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Phase I Clinical Trial of $(NPAz_2)_2NSOAz$: 'SOAz'

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Summary. *$(NPAz_2)_2NSOAz$ ('SOAz') is the first of a new class of cytotoxic agents containing an inorganic heterocyclic ring system to enter clinical trial. It was used to treat 31 patients with advanced cancer by IV infusion over 30 min on days 1, 2, 3, and 4 of a 21-day cycle, which was postponed if necessary to allow for hematological recovery. A total of 46 courses evaluable for toxicity was given and the tumor response was evaluable in 21 patients. Seven dose levels, ranging from 25 mg/m² to 300 mg/m², were studied, with three to six patients at each level.*

The only major toxicity was myelosuppression, especially thrombocytopenia, which was dose-limiting. Platelets decreased from the 14th day onward, with a nadir 4–5 weeks after administration. Leukopenia was less predictable and reached a nadir 3–5 weeks after administration. In most patients recovery was complete after 6–9 weeks. Myelosuppression was clearly cumulative in succeeding courses and proved irreversible in three patients. Anemia also occurred, but otherwise SOAz was remarkably well tolerated. There were no responses and no therapy-related deaths. The highest tolerated dose for patients who had received no or only minor chemotherapy prior to treatment with SOAz was 300 mg/m², and that for heavily pretreated patients, 175 mg/m².

Because of cumulative myelotoxicity phase II studies with SOAz are not recommended.

Introduction

The antitumor activity of aziridino-substituted inorganic heterocycles has been noted since 1959 [1] and has been ascribed to alkylating activity. Recently a new series of derivatives of $(NPCl_2)_3$ (the cyclophosphazenes) and several derivatives of the novel ring system $(NPCl_2)_2NSOCl$ (the cyclophosphathiazenes) [7] have been shown to have significant activity against L1210 leukemia, P388 leukemia and B16 melanoma in in vitro systems [3; H.B. Lamberts et al., 1983, unpublished work]. Experiments in tumor-bearing mice confirmed the in vitro findings and $(NPAz_2)_2NSOAz$, SOAz (Fig. 1), was selected for further study [4]. Subsequent studies in tumor-bearing mice and rats showed a broad spectrum of activity; sensitive tumors included P388 leukemia, L1210 leukemia, B16 melanoma, Yoshida sarcoma, Lewis lung carcinoma, YM12 tumor, Meth A tumor, and Walker carcinosarcoma [2].

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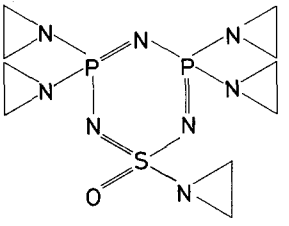

Fig. 1. $(NPAz_2)_2NSOAz$: 1,3,3,5,5 pentakis(aziridino)-$1\lambda^6$,2,4,6,$3\lambda^5$,$5\lambda^5$thiatriazadiphosphorine-1-oxide (SOAz)

Animal toxicity was evaluated in mice, rats, and dogs [5]. All species showed bone marrow suppression and damage to the digestive tract mucosa. Furthermore, atrophy of lymphoid organs and of the testes were noted. The dogs displayed emesis and diarrhea. Leukopenia, consisting of granulopenia and lymphocytopenia to a similar degree, occurred during the first week after administration and mild thrombocytopenia was noted during the second and third weeks. The hematological toxicity was reversible and dose-dependent. Dose-limiting toxicity included pneumonia, probably related to the leukopenia and gastrointestinal hemorrhage and perforation. The LD_{10} in mice was 1,000 mg/m², the TDL (toxic dose low) in dogs was 70 mg/m².

On the basis of these preclinical data we decided to initiate a phase I clinical study. As an initial dose we chose one-third of the TDL in dogs, 25 mg/m².

Patients, Materials, and Methods

All patients had histologically confirmed advanced malignant disease and were not candidates for known effective treatment regimens or protocol treatment. Each patient had a Karnofsky performance score (KPS) of at least 50 and an estimated life expectancy of at least 8 weeks. All patients who had received previous chemotherapy, immunotherapy, or radiotherapy had not received treatment for a minimum of 3 weeks and had no residual toxic effects. Patients were required to have adequate bone marrow function (WBC count $\geq$ 4,000/mm³, absolute granulocyte count $\geq$ 2,000/mm³ and platelet count $\geq$ 120,000/mm³), adequate renal function (creatinine clearance $>$ 50 ml/min), and adequate liver function (bilirubin $<$ 20 mmol/l). Informed consent acknowledging the investigational nature of the study was obtained from all patients. The study protocol 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 (cbc), including differential, reticulocyte, eosinophil, and platelet counts, chemistry panel (Na, K, Cl, BUN, creatinine, Ca, phosphorus, uric acid, SGOT, SGPT, LDH, alkaline phosphatase, gammaGT, total protein, albumin, total bilirubin, glucose), creatinine clearance, urinalysis, electrocardiogram and chest roentgenogram. On days 2, 3, and 4 and weekly, cbc and chemistry panels were repeated. Repeat physical examinations with tumor measurement were performed at 1-week intervals, while electrocardiograms and chest roentgenograms were repeated 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 0.9% NaCl solution by the Department of Pharmacy of the State University Hospital, Groningen, the Netherlands, and rendered sterile and pyrogen-free. The drug was then given as a 30-min IV infusion. SOAz was administered on days 1, 2, 3, and 4 (one course) and then withheld until day 22 or until full hematological recovery. Subsequent courses were given if the patient did not have progressive disease or residual toxicity.

The starting dose was 25 mg/m^2 per course, divided into four equal doses.

Subsequent dose escalations were carried out according to the Fibonacci scheme and are shown in Table 2. A minimum of three patients was treated at each dose level if no toxicity occurred, and otherwise the minimum was six. Dose escalations were not carried out in individual patients.

Conventional criteria for response were employed. Minimum requirements for a 'partial response' included reduction by at least 50% of the sum of the products of the two largest perpendicular diameters of all measurable disease without the appearance of a new lesion. 'Stable disease' was defined as less than 50% reduction or less than 25% increase of the measurable tumor mass.

Hematological toxicity (Tables 2 and 3) was graded according to WHO criteria [8]:
Grade 0: WBC $\geq 4.0 \times 10^6$/l, platelets $\geq 10 \times 10^9$/l.
Grade I: WBC $3.0-3.9 \times 10^6$/l, platelets $75-99 \times 10^9$/l.
Grade II: WBC $2.0-2.9 \times 10^6$/l, platelets $50-74 \times 10^9$/l.
Grade III: WBC $1.0-1.9 \times 10^6$/l, platelets $25-49 \times 10^9$/l.
Grade IV: WBC $< 1.0 \times 10^6$/l, platelets $< 25 \times 10^9$/l.

Results

A total of 31 patients (age 24–74 years) was entered in the study. Due to early tumor-related death two patients were not evaluable for toxicity or response. Three further courses were not evaluable: two patients died within a few days after their second courses and one patient refused follow-up after his second course because of rapid deterioration of his condition. Some patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Characteristic	No. of patients
Total	
Entered (female 10, male 21)	31
Evaluated	29
Evaluable disease	21
No. of courses	
Completed	50
Evaluated for toxicity	46
for response	30
Tumor type[a]	
Melanoma	9
Head and neck	8
Lung	4
Adeno (primary unknown)	2
Renal	2
Breast	2
Cervix	2
Colon	2
Esophagus	1
Prior therapy	
Chemotherapy	10
Radiotherapy	6
Both	8
Neither	7
Performance status (KPS)[b]	
80–90	13
60–70	14
50	4

[a] One patient had two malignancies (breast and colon)
[b] KPS, Karnofsky Performance Score

Myelosuppressive Toxicity

Myelosuppression was dose-limiting. When thrombocytopenia occurred the platelet count decreased from the 2nd or 3rd week onward, reaching a nadir 4 or 5 weeks after administration. Full recovery had generally taken place in the 6th to 8th week after administration. Low platelet counts were found in the 175, 225, and 300 mg/m^2 dose groups during first courses, and in the 125 mg/m^2 group in repeated courses. Patients who had received intensive chemotherapy prior to treatment with SOAz tended to have more severely depressed platelet counts.

Leukopenia was somewhat less predictable. Significant leukopenia after first courses was encountered in the 175, 225, and 300 mg/m^2 dose groups. The WBC count started to decrease at 2–4 weeks after administration, and reached its nadir at 3–5 weeks. After 5–8 weeks recovery was usually complete. No important shifts were observed in the differential counts.

A striking difference in tolerance to SOAz was observed between patients who had and patients who had not received previous intensive chemotherapy. Patients who had had no or only minor chemotherapy tolerated doses up to 300 mg/m^2, displaying severe reversible thrombocytopenia only at the highest dose level. Heavily pretreated patients, however, showed severe toxicity at 175 mg/m^2 (Tables 2 and 3). One patient, who additionally had renal function impairment with a creatinine clearance of 55 ml/min, developed irreversible bone marrow failure after one course at this dose level.

Nine patients received more than one evaluable course of SOAz (Table 4). Myelosuppression tended to be more severe in subsequent courses, and in two patients (J.W. and R.G.) severe and prolonged marrow aplasia occurred. J.W. died of her tumor 10 weeks after her last dose of SOAz and showed no signs of hematological recovery at that time. R.G. stayed in grade IV aplasia for 32 weeks; subsequently her WBC returned to normal over the next few weeks and her platelet count increased to 36×10^9/l at 36 weeks.

Table 2. Hematological toxicity after first courses of SOAz

Dose mg/m^2	No. of patients	Median nadir of cell counts (first courses)		
		WBC × 10^6/l	Granulocytes × 10^6/l	Platelets × 10^9/l
25	3	7.5 (6.7– 8.4)	6.1 (4.8– 7.5)	220 (160–280)
50	3	11.3 (4.8–17.8)	9.9 (3.9–16.0)	190 (106–274)
85	2	5.9 (5.7– 6.2)	5.1 (4.3– 5.9)	232 (163–301)
125	3	5.8 (5.4– 6.2)	4.0 (3.8– 4.3)	268 (230–307)
175[a]	4	2.1 (1.1– 3.1)	1.7 (1.0– 2.5)	99 (11–187)
175[b]	3	7.5 (5.2– 9.9)	5.8 (3.0– 8.7)	261 (127–395)
225[b]	6	8.1 (2.6–13.7)	6.6 (2.0–11.3)	230 (115–345)
300[b]	5	1.5 (0.5– 2.5)	0.8 (0.2– 1.4)	50 (7– 92)

[a] These patients were considered to have poor bone marrow reserve due to intensive chemotherapy and in three of four cases radiotherapy prior to treatment with SOAz

[b] These patients had had no or only minor chemotherapy or radiotherapy prior to treatment with SOAz

Table 3. Hematological toxicity after first courses of SOAz at toxic dose levels

Dose mg/m^2	No. of patients	Leukopenia grade[c]				Thrombopenia grade				Platelet transfusion
		I	II	III	IV	I	II	III	IV	
175[a]	4	1/4	–	2/4	1/4	1/4	–	1/4	1/4	1 patient
175[b]	3	–	–	–	–	–	–	–	–	–
225[b]	6	2/6	2/6	–	–	2/6	–	–	–	–
300[b]	5	–	1/5	3/5	1/5	–	2/5	1/5	2/5	1 patient

[a] These patients were considered to have poor bone marrow reserve due to intensive chemotherapy and in three of four cases radiotherapy prior to treatment with SOAz

[b] These patients had had no or only minor chemotherapy or radiotherapy prior to treatment with SOAz

[c] Grading of toxicity I through IV according to WHO/EORTC criteria [8]

Table 4. Bone marrow toxicity in patients who received more than one course of SOAz[a]

Patient	Dose mg/m^2	Course no.			
		I	II	III	IV
J. L.	25	0	0	–	–
C. P.	50	0	0	1	–
J. H.	85	0	1	1	–
H. O.	125	0	1	1	–
B. F.	125	0	0	0	4
M. T.	125	0	0	1	3
J. W.	175	2	4 (irreversible)		
R. G.	175	0	1	4 (irreversible)	
K. B.	225	0	0	–	–

[a] Grading of toxicity according to WHO/EORTC criteria. In each case the highest grading for leukopenia or thrombocytopenia is given

Progressive decrease in hemoglobin level ($\geq$ 0.4 g/dl/week) not explained by external blood loss was found in 14 of 46 courses, and tended to be more severe at the higher dose levels. Signs of intravascular hemolysis were not found.

Other Toxicities

Seven patients reported mild drowsiness or stated that they had 'slept unusually well' on the days of infusion, beginning several hours after administration and lasting up to 2 days. In only five of 46 courses was mild nausea reported, with minor emesis in two cases. One patient complained of mild vertigo during the first days after treatment. One patient had moderately severe phlebitis relating to his fourth course of SOAz, which resolved spontaneously after 1 week. In two cases about 20 mg SOAz dissolved in approximately 15 ml NaCl solution was inadvertently infused SC; in both cases the deposit was resorbed without pain or local tissue reaction.

One patient, who received three courses of 125 mg/m^2, showed slowly progressive infiltrative changes on his chest roentgenogram, localized in the right upper lobe. An anatomical diagnosis was not made and a connection with the treatment with SOAz could not be excluded.

There were no other signs of toxicity, subjective or objective. Diarrhea, reported in all animal species used for the preclinical evaluation, was not encountered at all. Several patients reported regrowth of hair after hair loss due to previous chemotherapy.

Antitumor Activity

There were no objective responses. In two cases stabilization of disease occurred, both for approximately 6 weeks. The first patient received 175 mg/m^2 for a renal cell carcinoma. The alkaline phosphatase activity ascribed to tumor activity returned to normal and there was some subjective improvement. A second patient, who received 225 mg/m^2 and had a large cell bronchial carcinoma, stabilized without subjective improvement.

There were no treatment-related deaths, though in three cases irreversible bone marrow aplasia persisted after treatment; platelet transfusions were repeatedly required in two cases until the patients died of their tumors. The third patient

showed gradual recovery beginning 32 weeks after her last dose of SOAz.

Discussion

The dose-limiting toxicity of SOAz was myelosuppression. Aplasia occurred late and often persisted for several weeks, resembling the pattern known from mitomycin or the nitrosurea derivatives. The tendency to cumulation of bone marrow toxicity seems considerable: three of five patients who experienced mild toxicity during one of their courses and received a subsequent one developed severe aplasia. In two cases this proved to be irreversible or extremely prolonged. When these risks became clear we decided to refrain from repeat courses unless the preceding course had objectively benefited the patient. As a result of this policy only one patient received a second course at 225 mg/m^2 and no second courses were given at 300 mg/m^2.

Pharmacokinetic studies in man revealed no cumulation of the drug in any body compartment [6]; after 48 h no traces of SOAz could be demonstrated in serum or urine. Since patients known to have a compromised bone marrow as a result of prior chemotherapy or radiotherapy seemed to be more at risk of developing serious myelosuppression or even irreversible aplasia, it seems probable that SOAz has some specific toxicity for marrow stem cells.

Apart from myelosuppression SOAz was remarkably well tolerated. The large majority of patients had no symptoms at all following treatment, and subjective tolerance was satisfactory even in those who reported drowsiness or slight nausea. Inadvertent SC administration presented no problems and treatment with SOAz was never followed by hair loss or digestive tract toxicity.

SOAz is the first of a large number of aziridino-substituted inorganic heterocycles that has recently become available to be used in clinical trials. It is to be hoped that stem cell toxicity is not a universal feature of these compounds and one or several other derivatives may combine more acceptable myelosuppression with useful clinical activity and the excellent patient tolerance of SOAz. Further animal studies and phase I trials seem indicated and are being planned at our institution.

In our opinion SOAz has no future place in conventional therapy.

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