Phase I and Pharmacological Study of Weekly Administration of the Polyamine Synthesis Inhibitor SAM 486A (CGP 48 664) in Patients with Solid Tumors

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ABSTRACT

A single-agent dose-escalating Phase I and pharmacological study of the polyamine synthesis inhibitor SAM 486A was performed. A dosing regimen of four weekly infusions followed by 2 weeks off therapy was studied. Fifty patients were entered into the study. Dose levels studied were 1.25, 2.5, 5, 8, 16, 32, 48, 70, 110, 170, 270, and 325 mg/m^2/week. Pharmacokinetic sampling was done on day 1, and trough samples were taken weekly during the first treatment cycle. Pharmacodynamic sampling was done on days 1 and 22. At 325 mg/m^2/week, dose-limiting toxicity was seen (one patient each with grade 4 febrile neutropenia, grade 3 neurotoxicity, and grade 3 hypotension with syncope and T-wave inversions on electrocardiogram). The recommended dose for further testing was set at 270 mg/m^2/week. Infusion time was increased from 10 to 180 min due to facial paresthesias and flushing and somnolence. Drug exposure increased linearly with dose. Mean ± SD $t_{1/2}$ at 70–325 mg/m^2 doses was 61.4 ± 26.2 h, with a large volume of distribution at steady state. In peripheral blood leukocytes, a clear relationship between dose and inhibitory effect on *S*-adenosylmethionine decarboxylase or changes in intracellular polyamine pools was not recorded. SAM 486A can be administered safely using a dosing regimen of four weekly infusions followed by 2 weeks off therapy. The recommended dose for Phase II studies using this regimen is 270 mg/m^2/week.

INTRODUCTION

The polyamines spermine and spermidine are present in all mammalian cells, and although their exact mechanism of action remains to be elucidated, their presence is essential for maintenance of cell function, growth, and proliferation. Biosynthesis and active transport on the one hand and catabolism and efflux on the other maintain polyamine homeostasis. The biosynthesis of spermine and spermidine involves several enzymatic steps, of which those involving ornithine decarboxylase and SAMDC[2] are rate limiting (1). Polyamine synthesis is summarized in Fig. 1.

Increased intracellular concentrations of spermine and spermidine are noted in tumor cells, and aberrant polyamine metabolism is thought to play a role in carcinogenesis. Therefore, SAMDC has long been considered to be a rational target for anticancer agent development (1–5). In the 1980s, specific and potent inhibitors of SAMDC were developed (6). SAM 486A is a cyclic analogue of MGBG with an IC_{50} for SAMDC of 4.7 nM, being approximately 200-fold more active than the parent compound. It only impacts mitochondrial function at doses 100-fold higher than those required for cellular growth inhibition. Spermine and spermidine pools are almost totally depleted, whereas putrescine pools are increased. *In vitro* studies showed growth-inhibitory effects of SAM 486A on human melanoma, lung cancer, breast cancer, and human epidermoid carcinoma cell lines; the T24 human bladder carcinoma cell line; and the L1210 murine leukemia cell line (7–10). *In vivo* growth-inhibitory activity showed a similar spectrum (7, 9, 11, 12). Preclinical data have been obtained suggesting additive and/or synergistic activity of SAM 486A in combination with currently available cytostatic agents (13).

Toxicology studies in rats and dogs revealed acute cardiovascular and respiratory symptoms with hyperemia, tachycardia, cyanosis, and reduced body temperature and dyspnea, gasping, and deep respiration, respectively. After long-term treatment,

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[2] The abbreviations used are: SAMDC, *S*-adenosylmethionine decarboxylase; V_{ss}, volume of distribution at steady state; MGBG, methylglyoxal-*bis* (guanylhydrazone); LVEF, left ventricular ejection fraction; DLT, dose-limiting toxicity; CTC, Common Toxicity Criteria; AUC, area under the curve.

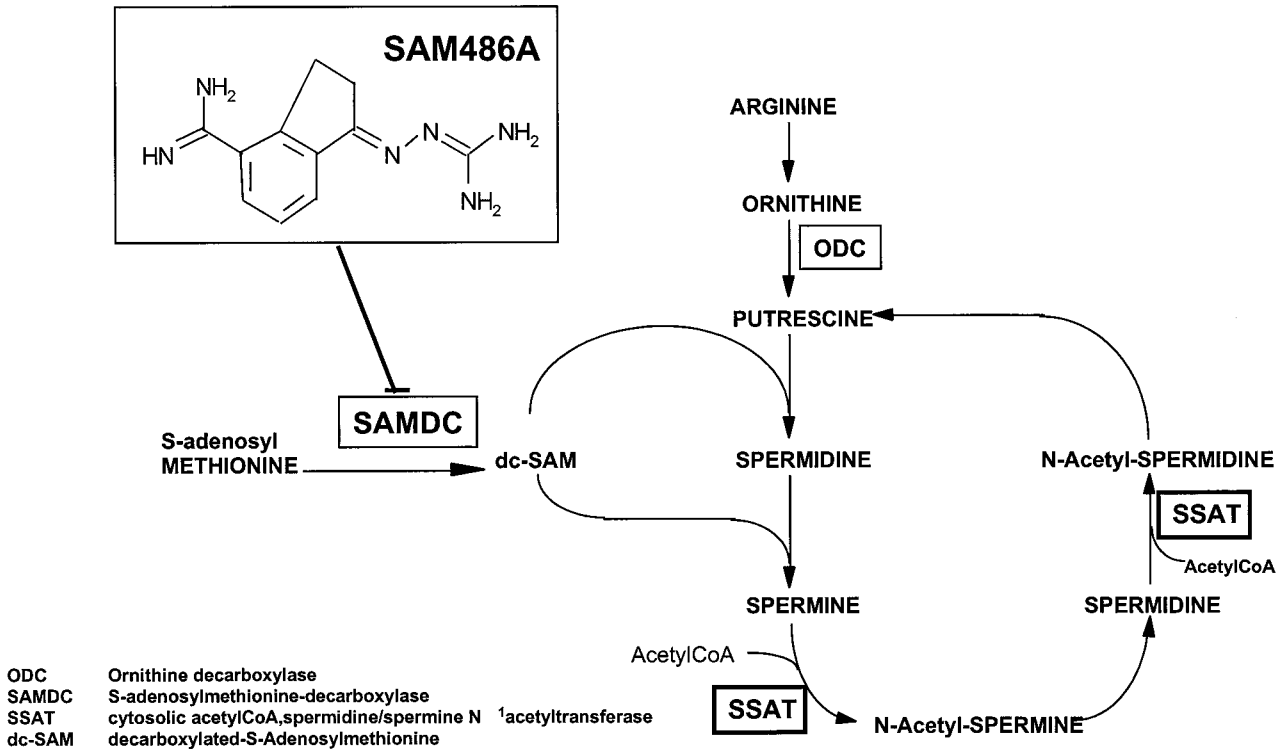

Fig. 1 Polyamine synthesis.

heterogeneous electrocardiogram alterations in dogs were observed together with morphological changes in liver and heart. Clearance of SAM 486A from plasma was multiexponential, with extensive distribution outside the plasma compartment and a high uptake into the liver and salivary glands. SAM 486A was hardly metabolized and was excreted predominantly through renal excretion.

We have performed a Phase I and pharmacological study with SAM 486A in patients with various advanced solid tumors, using a dosing regimen of four weekly infusions followed by 2 weeks off therapy. This schedule was chosen based on previous experiences with weekly administered MGBG showing a more favorable safety profile.

MATERIALS AND METHODS

Eligibility Criteria. Patients with a cytologically or histologically confirmed diagnosis of a solid tumor refractory to standard treatment or for whom no standard therapy was available were eligible for this study. Additional eligibility criteria included: (*a*) age $\geq$ 18 years; (*b*) WHO performance status $\leq$ 2; (*c*) life expectancy of $\geq$12 weeks; (*d*) no anticancer treatment in the previous 4 weeks (6 weeks for nitrosoureas, high-dose carboplatin/mitomycin C, or extensive radiotherapy); (*e*) adequate bone marrow function (WBC $\geq 4.10^9$/liter and platelets $\geq 100.10^9$/liter); (*f*) normal hepatic and renal functions (bilirubin $\leq$ 25 μmol/liter, aspartate aminotransferase and alanine aminotransferase within 2.5 times the normal upper limit, serum creatinine $\leq$ 120 μmol/liter, and normal age-adjusted creatinine clearance); and (*g*) a baseline LVEF within normal limits as measured by nuclear left ventricular ejection fraction determination scan or cardiac ultrasound. Exclusion criteria were pregnancy, active bacterial infections, fistulae, brain involvement and leptomeningeal disease, and a history of congestive heart failure or other cardiac disease with New York Heart Association classification 3 or 4. All patients gave written informed consent before the start of treatment. The study was approved by the local ethics committees.

Pretreatment and On-Treatment Assessments. Before therapy, a complete medical history was taken, and a physical examination was performed. A complete blood count including WBC differential and serum chemistries including sodium, potassium, calcium, phosphorus, creatinine, total protein, albumin, glucose, alkaline phosphatase, bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, and lactate dehydrogenase were performed, as were urinalysis, creatinine clearance assessment, electrocardiogram, chest X-ray, and LVEF assessment. Weekly evaluations included history, physical examination, toxicity assessment according to the National Cancer Institute CTC criteria (14), complete blood count, serum chemistries, urinalysis, and electrocardiogram. Tumor measurements were performed every 6 weeks and evaluated according to the WHO criteria for response (15). LVEF was reassessed by the same technique used before treatment every 6 weeks. In case of disease progression, patients were taken off study.

Drug and Drug Administration. SAM 486A is the free base of 4-(aminoiminomethyl)-2–3-dihydro-1H-inden-1-one-diaminomethylenehydrazone, and it is formulated as a salt with

D,L-lactic acid for i.v. administration. Novartis AG (Basel, Switzerland) supplied SAM 486A as a freeze-dried yellow compound (10 mg of SAM 486A dry substance in 2-ml vials). The dry substance had to be protected from light and stored at temperatures <30°C. SAM 486A was reconstituted by dissolving it in 1 ml of 5% dextrose solution and then diluting it in 100 ml of 5% dextrose. The reconstituted solution had to be stored at 2–8°C and used within 8 h after dissolving it in an infusion system completely protected from direct sunlight. Infusion time was initially 10 min and was increased to 20 min at doses of 48 and 70 mg/m^2, 1 h at doses of 110 and 170 mg/m^2, and 3 h at doses of 270 and 325 mg/m^2. Prophylactic antiemetics were not given routinely. A treatment cycle consisted of four weekly infusions followed by 2 weeks off treatment.

Dose and Dose Escalation. The starting dose was 1.25 mg/m^2/week. This dose corresponded to one-third of the human equivalent of the no adverse effect dose level, with daily dosing for 3 months in the most sensitive species, the rat, being 0.06 mg/kg or 10.8 mg/m^2/month. Dose escalation was performed with decreasing rates using a Fibonacci scheme, with dose doublings when no toxicities of grade > 2 were seen in a previous dose level. At each dose level, a minimum of three patients had to have one full course of treatment before dose escalation was allowed. When side effects with a toxicity of grade ≥2, excluding alopecia or inadequately treated nausea or vomiting, were seen at a given dose level, at least six patients had to be treated at that dose level. The maximum tolerated dose was the highest dose administered safely to a patient producing tolerable, manageable, and reversible grade 3 toxicity in at least two of six patients. No intrapatient dose escalation was allowed.

Pharmacological Studies. For the pharmacokinetic analysis of SAM 486A, 5-ml blood samples were taken from an i.v. cannula inserted in the arm opposite the infusion arm before the first drug administration, at the end of the infusion, and at 15, 30 and 60 min and 2, 4, 8, 10, and 24 h after the end of the infusion. When infusion time was 1 h, additional samples were taken 20 and 40 min after the start of the infusion. When infusion time was 3 h, additional samples were taken 1 and 2 h after the start of the infusion. For the second, third, and fourth administration, a blood sample was taken before the start of infusion. A blood sample was also taken at the two weekly visits after the fourth administration. The blood samples were immediately centrifuged at 3000 rpm for 5 min at room temperature. The separated plasma was transferred into a polyethylene tube and frozen at −18°C until analysis. Plasma samples were assayed by a specific and sensitive high-performance liquid chromatography assay (16). The lower limit of quantitation of the assay was 5 ng/ml (variability, 2.1–10.5 ng/ml). Concentration *versus* time data were used for calculation of the noncompartmental pharmacokinetic parameters $AUC_{0-\infty}$, peak plasma concentration (C_{max}), terminal $t_{1/2}$, and V_{ss} using WinNonlin Professional version 1.5 software. Excretion of SAM 486A in urine was measured for 24 h after the first administration. Urine was collected in three 8-h samples that were stored at 4°C during the collection period and subsequently frozen at −20°C until analysis. The volume of each 8-h urine sample was measured. Urine samples were assayed by the same high-performance liquid chromatography assay used for plasma analysis. The lower limit of quantitation of the urine assay was 11 ng/ml.

Table 1 Patient characteristics

Characteristic	
No. of patients entered	50
No. of patients evaluable	50
Male/female	30/20
Mean age (yrs)	55.8
Range	22–73
Median WHO performance status	1
Range	0–2
Prior therapy (excluding previous surgery)	
None	9
Immunotherapy only	1
Chemotherapy/hormonotherapy only	24
Radiotherapy only	3
Chemo- and radiotherapy	13
Histological diagnosis	
Colorectal cancer	16
Kidney cancer	7
Lung cancer	4
Unknown primary	4
Gastric cancer	3
Head and neck cancer	2
Melanoma	2
Gall bladder cancer	2
Miscellaneous cancer	10

For pharmacodynamic studies, 10-ml blood samples were taken from an i.v. cannula inserted in the arm opposite the infusion arm before therapy and 24 h after the end of the first and, optionally, the fourth infusion. Before the second, third, and fourth administration and during the 2 weeks off treatment, trough samples were taken. Samples were immediately centrifuged at 3000 rpm for 10 min at 4°C, and then plasma was frozen at −20°C until analysis. Polyamines were determined in leukocytes by a capillary gas chromatography method using nitrogen, phosphorus-detection. SAMDC activity was determined in leukocytes using an assay described previously (17).

RESULTS

Fifty patients were entered into this study, all of whom were eligible and evaluable for safety. Patient characteristics are summarized in Table 1. The total number of assessable treatment cycles was 78; most patients received 1 or 2 cycles, two patients received 4 cycles, and one patient received 5 cycles. There was no tendency toward longer treatment duration with increasing dose levels. Dose levels studied were weekly infusions of 1.25, 2.5, 5, 8, 16, 32, 48, 70, 110, 170, 270, and 325 mg/m^2. Dose escalation from 5 to 8 mg/m^2/week was performed because of the occurrence of one episode of grade 3 diarrhea at the lower dose. Infusion time was increased from 10 to 20 min at a dose of ≥48 mg/m^2/week and to 60 min at a dose of ≥110 mg/m^2/week due to acute reactions such as facial flushing and paresthesias. At 270 mg/m^2/week, infusion time was further increased to 180 min due to the additional occurrence of somnolence in three patients at this dose level.

Hematological Toxicity. Hematological toxicities are summarized in Table 2. Grade ≥2 hematological side effects were only recorded at the highest two dose levels. Uncomplicated grade 3 neutropenia lasting 8 days was seen in week 5 in one patient at 270 mg/m^2/week, and another patient at this dose

Table 2 Hematological toxicity (worst hematological toxicity per patient)

Dose level (mg/m^2/wk)	Patients/treatment cycles	Leukocytes (CTC grade)				Neutrophils (CTC grade)			
		1	2	3	4	1	2	3	4
1.25	3/4					1			
2.5	3/5								
5	4/6	1							
8	3/6								
16	4/10	1				1			
32	3/5								
48	3/4								
70	4/5	1							
110	4/6	1							
170	4/5								
270	8/15		2	1		1	1	2	
325	7/7	1			1				1

experienced uncomplicated grade 3 neutropenia lasting 8 days in the third treatment cycle. Grade 4 neutropenia lasting 3 days complicated by fever was seen in one patient at 325 mg/m^2/week in week 6 of the first treatment cycle. No grade 3 or 4 anemia or grade 2–4 thrombocytopenia was seen. Three patients developed grade 1 thrombocytopenia (one patient each at 16, 110, and 270 mg/m^2/week). There was no treatment delay due to myelosuppression.

Nonhematological Toxicity. Nonhematological toxicity was diverse but most frequently consisted of nausea and vomiting, fatigue and/or malaise, and facial flushing and paresthesias.

Fatigue, anorexia, nausea, vomiting, and diarrhea occurred at all dose levels, although the incidence tended to increase at the three highest dose levels. These side effects were usually mild and required no specific treatment. One patient at 5 mg/m^2/week had grade 3 diarrhea that subsided within 2 days without specific treatment.

Facial paresthesias and flushing occurred in 26 patients. One patient at 2.5 mg/m^2/week experienced grade 1 facial flushing. Twenty-two patients at $\geq$32 mg/m^2/week had grade 1 facial flushing and paresthesias, and two patients at the highest dose level had grade 1 flushing and grade 2 paresthesias. One patient at 32 mg/m^2/week experienced grade 3 hypersensitivity consisting of pruritis, facial flushing, dyspnea, and hypertension immediately after the start of the first infusion. The infusion was stopped, and antihistaminics and corticosteroids were administered. After a 30-min rest period, the infusion was restarted without sequelae apart from facial flushing. Subsequent infusions in this patient were preceded by antihistaminics and corticosteroids and were followed only by mild facial flushing.

Increasing the infusion time from 10 to 20 min at the 48 mg/m^2/week dose level and to 60 min at the 110 mg/m^2/week dose level was instrumental in the control of facial flushing and paresthesias. At 270 mg/m^2/week, due to the additional occurrence of somnolence in three patients, infusion time was further increased to 180 min. At 270 mg/m^2/week, grade 2 alopecia was seen in two patients, one of whom developed sclerodermia-like skin abnormalities. Grade 1–2 local erythematous skin reactions at the infusion site were noted in four patients at doses of 170–325 mg/m^2/week.

Cardiovascular abnormalities were recorded in five patients. At 110 mg/m^2/week, one patient experienced grade 3 tachyarrythmias with possible atrioventricular dissociation starting 11 days after the fourth administration in the second treatment cycle over a period of 6 days preceding death. Mild hyperkalemia (<6.1 mmol/liter) was recorded. Autopsy revealed mediastinal tumor localization and pulmonary embolism. At 270 mg/m^2/week, one patient had grade 4 cardiac ischemia after the third drug administration. This event was considered to be possibly related to the trial drug, although the patient was known to have hypertension and hypercholesterolemia. After the occurrence of this event, continuous electrocardiographic monitoring was performed in all subsequent patients during drug administration. At 325 mg/m^2/week, on the day of the third infusion, one patient with known hypertension developed grade 3 atrial flutter and sinus tachycardia lasting 5 days. One day later, the patient died due to progressive disease. At 325 mg/m^2/week, another patient developed transient grade 1 ventricular bigeminy and a first-degree atrio-ventricular nodal block during the first infusion of SAM 486A. This patient had a history of prior ventricular bigeminy and atrial fibrillation for which electric cardioversion had been attempted unsuccessfully. With subsequent administrations of SAM 486A, continuous electrocardiographic monitoring revealed no arrythmias. One other patient at the 325 mg/m^2/week dose level recorded transient grade 1 sinus tachycardia (130 beats/min) only during the third administration, whereas another patient at the 325 mg/m^2/week dose level recorded transient grade 1 sinus bradycardia (45 beats/min) during the first administration only. No further administrations were given to this patient because of a rapid decline in general condition. Repeated assessments of LVEF with nuclear ejection fraction determination showed no changes in cardiac contractility in any patient. Continuous electrocardiographic monitoring in subsequent patients treated at the next lower dose level of 270 mg/m^2/week revealed no arrythmias.

Renal or hepatic toxicity related to the study drug of grade 2 or greater was not recorded.

DLTs. At 325 mg/m^2/week, grade 4 neutropenia in week 5 of treatment lasting 3 days but complicated by fever occurred in one patient. Grade 3 hypotension with syncope and reversible T-wave inversions on electrocardiogram occurring immediately after the first infusion was seen in another patient. Grade 3 neuromotor and neurosensory toxicity of the left hand after the second administration of SAM 486A was seen in a third patient. Cerebral magnetic resonance imaging in this patient revealed no abnormalities, and the complaints subsided gradually after treatment was stopped. Accordingly, the recommended dose for further activity testing was set at the next lower dose level, *i.e.*, 270 mg/m^2/week. At this dose, one episode of grade 4 cardiac ischemia and two episodes of uncomplicated grade 3 neutropenia were seen. Other side effects recorded at this dose level were mild facial flushing and paresthesia, nausea, and vomiting.

Reasons for Discontinuation of SAM 486A. In 37 patients, progressive disease was the reason for discontinuation of SAM 486A. In 24 of these patients, SAM 486A was withheld due to progressive disease before the second treatment cycle had been completed. Two patients died before completion of two treatment cycles, three patients discontinued treatment due to toxicity, two patients withdrew consent, and six patients discon-

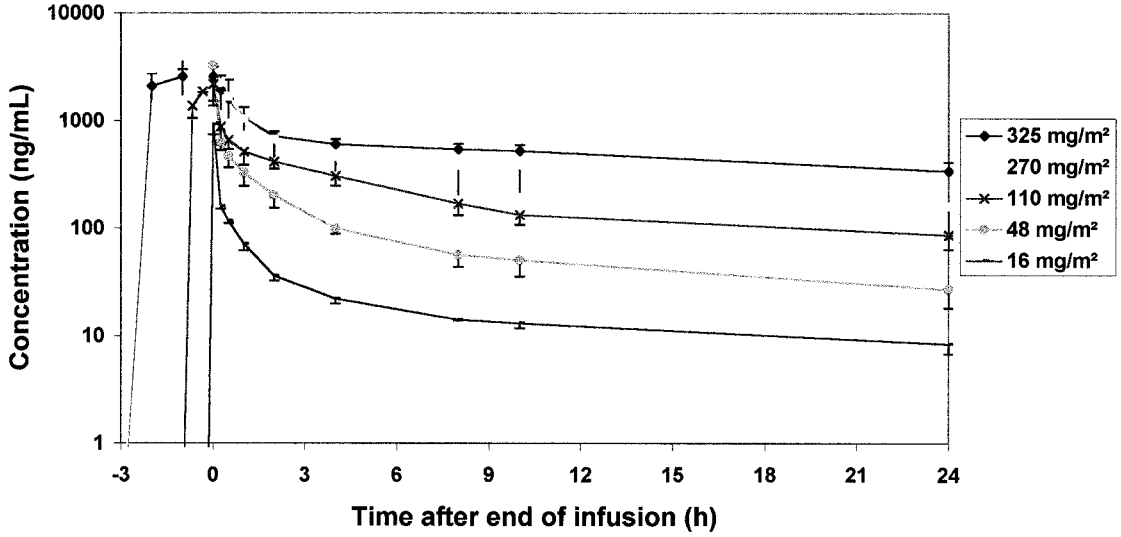

Fig. 2 SAM 486A mean (SD) plasma concentration-time profiles for representative 16–325 mg/m^2 doses.

tinued treatment for various reasons (three patients discontinued treatment due to adverse events, two patients discontinued treatment due to deterioration in general condition, and one patient discontinued treatment due to increased liver enzymes suggestive of disease progression).

Pharmacokinetics and Pharmacodynamics. At dose levels 1.25–8 mg/m^2/week, the limits of the pharmacokinetic assay influenced calculation because plasma concentrations of SAM 486A were below the limit of quantitation for prolonged periods of time. Mean ± SD plasma concentration *versus* time profiles for the 16–325 mg/m^2/week dose levels are shown in Fig. 2. The relation of AUC to dose is shown in Fig. 3. Mean ± SD $t_{1/2}$ for the dose range of 70–325 mg/m^2/week was 61.4 ± 26.2 h. Mean ± SD V_{ss} for the dose range of 70–325 mg/m^2/week was 1540 ± 926 liters, indicating extensive distribution outside the plasma compartment. The interpatient variability of the parameters $t_{1/2}$ and V_{ss} was high, with coefficient of variation values of 43% and 60%, respectively. C_{max} was generally related to dose, but because this parameter is influenced by infusion time, no relation across all dose levels was made.

Analysis of the urine showed that 24 h excretion of SAM 486A was dependent on the dose and/or duration of infusion. Mean 24 h urinary excretion for the 2.5–70 mg/m^2/week cohorts was 15–25% of the dose. Mean 24 h urinary excretion for the 110–325 mg/m^2/week cohorts was 4–9% of the dose.

An exploratory analysis to investigate whether the peripheral leukocyte compartment could provide suitable material for analysis of polyamine and SAMDC activity fluctuation in response to SAM 486A administration was performed on nine patients treated with ≥70 mg/m^2/week. All patients demonstrated a moderate increase in SAMDC activity after SAM 486A administration, but the results were variable and were not maintained with subsequent dosing. Analysis of polyamine pools showed high intra- and interpatient variability. Intracellular concentrations of putrescine were increased in some patients and decreased in others after administration of SAM 486A at different doses. There was no discernable relationship between polyamine or SAMDC fluctuation and the dose of SAM 486A administered.

Responses. No partial or complete responses were seen. Stable disease was seen in seven patients. There was no tendency toward increased time to disease progression with increasing doses of SAM 486A among either the 16 patients with colorectal cancer or the 7 patients with renal cell carcinoma (data not shown separately).

DISCUSSION

We have performed a Phase I and pharmacological study on the novel polyamine synthesis inhibitor SAM 486A. Hematological side effects consisted of dose-dependent, short-term, and noncumulative neutropenia. In one patient, grade 4 febrile neutropenia caused a DLT. Myelosuppression was also recorded in two other Phase I studies with SAM 486A using different treatment schedules (18, 19). Thrombocytopenia was mild, even more infrequent, and not dose dependent. Nonhematological side effects of SAM 486A were diverse. Gastrointestinal side effects occurred frequently and at virtually all dose levels, with an increasing incidence of nausea and vomiting at the three highest dose levels. These side effects were usually mild, required no specific treatment, and did not lead to interruption or withholding of treatment. Fatigue occurred in 44% of patients on study, and the incidence of this specific complaint tended to increase at the two highest dose levels. Taking into consideration the characteristics of patients entering clinical Phase I studies, *i.e.*, those with advanced or end-stage malignant disease, interpreting the causality of anticancer treatment with this side effect is always somewhat hazardous. However, fatigue and weakness, on two occasions even leading to hospitalization, have also been ascribed to the parent compound MGBG when given weekly (20–23). Considering the structural similarity between SAM 486A and MGBG, it cannot be excluded that

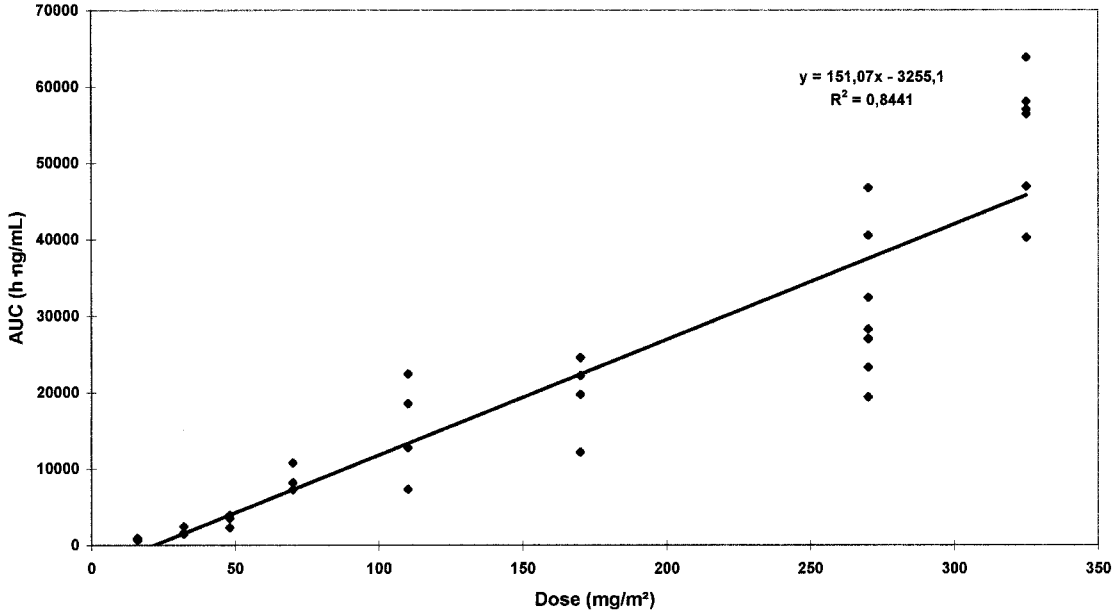

Fig. 3 AUC *versus* dose (16–325 mg/m^2).

fatigue is caused by SAM 486A. Mild (usually grade 1) facial paresthesias and flushing were recorded in 52% of patients on study, occurred at dose levels of ≥32 mg/m^2/week (except for one patient at the 2.5 mg/m^2/week dose level with grade 1 flushing), and usually occurred immediately after the start of the infusion. These symptoms were of short duration, completely reversible, and noncumulative and required no dose reduction or treatment delay. With increasing doses, concurrently increasing infusion time from 10 to 60 min alleviated these side effects. Additionally, somnolence considered drug-related occurred in three patients at the dose level of 270 mg/m^2/week and onward, and because of this, infusion time was further increased to 180 min. Paresthesias have been described in relation to MGBG when given weekly (21, 24). The fact that higher doses of SAM 486A were better tolerated with prolonged infusion time corresponds with results of a Phase I study of MGBG (21). The mechanism of action responsible for facial paresthesias and somnolence has not been clarified. Side effects such as ataxia, myopathy, hypoglycemia, vasculitis-like syndromes, or skin ulcerations previously related to MGBG were not recorded in the present study, although mild mucositis and erythematous skin reactions at the infusion site were recorded. Five patients developed alopecia; in one patient this was combined with sclerodermia-like skin abnormalities.

Adverse events related to the cardiovascular system, including arrhythmias and myocardial ischemia, have been recorded in the present study. Preclinical studies with MGBG reported some cardiotoxicity in animals, and one single case of reproducible ventricular arrhythmias after exposure to MGBG in a patient deemed susceptible for cardiac toxicity because of disease state and previous treatment has been published (3, 21). Including our study, three single-agent Phase I studies with SAM 486A using different treatment schedules have been performed, including 112 patients (18, 19). In addition to the patients described in this report, thus far only one patient (with a prior history of atrial fibrillation and hypertension) receiving continuous infusion of SAM 486A has developed atrial fibrillation while on treatment. Because of the diversity of cardiovascular side effects recorded in the current study and the fact that several patients likely suffered from asymptomatic premorbid cardiac conditions, it is difficult, at this moment, to ascribe or exclude a relationship between SAM 486A and these cardiac findings. The patient with hypotensive collapse and concurrent T-wave inversions at the electrocardiogram immediately after the first infusion of the nontolerated dose (325 mg/m^2/week) of SAM 486A in this study, for example, was shown at subsequent exercise testing to develop T-wave flattening on his electrocardiogram, indicating a probable preexisting coronary atherosclerosis. Electrocardiograms after the subsequent infusions at the next lower dose level (270 mg/m^2/week) all remained normal. Because a possible relationship between the trial drug and the occurrence of cardiac arrhythmias or ischemia could not be ruled out at the time of occurrence of the first cardiac event, continuous electrocardiographic monitoring during SAM 486A administration was performed for all subsequent patients. This resulted in the recording of three episodes of grade 1 cardiac arrythmias, but only in patients treated at the nontolerated dose (325 mg/m^2/week) of SAM 486A (one episode each of transient grade 1 ventricular bigeminy, sinus bradycardia, and sinus tachycardia only during the first infusion). None of the patients receiving SAM 486A at the next lower dose level showed any cardiac arrhythmia. At present, a definitive statement concerning the potential of SAM 486A to elicit cardiovascular toxicity cannot be made. In currently ongoing studies with SAM 486A, electrocardiograms are collected on a regular basis, and centralized review is being performed. Thus far, additional abnormalities have not been reported.

Neurotoxicity was seen in one patient treated at the non-

tolerated dose of SAM 486A. Neuropathy, although infrequent, has been described in relation to MGBG (25).

Clearly, the dose-limiting side effects recorded in this study were diverse, but because DLT involved hematological, cardiovascular, and neurological toxicity, it was felt by all participants that further escalation of the dose was not warranted. At the dose recommended for further studies using this schedule of administration, organ toxicities were minor, rapidly reversible, and therefore manageable.

The pharmacokinetic profile of SAM 486A shows many similarities with that of MGBG, *i.e.*, a triphasic plasma elimination, a large V_{ss}, indicating tissue distribution outside the plasma compartment, and incomplete renal excretion (3, 20, 25, 26). The mean peak plasma concentration of the 270 mg/m^2/week patient cohort was higher than that of the 325 mg/m^2/week patient cohort until 1 h after the end of the infusion as a result of large interpatient variability, with two patients at 270 mg/m^2/week having much higher peak levels than average during this period. Mean $\pm$ SD $t_{1/2}$ at doses of 70–325 mg/m^2/week was 61.4 $\pm$ 26.2 h, compared with a mean $\pm$ SD $t_{1/2}$ of MGBG of 175 $\pm$ 84 h (26). Mean $\pm$ SD $t_{1/2}$ at doses $<$ 70 mg/m^2/week could not be calculated because plasma levels at 168 h after dose administration were below the limit of quantitation of the assay. The linear relationship between exposure to SAM 486A as represented by $AUC_{0-\infty}$, and dose administered indicates that the processes of distribution and elimination are not saturated, inhibited, or induced.

An exploratory analysis of polyamines and SAMDC activity in leukocytes after SAM 486A administration showed variable and seemingly unpredictable effects. SAMDC activity was marginally increased after the first administration of SAM 486A in all patients. This may reflect a transient stabilization of the enzyme coupled with a compensatory increase in biosynthetic activity, both known consequences of SAMDC modulation (6). However there was high interpatient variability and no correlation with the dose of SAM 486A administered, and this effect did not persist after multiple administrations. Intracellular concentrations of putrescine, spermine, and spermidine varied widely after the administration of SAM 486A. The likely reason for these disappointing results may be related to the nonproliferative nature of peripheral blood leukocytes. This being so, the relative importance of SAMDC activity and polyamine synthesis in general may well be rather minimal compared to that seen in proliferating tissue. From these scant observations, it must be concluded that peripheral blood leukocytes are not suitable for measuring changes in polyamine pools and activity of SAMDC in response to treatment with SAM 486A.

In conclusion, based on the results of this Phase I and pharmacological study with the polyamine synthesis inhibitor SAM 486A, which was given as four weekly infusions followed by 2 weeks off treatment, the recommended dose for additional studies is 270 mg/m^2/week. At this dose, SAM 486A can be administered safely with acceptable toxicity.

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