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Phase-I Study of α-1,3,5-Triglycidyl-*s*-triazinetrione (NSC 296934)

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Summary. *α-1,3,5-Triglycidyl-s-triazinetrione (TGT) is a triepoxide derivative with alkylating properties discovered by random screening. TGT has been found to be active against a wide variety of murine tumors, including a P388 subline resistant to cyclophosphamide.*

The starting dose in this phase-I study was 30 mg/m² as a single dose IV, repeated every 3–4 weeks, increasing up to 2,700 mg/m². Severe dose-limiting toxicity took the form of phlebitis becoming apparent a few days after treatment. This was initially seen at the 480 mg/m² dose level, and was observed with increasing frequency and intensity at higher dose levels. Leukopenia occurred regularly at dose levels above 1,800 mg/m² and resulted in life-threatening leukopenia in one patient, and in a toxic death at 2,700 mg/m² in another patient. Other toxic side-effects included moderate reversible thrombocytopenia, nausea, and vomiting.

It is recommended that further trials with TGT await the development of more water-soluble formulations or of other triepoxide derivatives.

Introduction

α-1,3,5-Triglycidyl-*s*-triazinetrione is a new antineoplastic compound with three epoxidic functions in the molecule (Fig. 1).

The drug was originally synthesized by Budnowski [3]. It consists of an α- and a β-isomer with alkylating activities [7].

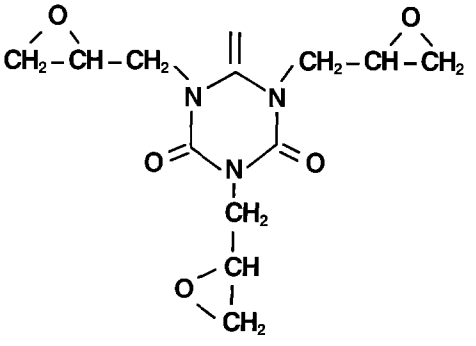

Fig. 1. Chemical structure of TGT

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The α-stereoisomer, which is 20 times more soluble than the β-isomer, has shown promising activity especially when given IP in experimental murine tumors such as P388 leukemia, early and advanced L1210 leukemia, and different solid tumors including the Lewis lung carcinoma [2, 7]. Schedule-dependency was demonstrated in the L1210 system with daily treatment IP on days 1–5 or 1–9, which resulted in increases of more than 600% in lifespan and 70% long-term survival, while single treatments or intermittent treatment resulted in increases of only 119% in lifespan. Of special interest was the observation that the drug had activity against a P388 cyclophosphamide-resistant subline [2]. Pharmacokinetic data in mice showed that following IV drug administration the plasma disappearance curve was biphasic with a terminal half-life of less than 2 min [1].

On the basis of the interesting chemical structure of the drug, its attractive anticancer activity in mice, including its lack of cross-resistance to cyclophosphamide, a phase-I study was initiated using a single intermittent treatment. The study was part of several phase-I trials performed with this compound within the program of the Early Clinical Trials Group of the EORTC. The results of the other trials have been published elsewhere [4, 6].

Materials and Methods

Patients included in the trial had histologically confirmed solid tumors and were no longer suitable for conventional therapy. Criteria for inclusion were age below 70 years, expected survival at least 6 weeks, and performance status (according to WHO criteria) 3 or below [8]. Hematological requirements for inclusion were WBC > 4,000/μl, platelets > 100,000/μl, and no antineoplastic medical therapy during the last 4 weeks, or the last 6 weeks for the nitrosoureas. Normal kidney function (serum creatinine < 120 μmol/l) and liver function (bilirubin < 17 μmol/l and normal prothrombin time) were mandatory. Informed consent was obtained according to the Helsinki declaration.

TGT was supplied by Asta-Werke AG, Bielefeld, West Germany in vials containing 100 mg of the drug as a dry substance. In the initial part of the study a dose of 480 mg/m² TGT was reconstituted at a concentration of 100 mg in 15 ml dextrose 5% (6.66 mg/kg). Because of difficulties in dissolving the drug, 100 mg was dissolved in 60 ml dextrose at doses of 640 mg/m² and above (1.66 mg/ml). The solution was filtered through a Sartorius SM 16527 filter as recommended by the

manufacturer to ensure sterility of the injected drug, and it was given as an infusion over no less than 30 min. At concentrations of 640 mg/m^2 and above the infusion time was from 2 to 4 h, as according to the manufacturer TGT was stable for at least 4 h.

The trial was initiated at a dose roughly corresponding to one tenth of the LD_{10} (mg/m^2) in mice [2, 5]. TGT was given as a single treatment repeated every 3–4 weeks. Doses were escalated with decreasing increments, and the patients were re-treated at higher dose levels when no toxic effects were observed in the previous course.

Before and during treatment the following examinations were performed weekly: Clinical examination, body weight, performance status, complete blood cell counts, serum creatinine, urea, prothrombin, bilirubin, alkaline phosphatase, lactic dehydrogenase, glutamic oxaloacetic transaminase, electrolytes, calcium, and glucose, and urinalysis. Every third to fourth week an ECG and a chest X-ray were performed. In patients with measurable disease, tumor response was assessed according to the WHO criteria [8].

Results

Thirty-seven patients were included. Their characteristics are shown in Table 1.

The starting dose of TGT was 30 mg/m^2 and doses were escalated up to 2,700 mg/m^2 (Table 2). Three to five patients and three to six courses were evaluated per dose level. The drug-induced side-effects are shown in Tables 2 and 3. The main dose-limiting toxic side-effect was local phlebitis, which usually developed at the injection site within a few days after drug administration and lasted for several weeks. The phlebitis started in most patients as an immediate local burning pain followed by thrombophlebitis. The phenomenon was first noted at a dose of 480 mg/m^2 in one of five courses. The frequency and severity of phlebitis seemed to increase with drug dose and was most pronounced in patients previously treated with the drug. In two patients, treated at the 2,100 and 2,400 mg/kg dose levels, local ulceration developed at the injection site, preceded by the formation of vesicles. It did not disappear with longer infusion times or lower drug concentrations. Shorter infusion times than 30 min were not possible due to the poor solubility of the drug and the large amount of fluids to be infused.

Leukopenia was first observed at the 1,800 mg/m^2 dose level, and it became more pronounced with increasing doses, resulting in life-threatening infections at doses of 2,400 and 2,700 mg/m^2. At 2,700 mg/m^2 one patient died due to pancytopenia with WBC 0.2×10^9/l and thrombocytes 13×10^9/l.

No cumulative hematologic toxicity was observed.

Other minor (not dose-limiting) toxic side-effects included nausea, vomiting, and alopecia. No liver, kidney, or cardiac toxicity was observed.

No clinical evidence of antitumor activity was observed.

Table 1. Patient characteristics

Total number entered	37
Men	19
Women	18
Age (years)	
Median	59
Range	29–69
Performance status	
Median	1
Range	0–3
Tumor type	
Lung	19
Ovary	5
Miscellanous	13
Previous treatment	
Chemotherapy	16
Chemotherapy and radiotherapy	13
Radiotherapy	3

Table 2. Drug-induced toxic effects

Dose (mg/m^2)	No. of patients/ courses	No. of patients previously treated with a lower dose level of TGT	No. of patients with toxic side-effects	No. of patients with			
				Leucopenia	Phlebitis	Nausea and vomiting	Alopecia
30	2/3	0	0	0	0	0	0
60	4/4	2	1	0	0	1	0
100	5/6	2	3	0	0	2	1
150	5/6	2	1	0	0	1	0
210	5/5	1	1	0	0	1	0
270	4/5	1	1	0	0	1	1
360	3/4	1	1	0	0	1	1
480	4/5	1	1	0	1	0	0
640	3/5	2	3	0	1	3	1
900	4/6	3	2	0	1	1	0
1,050	2/3	1	1	0	1	0	0
1,300	2/3	0	1	0	1	0	0
1,800	4/4	0	2	1	1	1	0
2,100	3/4	0	3	1	3	1	0
2,400	2/3	0	2	2	2	1	0
2,700	3/3	0	3	2	2	2	0

Table 3. Drug-induced myelosuppression at day 14 after TGT

Dose (mg/m^2)	WBC × $10^9/l$		Platelets × $10^9/l$	
	Median	Range	Median	Range
30	6.9	6.6– 7.3	491	455–527
60	7.8	6.6–10.5	366	165–544
100	7.0	5.7–10.2	310	199–406
150	7.0	5.3– 8.6	292	256–359
210	7.5	5.5– 9.6	273	205–535
270	6.1	4.9–12.5	291	248–926
360	7.8	6.9– 8.0	378	72–558
480	6.7	4.4–10.5	340	132–395
640	8.0	4.8–11.2	237	131–356
900	6.9	5.7–13.4	303	161–399
1,050	5.7	4.8– 5.9	342	301–383
1,300	6.2	4.8– 9.4	480	324–629
1,800	3.8	2.7– 9.3	234	93–407
2,100	5.5	1.3– 7.0	289	87–377
2,400	1.9	0.4– 3.8	99	11–138
2,700	0.7	0.2– 3.7	45	13–115

Discussion

In the present phase-I study of intermittent administration of α-TGT the dose-limiting factors were phlebitis and hematologic toxicity. The phlebitis was related to some degree to the dose and previous treatment with TGT. Longer infusion times or further dilution was not possible due to the relatively poor stability of the compound in solution. On the other hand, the present poor solubility did not permit a short infusion time. Hematologic toxicity was dose-related but inconsistent. The first sign of hematologic toxicity was leukopenia, observed at a dose level of 1,800 mg/m^2, while thrombocytopenia occurred at the higher dose levels used in the study. The other toxic effects observed in our study had minimal clinical significance.

The starting dose selected for the study was based on the LD_{10} in mice. From the data recorded in mice human toxicity might be expected to develop at a much lower dose level than 1,800 mg/m^2 [5]. It was thought that drug loss caused by filtration could explain this, but measurements showed that losses in the filters were less than 5% (G. Atassi, personal communication), which is also supported by kinetic data [6].

In another phase-I study using this compound Piccart et al. [6] observed that TGT given intermittently caused phlebitis at dose levels of 600 mg/m^2. At their highest dose level of 2,000 mg/m^2 all patients developed phlebitis, while the other side-effects were minor. Corticosteroids, heparin, and isoproterenol could not diminish these severe dose-limiting problems.

In conclusion, the present schedule and method of administration of TGT is unacceptable. The possibility of other formulations or PO preparations of the drug should be explored. Furthermore, the use of daily IV injections should be further tested; although Cavalli et al., in their study with daily injections for 5 days, also observed some phlebitis they found a more clearly dose-related hematologic toxicity [4].

New and more water-soluble triepoxide derivatives are at present being subjected to preclinical testing, so that there are posibilities for further clinical development of this interesting group of compounds.

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