisplatin was effective at a dose of 3 mg/m^2, but killed 3 of 5 mice at this dose due to its delayed-type toxicity. On the other hand, J-107088 at doses of 1 to 100 mg/m^2 overcame the multi drug-resistance and increased the survival time of mice implanted with the resistant cells. Therefore, it was concluded that J-107088 is effective on multi drug-resistant cells *in vivo*.

Anti-metastatic effect of J-107088 We also examined the anti-metastatic effect of J-107088 on IMC-HM liver metastases.[4] IMC-HM murine carcinoma cells metastasize to the liver within 3 days after their implantation into the flank of CDF_1 mice, and the tumor cells proliferate very rapidly in the liver and kill all mice by day 18 due to metastases to multiple organs. J-107088 was administered i.v. twice a week for 2 consecutive weeks from day 4 after tumor implantation, either with or without resection of the primary tumor. As shown in Table VI, J-107088 markedly

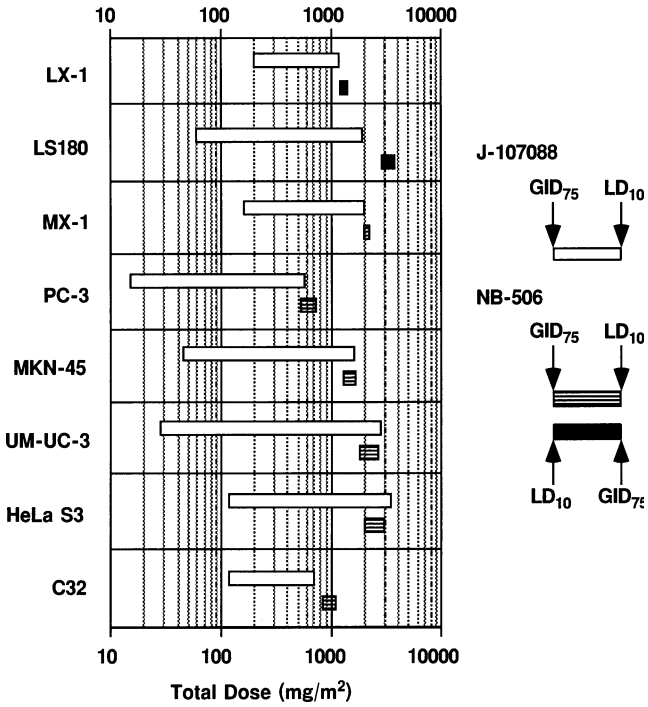

Fig. 4. Therapeutic windows of J-107088 and NB-506 against various tumor cell lines.

inhibited proliferation of micro-metastases in the liver. A synergistic effect of J-107088 and surgical resection of transplanted tumors was observed at doses of 2.25 and 7.5 mg/m^2. A dose of 22.5 mg/m^2 or 75 mg/m^2 of J-107088 had a dramatic anti-tumor effect on both primary tumors and micrometastases. Administration of 75 mg/m^2 of J-107088 resulted in survival of all the mice even 90 days after tumor transplantation. Thus J-107088 markedly inhibited proliferation of micrometastases of tumor cells in the liver and other organs.

Table V. Life-span-prolonging Effects of J-107088 in Mice with Implanted Doxorubicin-resistant P388 (P388/ADM) Murine Leukemia Cells

Compound	Dose (mg/m^2)	Survival days		Survivors[a)] (day 60)
		Mean±SD	T/C%	
Control		12.2±0.8	100	0/10
J-107088	0.1×10	16.8±1.3**	138	0/5
	1×10	21.2±2.2**	174	0/5
	10×10	25.8±6.5**	211	0/5
	100×10	>60.0±0.0**	>492	5/5
	1000×10	3.2±0.4**	26	0/5
Doxorubicin	5×10	12.2±0.4	100	0/5
	50×10	6.8±0.4**	56	0/5
Cisplatin	3×10	>51.2±8.7**	>420	2/5
	30×10	4.8±0.4**	39	0/5
Control		11.7±0.8	100	0/10
Paclitaxel	5×10	11.8±0.4	101	0/5
	50×10	13.2±1.3*	113	0/5

a) No. of mice surviving on day 60/No. after implantation of P388/ADM cells (1×10^6 cells/mouse) i.p. on day 0.
* and **: $P<0.05$ and 0.01 by the *U*-test.
Drugs were injected i.p. once daily for 10 consecutive days from day 1.

DISCUSSION

Currently available anti-tumor agents are in general not very effective for treatment of solid tumors, and show adverse effects at doses near their maximum therapeutic doses. Furthermore, anti-tumor agents used in first chemotherapeutic treatments are no longer effective subsequently, because of the rapid development of drug resistance. Thus, more effective anti-tumor drugs are required for treatment of solid tumors.

We previously developed the anti-tumor agents BE-13793C,[8] ED-110[9, 10] and NB-506.[1, 2] NB-506 is an indolocarbazole compound targeting topoisomerase I. During a phase I clinical trial on NB-506, we obtained a more potent agent than NB-506 by synthesizing and testing several hundred of its derivatives.

The new drug, J-107088 has several advantages over NB-506 or camptothecin derivatives. First, J-107088 induced topoisomerase I-mediated DNA cleavage 8-fold more potently than did camptothecin or NB-506. In addition, J-107088 increased the formation of DNA-protein complex in cells in a time-dependent manner and when J-107088 was removed from the medium, the amount of protein-linked DNA decreased very slowly. In contrast, the amount of DNA-protein complex increased rapidly with the addition of camptothecin and decreased very rapidly following its withdrawal.[3] Thus, the DNA-protein complex induced by J-107088 persisted for a much longer period of time after washing of the cells in fresh culture medium than did that formed in the presence of NB-506 or camptothecin. The much better *in vivo* anti-tumor efficacy

Table VI. Life-span-prolonging Effect of J-107088 with and without Resection of the Primary Solid IMC-HM Tumor

Drug (mg/m^2×day)	Mean survival days±SD (T/C%) [S/A[a)]]			
	Without resection		With resection	
Control				
	17.6±1.4	(100) [0/10]	18.2±1.9	(100) [0/10]
J-107088				
0.75×4	18.8±1.9	(107) [0/5]	20.8±3.1	(114) [0/5]
2.25×4	22.4±1.1**	(127) [0/5]	>42.0±29.0**	(>231) [1/5]
7.5×4	58.8±7.6**	(334) [0/5]	>77.8±16.7**	(>427) [3/5]
22.5×4	>69.6±18.7**	(>395) [2/5]	>68.8±13.1**	(>378) [1/5]
75×4	>90.0±0.0**	(>511) [5/5]	>90.0±0.0**	(>495) [5/5]

a) No. of mice surviving on day 90 / No. of mice tested.
**: $P<0.01$ by the *U*-test.
Surgery was performed on day 3 and the drug was administered i.v. twice a week for 2 consecutive weeks from day 4.

of J-107088 against nude mice transplanted with various human cancer cells may be attributed to these unique biological properties.

Another important attribute related to the efficacy and safety of J-107088 is that it is more effective when injected intermittently, e.g. once or twice a week for two weeks. Intermittent injections of J-107088 had sufficient therapeutic effects, while daily injections at higher doses caused weight loss and death due to toxicity. This type of toxicity was different from that of NB-506, which shows low cumulative toxicity and has a good therapeutic effect on consecutive injections.

Because of its lower toxicity and stronger anti-tumor activity, the therapeutic windows of J-107088 on several human tumor xenografted models were found to be wide. The therapeutic window, defined as the ratio of the LD_{10} on the treatment schedule to the 75% tumor growth inhibitory dose (GID_{75}), was 6 or more. That of UM-UC-3 was more than 100. We compared the *in vivo* anti-tumor efficacy of J-107088 with those of some other anti-tumor drugs in current use. While the therapeutic window of NB-506 was 1.3, those of paclitaxel, cisplatin and doxorubicin were less than 1.0 in most experiments, indicating the superiority of J-107088.

The difference between the safety margins of NB-506 and J-107088 may be related to their structures. The shift of OH groups of NB-506 from the 1, 11 to the 2, 10 positions considerably increased the potency of topoisomerase I inhibition and cytotoxicity (Ohkubo *et al.*, manuscript in preparation). The change of the substituent at the 6-*N* position of NB-506 from a formylamino moiety to a diol moiety also increased topoisomerase I inhibition, DNA binding and cytotoxicity.[11, 12] However, toxicity to mice was almost the same in spite of the shift of the OH groups and the 6-*N* substituent. Thus, the increase in the safety margin of J-107088 is due to the increase in the potency.

J-107088 did not show any cross resistance to multi drug-resistant P388/ADM *in vivo*. It prolonged the life of mice implanted with multi-drug-resistant P388 cells, whereas doxorubicin and paclitaxel were ineffective in this model. Thus, J-107088 may inhibit the tumor growth of P-glycoprotein-mediated multi-drug-resistant cells in the clinical situation.

J-107088 was also found to be more effective against tumor metastases in the liver and other organs of mice. NB-506 completely inhibited the growth of primary solid IMC-HM tumors at 300 mg/m^2 or more, and also inhibited the growth of micro-metastases of tumor cells in the liver at 30 mg/m^2.[4] The inhibitory potency of J-107088 was greater than that of NB-506. When treatment was started 4 days after tumor implantation, it inhibited the growth of IMC-HM cells in the liver, resulting in an increase in the life span of tumor-bearing mice. These data suggested that J-107088 was effective against not only growth of the primary tumor, but also metastases. Moreover, doses of 75 mg/m^2 of J-107088 caused survival of all the mice. In this model of micro-metastasis, cisplatin, doxorubicin and paclitaxel did not show any anti-metastatic effect, even at their maximum tolerated doses.[4]

Judging from these data, J-107088 should be a very good anti-tumor agent, with a wide therapeutic window and activity against various solid tumors. It may also be useful as an anti-metastatic agent for adjuvant chemotherapy after surgery.

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