Eur J Cancer Clin Oncol, Vol. 20, No. 5, pp. 645–649, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Phase I Evaluation of SOAz (1,3,3,5,5Pentakis(aziridino)-1λ⁶,2,4,6,3λ⁵,5λ⁵thiatriaza-diphosphorine-1-oxide) in a Weekly Schedule

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Abstract—*Eleven patients with advanced cancer were treated with SOAz, the first aziridino substituted inorganic heterocyclic compound to undergo phase I clinical trials. The agent was administered as a rapid i.v. infusion once a week in a dose of* 50, 75 *or* 100 mg/m². *Severe myelotoxicity, which was prolonged and delayed in onset, precluded continuing treatment for more than three courses in* 9 *of* 11 *patients. In two patients thrombocytopenia showed no signs of recovery* 9 *and* 11 weeks *after the last infusion. Two minor responses were noted and there was one therapy-related death. Because of severe myelotoxicity, which is cumulative and may be irreversible, this treatment schedule seems unsuitable for phase II studies.*

INTRODUCTION

THE AZIRIDINO substituted inorganic heterocycles [1, 2] constitute a new class of compounds with antitumor activity, of which 'SOAz' (Fig. 1) is the first to be evaluated in clinical trials. The agent is active against a broad range of *in vitro* tumor systems, including L1210 and P388 leukemias and B16 melanoma,§ Yoshida sarcoma, Lewis lung carcinoma, YM12 tumor, Meth A tumor and Walker carcinosarcoma,‖ L5178Y lymphoma and Ehrlich ascites [3]. Activity in tumor-bearing mice was confirmed‖ [4, 5] and SOAz appeared to be more active than two closely related compounds, especially when administered repeatedly.

Preclinical toxicity studies were performed in mice, rats and dogs [6]. All species showed bone marrow suppression, damage to the digestive tract mucosa and atrophy of lymphoid organs. In dogs hematological toxicity was dose-dependent and reversible. Granulocytopenia and lymphocytopenia occurred during the first week after administration and thrombocytopenia was noted during the second and third weeks. Dose-limiting toxicity included pneumonia, probably related to leukopenia and gastrointestinal hemorrhage and perforation. The LD_{10} in mice was 1000 mg/m², the T.D.L. (toxic dose low) in dogs was 70 mg/m².

In two previously published phase I studies, using a single dose [7] or a daily × 4 regimen [8], myelosuppression was dose-limiting. Platelet counts and white blood cell counts decreased from day 14 onward, with a nadir 4–5 weeks after administration. Full hematological recovery usually took 6–8 weeks. In the single-dose study [7] no repeat courses were given and an M.T.D. of 220 mg/m² was proposed for patients who had had extensive prior myelosuppressive treatment,

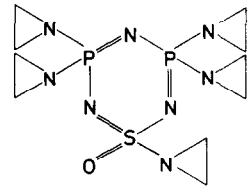

Fig. 1. $(NPAz_2)_2NSOAz$, *'SOAz'.*

Accepted 7 November 1983.

§EORTC Screening and Pharmacology Group, unpublished results.

‖Otsuka Chemical Co. Ltd, Japan, unpublished results.

and of 330 mg/m² for patients who had uncompromised bone marrow. In the study employing a daily × 4 regimen [8], however, myelotoxicity was clearly cumulative in subsequent courses and three of 31 patients developed irreversible bone marrow failure.

Pharmacokinetic studies [9, 10] have shown that achievable serum concentrations in patients on the first days of their 4-day courses were equal to or somewhat lower than concentrations known to be effective *in vitro*, suggesting a possible advantage in terms of efficacy for unsplit treatment courses. From 36 hr after i.v. infusion no traces of SOAz can be detected in serum samples, indicating that the cumulative toxicity of the agent is not the result of cumulation in any body compartment.

In view of these data we decided to initiate a phase I study, employing a regimen of weekly infusions, that allowed for some individualizing of doses: identification of patients at risk for developing severe aplasia was hoped to be possible by finding depressed platelet counts before the third or fourth administration, whereupon subsequent doses were to be omitted until hematological recovery. On the basis of the previous phase I studies, we chose 50 mg/m² as a starting dose, which should allow for four consecutive courses without exceeding M.T.D. in heavily pretreated patients.

MATERIALS AND METHODS

All patients had histologically confirmed advanced malignant disease and were not candidates for known effective treatment regimens. Each patient had a Karnofsky performance score (KPS) of at least 60 and an estimated life expectancy of at least 6 weeks. Previous chemotherapy or radiotherapy had been stopped for at least 3 weeks and there were no residual toxic effects. Patients had not received any drugs that are known to cause prolonged myelosuppression for a minimum of 6 weeks. Patients were required to have adequate bone marrow function (WBC count $\geqslant$4000/mm³, absolute granulocyte count $\geqslant$2000/mm³ and platelet count $\geqslant$120,000/mm³), adequate renal function (creatinine clearance $\geqslant$50 ml/min) and adequate liver function (bilirubin <20 mmol/l). Informed consent was obtained according to institutional policy and the study was approved by the Hospital Ethical Committee.

Pretreatment evaluation included a complete history and physical examination with documentation of metastatic disease and objective tumor measurement when possible. Laboratory studies included a complete blood count, chemistry panel, creatinine clearance, urinalysis, electrocardiogram and chest roentgenogram. Physical examination, blood counts and chemistry panels were repeated weekly, E.K.G.s and chest roentgenograms at 3-week intervals.

SOAz was supplied by Otsuka Chemical Co., Tokushima, Japan. The required amount of drug for infusion was reconstituted with 100 ml of 0.9% NaCl solution and administered as a rapid i.v. infusion over 3–5 min. Dose levels of 50, 75 and 100 mg/m²/week were studied. At least three patients were treated at each dose level. Weekly doses were withheld when the WBC count or platelet count was less than 4000/mm³ or 100,000/mm³ respectively, or when the platelet count had dropped more than 20% in a single week. Treatment was not resumed until full hematological recovery. Because of the anticipated risk of severe aplasia, treatment with SOAz was discontinued if after three courses progression of disease was still evident (e.g. weekly increasing number of skin metastases). Conventional criteria for response were employed and hematological toxicity was graded 0–IV according to EORTC-WHO criteria [11].

RESULTS

A total of 30 courses of SOAz was administered to 11 patients (aged 28–66 yr). The only major toxicity was myelosuppression, especially thrombocytopenia, which was dose-limiting. Low platelet counts occurred late, usually 2–4 weeks after the first dose. Hematological recovery was slow and took at least another 4 weeks, while platelet counts never returned to pretreatment levels. Granulocytopenia was less predictable, but also tended to occur late.

Only two patients tolerated more than three consecutive courses, and of these one developed irreversible thrombocytopenia after his 6th course (H.N., Fig. 2 and Table 3). A second patient (M.W., Fig. 2 and Table 3) entered irreversible aplasia after three courses at the 100-mg/m² dose level. A 37-yr-old woman (E.M., Table 2) with a disseminated colon carcinoma who received two courses of 100 mg/m² developed severe thrombocytopenia and died 3 weeks after the first infusion while receiving a blood transfusion (platelet count 16,000/mm³). The presumptive cause of death was cerebral hemorrhage, and although no autopsy was performed, the event was classified as a therapy-related death. Prior to treatment with SOAz, this patient had been treated with CCNU and fluorouracil, having received the last dose of CCNU 6 weeks and of fluorouracil 3 weeks before her first course of SOAz.

Extramedullary toxicity was unimportant. Two patients complained of nausea and

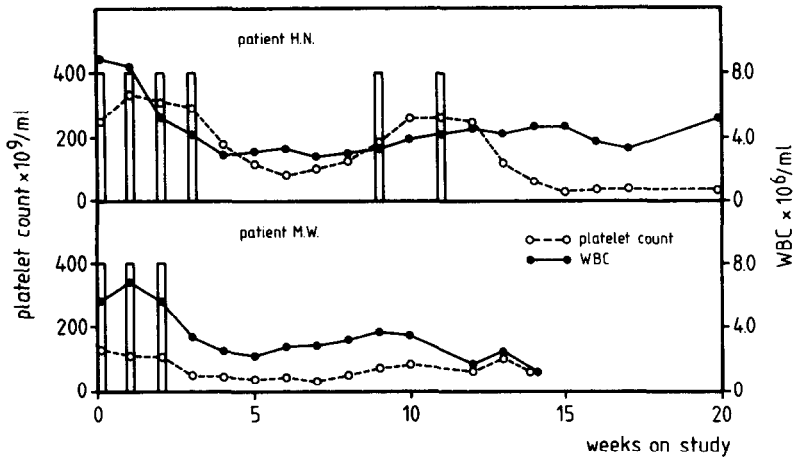

Fig. 2. Hematologic toxicity in two patients receiving SOAz at a dose of 100 mg/m²/week. *Bars represent times of administration of SOAz.*

Table 1. Patient characteristics

Characteristic	No. of patients
Total:	11
male	4
female	7
Evaluable for response	9
Previous treatment:	
chemotherapy only	6
radiotherapy only	-
both	4
neither	1
Tumor:	
melanoma	3
breast	2
head and neck	1
kidney	1
colon	1
ovarian	1
liposarcoma	1
lung	1

occasional vomiting on the days of infusion and one patient reported fever and abdominal discomfort on treatment days. No other signs of toxicity were observed.

There were no complete or partial responses. Two minor responses were noted however: one patient with a rapidly progressive liposarcoma, treated with two courses of 75 mg/m², showed 50% reduction of supraclavicular lymph nodes and slight improvement of lung metastases lasting for about 2 weeks. A second patient (M.W.) experienced 35% reduction of skin metastases of her breast carcinoma after three courses of 100 mg/m². Both patients experienced severe bone marrow suppression (grades IV and III respectively), which proved irreversible in the latter case. One patient (H.N.) with a rapidly progressive melanoma, who received 4 courses of 100 mg/m², had stable disease for 5 weeks. Because of thrombocytopenia further courses had

*Table 2. Myelotoxicity and recovery at different dose levels**

Level (mg/m²)	Patient	Cumulative dose (mg/m²)	WBC (Nadir)	Platelets (Nadir)	Recovery
50	J.V.	100	0	III	uncertain†
50	J.L.	150	0	II	recovery
50	D.S.	150	0	0	-
75	A.L.	150	0	III	uncertain†
75	E.H.	150	IV	IV	recovery
75	G.B.	75	I	0	recovery
75	B.O.	150	0	0	-
100	G.L.	400	I	I	recovery
100	E.M.	200	III	IV	T.R.D.‡
100	M.W.	300	III	III	irreversible
100	H.N.	600	II	III	irreversible

*Grading of toxicity according to WHO-EORTC criteria [11].
†Recovery not evaluable because of early death.
‡T.R.D., therapy-related death.

Table 3. Characteristics of patients with irreversible myelotoxicity

Patient	Sex	Age	Cumulative dose (mg/m²)	Tumor type	Creatinine clearance (ml/min/1/73 m²)	Prior radiotherapy	Prior chemotherapy
H.N.	m	28	600	melanoma	130	yes	dacarbazine, bleomycin, dactinomycin, vindesine
M.W.	f	67	300	breast	55	yes	cyclophosphamide, methotrexate, fluorouracil, doxorubicin, vincristine, mitomycin C
J.W.*	f	71	350	breast *and* colon	64	yes	cyclophosphamide, methotrexate, fluorouracil
R.G.*	f	63	480	adenocarcinoma	80	none	none
T.H.*	f	53	175	cervix	55	yes	bleomycin, vincristine, mitomycin C, cisplatin

*These patients were treated with a daily × 4 regimen [8].

to be delayed until the 9th week (Fig. 2), whereupon stabilization occurred for about 4 weeks. Severe thrombocytopenia developed and persisted until the patient died of his tumor.

DISCUSSION

Our previously reported phase I study [8] has demonstrated that SOAz shows a strong tendency for cumulation of toxicity in subsequent courses and may cause irreversible aplasia even after a single course. Patients who had received no or only minor chemotherapy prior to treatment with SOAz tolerated up to 300 mg/m² in a daily × 4 regimen, while heavily pretreated patients experienced major toxicity when treated at the 175-mg/m² level.

The weekly regimen employed in the present study was adopted in order to evaluate possible schedule dependency of the toxicity pattern and because it was hoped that individualizing of doses could prevent grade IV myelosuppression and irreversible aplasia. Unfortunately, however, the regimen seems not to have any toxicological advantage and may even be more toxic than the daily × 4 regimen. Again, two cases of irreversible aplasia occurred and cumulation of toxicity was evident. Deleting weekly doses in response to signs of developing myelosuppression was generally ineffective in preventing severe aplasia because of the delayed onset of toxicity: first drops in platelet counts were seldom observed before the third or fourth week, when the cumulative dose of SOAz already made grade III or IV toxicity unavoidable. When it became clear that the weekly schedule would not be satisfactory in phase II clinical trials, we decided not to admit further patients to the study.

The pattern of toxicity observed in patients treated with SOAz is consistent with the assumption that the agent is toxic to bone marrow stem cells, more pronounced but otherwise similar to the toxicity of mitomycin C or the nitrosourea derivatives. In fact, the only patient in this study who had received mitomycin prior to SOAz developed irreversible bone marrow failure.

A second subset of patients predisposed to excessive myelosuppression consists of patients with impaired renal function [8, 10]. Some characteristics of the patients with irreversible bone marrow failure from the present and from our previous study are presented in Table 3. Combining the findings of both our phase I studies, we anticipate that even patients with uncompromised bone marrow and normal renal function will enter prolonged aplasia after a cumulative dose of 500–600 mg/m².

In contrast to both earlier phase I trials [7, 8], two minimal responses were noted. This observation suggests that SOAz may have antitumor properties in humans and encourages the search for related compounds that may combine useful clinical activity with more acceptable toxicity. The development of an animal model or an *in vitro* laboratory test for the cumulation of toxicity observed in humans would be of great importance in the selection of one of the many active analogues of SOAz for clinical studies.

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