Optimal Treatment Schedule and Antitumor Spectrum of 4-Carbamoylimidazolium 5-Olate (SM-108) in Murine Tumors

Noboru Yoshida,1 Makoto Nakamura, Masaru Fukui, Shinya Morisada, Shigeo Ogino, Makoto Inaba, Shigeru Tsukagoshi, and Yoshio Sakurai

ABSTRACT

By designing optimal administration schedules, it was found that 4-carbamoylimidazolium 5-olate (SM-108) showed an excellent antitumor potency against a number of murine tumors.

The optimal administration schedule of SM-108 was an intermittent multiple administration, in which the drug was multiply administered to mice at definite intervals of less than 3 hr for about 1 day on Days 1, 5, and 9 following tumor implantation. Although usual daily administration of SM-108 exhibited poor efficacy, the intermittent multiple administration of SM-108 exhibited potent antitumor activity against a wide variety of tumors, such as Ehrlich carcinoma, P388, 6-mercaptopurine-sensitive and -resistant L1210, Lewis lung carcinoma, Colon 26 adenocarcinoma, and Sarcoma 180. Among them, Ehrlich carcinoma showed the most prominent susceptibility to SM-108. With the intermittent multiple administration of SM-108, complete suppression was obtained in both the ascitic and solid forms of this tumor over a wide dose range.

The schedule dependency of the antitumor effect of SM-108 described above was reasonably explained by its in vitro growth-inhibitory effects and pharmacokinetics in the mice.

INTRODUCTION

SM-1082 (Chart 1) is the aglycone of a nucleoside antibiotic, bredinin (4). Sakaguchi et al. (5) showed that SM-108 as well as bredinin inhibited the growth of L5178Y cells in vitro, but Sakurai et al. (6) reported that this aglycone had little or no activity against P388 murine leukemia in vivo when tested according to an intermittent schedule on Days 1 and 5.

In a previous paper (8), we reported that new derivatives of SM-108, SL-1233 and SL-1250, showed potent antitumor activities against many experimental tumors. Subsequent investigations revealed that these agents exerted their antitumor effects by their conversion to SM-108 in mice. SM-108 was further phosphoribosylated to its nucleotide form by adenosine phosphoribosyltransferase (EC 2.4.2.7) in the tumor cells, and this nucleotide inhibited IMP dehydrogenase (EC 1.2.1.14), the key enzyme of GMP de novo biosynthesis (1).

With these results, it was supposed that SM-108 itself would show antitumor effects equal to those of SL-1233 and SL-1250 if its optimal administration schedules were designed. Therefore, we investigated the administration schedule of SM-108 for exerting potent antitumor effects on various tumors and present the results in this paper.

MATERIALS AND METHODS

Chemicals. SM-108 was prepared in our laboratories by the modified method of Schipper and Day (7). 6-MP and 5-FU were obtained from Kojin Co., Ltd. (Tokyo, Japan), and Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan), respectively. The solubility of SM-108 in water is 4.7 mg/ml. The arginine preparation of SM-108, which contained 100 mg of SM-108, 200 mg of L-arginine, and 5 mg of NaHCO3 in one vial, was used for in vivo experiments. This preparation was dissolved with 0.85% NaCl solution to appropriate concentrations. For in vitro culture, SM-108 was dissolved with 0.85% NaCl solution and diluted with culture medium.

6-MP was suspended in 0.85% NaCl solution containing 1% (w/v) Tween 80. 5-FU was diluted with 0.85% NaCl solution. These drugs were administered to tumor-bearing mice at the volume of 0.1 ml/10 g body weight. Newborn calf serum, Hanks’ balanced buffer solution, 2-mercaptoethanol, and RPMI 1640 were purchased from Dainihon Pharmaceuticals Co., Ltd. (Osaka, Japan), Nakarai Chemicals Co., Ltd. (Kyoto, Japan), and Nissan Pharmaceuticals Co., Ltd. (Tokyo, Japan), respectively.

Animals and Tumors. Male ICR/Jcl mice were purchased from Shizuoka Experimental Animals Corp. (Hamamatsu, Japan). C57BL/6, BALB/c, BALB/c x DBA/2 F1 (hereafter called CD2F1) and C57BL/6 x DBA/2F1 (hereafter called B6D2F1) mice were obtained from Charles River Japan, Inc. (Kanagawa, Japan). Sarcoma 180 and Ehrlich carcinoma were maintained by weekly i.p. passage in ICR/Jcl mice. Lewis lung carcinoma, Colon 38 adenocarcinoma, and Colon 26 adenocarcinoma were carried i.m. in C57BL/6 mice, s.c. in C57BL/6 mice, and s.c. in BALB/c mice, respectively. L1210, P388, and L1210/6-MP were maintained by serial i.p. passage in DBA/2 mice. L1210/6-MP was kindly supplied by Dr. T. Kataoka, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research. Evaluation of Antitumor Activity. Standardized protocols of the Drug Research and Development Program, National Cancer Institute (2), were followed for the chemotherapy experiments. L1210 and L1210/6-MP leukemia, P388 leukemia, Lewis lung carcinoma, and Colon 26 adenocarcinoma were implanted i.p. in CD2F1 mice at 106 cells/mouse, i.p. in CD2F1 mice at 105 cells/mouse, s.c. in B6D2F1 mice at 2 x 106 cells/mouse, and i.p. in CD2F1 mice at 3 x 106 cells/mouse, respectively. With Colon 38 adenocarcinoma, fragments of nonneocritic tissue were implanted s.c. in B6D2F1 mice, using a trocar. Sarcoma 180 and Ehrlich carcinoma were implanted i.m. in ICR/Jcl mice at 106 and 3 x 106 cells/mouse, respectively. Both were implanted i.p. in ICR/Jcl mice at 106 cells/mouse. Each experimental group was composed of 6 or more mice.

The growth inhibition of i.m. implanted Ehrlich carcinoma and Sarcoma 180 was determined by weighing the tumor masses removed from the mice at 15 and 13 days after tumor implantation, respectively. The growth of s.c. implanted Lewis lung carcinoma and Colon 38 adenocarcinoma was monitored by the measurement of perpendicular diameters with vernier calipers. Tumor weight in mg was estimated by the formula for the volume of a prolate ellipsoid, assuming unit density: 4/3 x major diameter (mm) x minor diameter (sq mm). All mice used for chemotherapy...
experiments were kept in a specific-pathogen-free condition and were
given water and pelleted food ad libitum.

Osmotic Minipump. The Alzet osmotic minipump (No. 2101; 1-week
type) was purchased from Alza Pharmaceuticals Co. This pump was
surgically buried in the intraperitoneal cavity of the mouse on the day
following the tumor implantation. One µl of drug solution per hr was
osmotically and continuously exuded for 170 hr.

Multiple Administration. In this paper, the administration schedule in
which the drug is administered multiply at definite intervals for a certain
period, e.g., every hr for 36 hr or every 2 hr for 24 hr, is called multiple
administration.

In Vitro Growth Inhibition Assay. Ehrlich carcinoma cells were incu-
bated with SM-108 in RPMI 1640 supplemented with 10% newborn calf
serum, penicillin (100 units/ml), streptomycin (100 µg/ml), and 4 µM 2-
mercaptoethanol at 37° in a humidified atmosphere of 5% CO2 for various
periods. After incubation, the cells were harvested by centrifugation and
washed twice with phosphate-buffered saline (a solution containing 8.0
g of NaCl, 0.2 g of KCl, 2.9 g of NaH2PO4·12H2O, and 0.2 g of KH2PO4
in 1 liter of distilled water). Then the cells were resuspended in the fresh
RPMI 1640 and recultured in the above condition for 48 hr. The cell
number was counted with a Coulter Counter (Model ZBI; Coulter Elec-
tronics, Inc., Hialeah, Fla.), and the growth rate was calculated according
to the formula

\[
\text{Growth rate} \, (\%) = \frac{T - C_0}{C} \times 100
\]

where T is the cell count after culture (test group), C is the control cell
count after culture, and C0 is the cell count at the start of culture. Control
cells were treated similarly after incubation without any drug for various
periods.

Measurement of Total Number of Femoral Bone Marrow Cells. For
the toxicity test, the specified drugs were given on Day 0 to each group
of ICR/Jcl male mice, and the animals were sacrificed by cervical dislo-
cation at definite intervals. The femurs were removed rapidly, and any
adherent tissues were wiped away. Bone marrow cells were flushed out
with 2 ml of chilled Hanks' buffer solution by injection of the buffer at
one end of the bone. The bone marrow cell suspension was diluted 100-
fold with 0.85% NaCl solution, and the cell number of this suspension
was counted with a Coulter Counter. The relative number of bone marrow
cells of the treated groups to that of the control groups was calculated.

RESULTS

Effects of SM-108 on Tumor Cell Growth In Vitro. To char-
acterize the cytotoxic effects of SM-108 on tumor cells, the
growth ability of tumor cells after exposure to SM-108 was
examined. As shown in Chart 2, the growth rates decreased
with the prolongation of the exposure time, whereas they were
unchanged at various concentrations of the drug. Thus, the
effects of SM-108 on tumor cell growth were dependent on the
exposure time rather than on drug concentration. At least 1 day
of exposure to SM-108 was necessary for sufficient reduction of
tumor cell growth.

Schedule Dependency of in Vivo Antitumor Effects of
SM-108. The results of the schedule dependency of the in vivo
antitumor activity of SM-108 are shown in Table 1. The treatment
at intervals of less than 3 hr brought about a marked prolongation
of life and produced many tumor-free mice over a wide dose

![Chart 1. Chemical structure of SM-108.](image)

![Table 1](image)

<table>
<thead>
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<th>Dose* (mg/kg/day)</th>
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<th>3q8hr</th>
<th>4q6hr</th>
<th>6q4hr</th>
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</table>

* Injection i.p.

* Control median survival time was 21.3 days.

* —, not tested.

* Numbers in parentheses, survivors on Day 90/total number in group.

![Chart 2. Effect of SM-108 on the growth of Ehrlich carcinoma cells. Ehrlich
carcinoma cells were incubated with SM-108 in the medium for each time indicated
at concentrations of 10^{-3} mm (B), 10^{-2} mm (•), 10^{-1} mm (B), and 1 mm (ß).
In the case of controls (D), Ehrlich carcinoma cells were incubated without SM-108 in the
medium. Then they were washed with phosphate-buffered saline twice and cultured
in the fresh medium for 2 days. Columns, means of triplicate cultures. Bars, S.E.
range of SM-108. On the contrary, the treatment at intervals of more than 6 hr showed slight effects even at high doses, and treatment at 4-hr intervals showed potent effects only at high doses. Thus, in vivo antitumor effects of SM-108 were markedly dependent on its administration schedule.

Effect of Multiple Administration of SM-108 on the Host. The MTDs of SM-108 on various administration schedules are shown in Table 2. The MTDs of SM-108 with single-dose, intermittent (Days 1, 5, and 9), and daily (Days 1 to 9) treatments were 2000, 480, and 100 mg/kg/day, respectively. With continuous administration using an osmotic minipump (1-week type), the MTD of SM-108 showed a particularly marked decrease, to 14 mg/kg/day. This shows that the MTD of SM-108 decreased as the interval of administration was shortened. The MTD on the schedule of every 2 hr for 24 hr on Days 1, 5, and 9, however, was almost the same as that of q4d (Days 1, 5, and 9), although on the former schedule SM-108 was given to mice at very short intervals.

Chart 3 shows the change in bone marrow cell number and body weight with multiple administration. When an 80-mg/kg/injection of SM-108 was administered every 2 hr for 24 hr, the number of bone marrow cells decreased immediately after the end of the administration, but 4 days later it recovered to the level of the untreated mice. The mice recovered from the bone marrow toxicity caused by the i.p. multiple administration of SM-108 more rapidly than they did from that caused by the i.p. administration of 6-MP. The body weight also decreased just after multiple administration but began to increase again 2 days later and recovered to the level of the untreated mice at 8 days after administration. Thus, mice were able to recover rapidly from the toxicity caused by 24-hr multiple administration of SM-108 to the normal state in about 3 days. This was reflected in the very high MTD of SM-108 on the intermittent multiple administration schedule, every 2 hr for 24 hr on Days 1, 5, and 9 (Table 2).

Antitumor Spectrum of SM-108. The therapeutic effects of SM-108 with 2 treatments, i.e., intermittent multiple administration and daily treatment, were examined against various tumors.

Table 3 shows the therapeutic efficacy of SM-108 against i.p. implanted Sarcoma 180. While its daily administration increased the life span by only 23%, the schedule every 2 hr for 24 hr on Days 1, 5, and 9 resulted in an increased life span of more than 150% at a wide dose range of 2.5 to 80 mg/kg/injection. Moreover, with the treatment on the latter schedule, many long-term survivors were obtained on Day 60 at dose levels ranging from 5 to 80 mg/kg/injection. The effects of SM-108 against Sarcoma 180 exceeded those of 6-MP.

The prolongation of the duration and/or the shortening of the

### Table 2

<table>
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<tr>
<th>Schedule</th>
<th>MTD&lt;sup&gt;2&lt;/sup&gt; (mg/kg/day)</th>
</tr>
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<tr>
<td>Single dose</td>
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<td>q4d; Days 1-9</td>
<td>480</td>
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<tr>
<td>q1d; Days 1-9</td>
<td>100</td>
</tr>
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<td>osmotic minipump (1-wk type)</td>
<td>14.1</td>
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<tr>
<td>12q2hr; Days 1, 5, and 9</td>
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</table>

<sup>2</sup> Injection i.p.
day, inhibited tumor growth by only 34%. SM-108 was much more effective than 5-FU with respect to the potency of antitumor activity and the extent of effective dose range.

Chart 4 shows the therapeutic efficacy of SM-108 against s.c. implanted Lewis lung carcinoma, a syngeneic solid tumor. With an intermittent multiple administration, i.e., every 2 hr for 24 hr on Days 1, 5, and 9, a greater than 90% inhibition of tumor growth was observed over a wide dose range on Day 13, and there were nearly 10-day delays in tumor growth with a resultant 43 to 84% prolongation of survival time. However, tumor-free mice were not obtained. Multiple administrations of a vehicle corresponding to SM-108 (160 mg/kg) did not bring about any tumor growth inhibition or prolongation of life (data not shown).

The antitumor activities of SM-108 against the other tumors are summarized in Table 6. Intermittent multiple administration produced significant life-prolonging effects against Colon 26 adenocarcinoma and potent growth-inhibitory effects against solid-type tumors, such as Colon 38 adenocarcinoma and Sarcoma 180. With the intermittent multiple administration, L1210/6-MP showed more marked collateral sensitivity against SM-108 than previously reported (3).

DISCUSSION

The antitumor activity of SM-108 has been overlooked in spite of its early discovery. In the previous papers, we reported that 2 new derivatives of SM-108, SL-1233 and SL-1250, possessed potent antitumor activity (8) and that SL-1250 was converted to SM-108 to exert its antitumor activity (1). Although the effects of SM-108 against tumor cell growth in vitro were the same as those of SL-1250, SM-108 exhibited only slight efficacy in vivo with daily or intermittent treatment. The cytotoxicity of SM-108 in vitro is extremely dependent on the exposure time, and approximately 1 day of exposure is necessary for the striking effects observed in vivo. The results in vivo also showed that the cytotoxicity of SM-108 is extremely dependent on the exposure time, and approximately 1 day of exposure is necessary for the striking effects observed in vivo.

### Table 3

<table>
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<tr>
<th>Experiment</th>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Total dose (mg/kg)</th>
<th>Median</th>
<th>Range</th>
<th>% of increased life span</th>
<th>Survivors on Day 60/total no. in group</th>
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### Table 4

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<th>Drug</th>
<th>Schedule</th>
<th>Dose (mg/kg)</th>
<th>Survival time (days)</th>
<th>% of increased life span</th>
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### Table 5

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<th>Drug</th>
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A 160-mg/kg/injection dose of L-arginine and a 4-mg/kg/injection dose of NaHSO3.
exudation of SM-108 but failed to show potent antitumor activities against many tumors (data not shown). This may be due to extremely increased toxicity with osmotic minipump treatment (Table 2); these results suggest that prolonged continuous administration does not result in selective toxicity against tumor cells. The host toxicity accompanied by multiple administration, however, was clearly diminished by setting up certain days of interval between multiple administration (Table 2). Mice needed about 3 days to recover from the bone marrow toxicity and body weight loss after multiple administration of SM-108 for 24 hr (Chart 3).

Thus, from the results of the activity against the tumor cells and the toxic effects on the host, the optimal regimen for SM-108 was thought to be intermittent multiple administration, such as every 2 hr for 24 hr on Days 1, 5, and 9.

When intermittent multiple administration was compared with daily treatment, the former exhibited much stronger effects on the prolongation of life and on tumor growth inhibition (Tables 1 and 3 to 6; Chart 4). The wide effective dose range was another advantage of this optimal regimen. This may reflect the findings that 22-hr contact of SM-108 with tumor cells strongly inhibited in vitro tumor cell growth over a wide range of concentrations (Chart 2).

As mentioned above, by designing administration schedules, SM-108, which had been believed to be inactive in vivo, was found to show antitumor activities against various murine tumors.

The antitumor spectrum of SM-108 obtained with its optimal regimen was somewhat similar to that of SL-1250. Recently, Fukui et al.3 established the resistant sublines of Ehrlich carcinoma to SL-1250 and found definite cross-resistance of its SL-1250-resistant sublines to SM-108. These results as well as other data suggest that SL-1250 exerts its antitumor activity via SM-108 in the mouse body.

Ehrlich carcinoma was especially sensitive to SM-108 among the murine tumors tested (Tables 1 and 5). The collateral sensitivity of L1210/6-MP to SM-108, which was revealed by Inaba et al. (3), was shown more clearly with intermittent multiple administration (Table 6). Inaba et al. (3) reported that Ehrlich carcinoma lacks hypoxanthine-guanine phosphoribosyltransferase and is insensitive to 6-MP, similar to the response of L1210/6-MP. In Ehrlich carcinoma and L1210/6-MP cells, the quantity of GMP biosynthesized by hypoxanthine-guanine phosphoribosyltransferase may be so small that the effect of inhibition of de novo GMP synthesis by SM-108 is strengthened further. Thus, SM-108 is expected to exert strong antitumor effects against human tumor cells with a low activity of hypoxanthine-guanine phosphoribosyltransferase.

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