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Early Clinical Studies of (NPAz2)2NSOAz

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Summary

$(NPAz_2)_2NSOAz$ ('SOAz') has been the first of a large number of new inorganic heterocycles to undergo clinical trials. The majority of these compounds, in particular the aziridino substituted agents, display cytotoxic activity in *in vitro* systems. A limited number of these have been tested in tumor-bearing laboratory animals, and activity was confirmed. These findings generated hope, that one or more of the derivatives might have clinically useful activity, and clinical studies were initiated. The objective of these investigations was to provide first experience with one of the agents in administration to humans and to obtain pharmacological data that would be helpful in establishing structure-activity relationships of the heterocyclic compounds.

In chapter 2, the results of a phase I clinical study in 31 patients are reported. Treatment took place by IV infusion of SOAz on four consecutive days, to be repeated after full hematological recovery had taken place. 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/m^2 to 300 mg/m^2 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 on, with a nadir 4 to 5 weeks after administration. In most patients, recovery was complete after 6 to 9 weeks. Myelosuppression was clearly cumulative in subsequent courses and proved irreversible in two patients. Furthermore, anemia occurred, but otherwise SOAz was remarkably well tolerated. Patients who had received no or only minor chemotherapy prior to treatment with SOAz, tolerated up to 300 mg/m^2, heavily pretreated patients tolerated only 175 mg/m^2. No objective responses were observed. Because of cumulation of myelotoxicity and the risk of irriversible aplasia, phase II studies using this regimen are not recommended.

In chapter 3 a second phase I trial is reported, that evaluates the feasibility of a regimen employing weekly administrations. Eleven patients were treated with doses of 50, 75 or 100 mg/m^2 as a rapid IV infusion once a week. The treatment was discontinued at the first signs of developing thrombocytopenia. Nevertheless, 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 observed, but because of the risk of inacceptably prolonged bone marrow aplasia, this regimen seems equally unsuitable for phase II studies as the one reported in chapter 2.

Chapter 4 deals with the development of a sensitive assay for the determination of SOAz and other inorganic heterocycles in biological fluids. The method is based on capillary gaschromatography used in conjunction with a thermionic detector. A structural analogue of SOAz, $(NPAz_2)_2NSOPh$ ('SOPh'), is used as an internal standard. The detection limit for SOAz using this method is 0.01 mg/l for serum and 0.04 mg/l for urine, which makes it sufficiently sensitive for the determination of pharmacokinetic parameters in man.

Chapter 5 presents the results of pharmacokinetic studies in six patients treated with SOAz. The drug was administered as a rapid IV infusion. Serum decay curves could be fitted to an open two-compartment model of drug disappearance. After a short initial phase with a $t_{1/2}$ ($\pm$ S.D.) of 7.8 $\pm$ 4.2 minutes, a terminal phase with a dose-independent half life of 203 $\pm$ 17 minutes occurred. The coefficient of apparent distribution was 0.71 $\pm$ 0.13. The renal clearance was 75 $\pm$ 11 ml/min and the total body clearance 162 $\pm$ 23 ml/min. A percentage of 46.5 $\pm$ 6.6 of the administered drug could be recovered unchanged in the urine within 24 hours. Since achievable peak serum concentrations were somewhat lower than concentrations known to be active *in vitro*, it is concluded that a regimen employing large single doses may be advantageous. Dose adjustments should be made for patients with impaired renal function.

Chapter 6 touches upon the sensitive issue of 'informed consent' of research subjects, a problem which is even more complex in phase I studies of new antitumor agents than in other research settings. In order to evaluate the quality of an informed consent procedure, forty-seven patients with advanced cancer were offered participation in one of the trials. The procedure consisted of three separate conversations. In the first session, the possible risks and benefits of a phase I study were informally explained by the patient's personal physician. The second session was attended by the patient, a relative or trusted friend, a registered nurse and a physician. The third session was held at least five days after the second. Forty-one patients gave their consent, motivated by hope for improvement of their conditions, pressure exerted by relatives and friends, the desire to contribute to the progress of medicine or simply because they felt to have 'no choice'. Encouragement by relatives or friends seems to be a powerful incentive to participate. A period of a few days to consult with relatives, friends or trusted physicians seems helpful in arriving at a well-considered decision.

Although further clinical trials of SOAz cannot be recommended at this time, several properties of the agent found in the present study, are of potential interest. The delayed type of myelosuppression and the pronounced tendency to cumulation of toxicity in the almost complete absence of ex-

tramedullary toxicity, strongly suggest that SOAz is specifically toxic for human bone marrow stem cells. Experiments in mice in order to establish a model for this toxicity have yielded encouraging results (Rodenhuis S, Mulder NH, van de Gampel JC, unpublished).

Evidently, it would be of great importance to develop a screening method, in order to select other derivatives for clinical studies on the basis of the absence of this specific toxicity.