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Phase I Trial of 1,2,4-Triglycidylurazol (TGU, NSC 332488): a New Triepoxide Cytostatic Agent

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Abstract—*1,2,4-Triglycidylurazol, a new triepoxide derivative, was chosen for phase I trial because of its favorable water solubility, stability and antitumor activity in murine systems. Fifty-seven patients were evaluable. Hematologic toxicity was dose-limiting, with a steep dose-toxicity curve. At* 650 mg/m² *2/10 patients developed grade II toxicity. Seventeen patients were treated at* 800 mg/m² *and seven developed grade III or IV toxicity according to WHO. Five of these patients had received >3 cytotoxic agents and/or extensive radiotherapy. One toxic death was seen. Cumulative toxicity was observed with respect to hematologic values in a comparison of the first and second courses. Sixteen patients developed phlebitis after injection, not dose-dependent and not dose-limiting. Response was noted in three patients, two non-small cell lung cancers and one bladder cancer. Recommended doses for phase II trials are* 800 mg/m² *q* 4 weeks *for patients who have received ⩽3 cytotoxic agents and* 650 mg/m² *q* 4 *weeks for heavily pretreated patients.*

INTRODUCTION

SINCE the introduction of cytostatic treatment, mono- and bifunctional alkylating agents have been used extensively in the treatment of hematologic malignancies and solid tumors. Alkylating agents containing more than two epoxide groups were not evaluated for clinical activity until recently, when high activity of this group of compounds was demonstrated in various experimental animal tumors, including P_{388}, L_{1210} leukemia, L_{5222} rat leukemia and B_{16} melanoma [1]. Of special interest is the observation that they also show significant activity in cyclophosphamide-resistant P_{388} leukemia in mice, suggesting a lack of cross-resistance with this class of alkylating agents [1].

The first triepoxide compound to undergo extensive animal screening with subsequent clinical phase I studies was α-1,3,5-triglycidyl-*s*-triazinetrione (NSC-296934, Henkel compound, TGT) [2, 3]. Pronounced and dose-limiting phlebitis was observed at the injection site and, due to relative instability in solution and poor water solubility of the compound, variations in the mode of application were not feasible. It was therefore recommended that further clinical trials be delayed until more water-soluble formulations of other triepoxide-derivatives were developed.

Among the latter the racemic compound 1,2,4-triglycidylurazol (TGU) NSC-332488 (Fig. 1) was selected for phase I trial, because its stability and water solubility were superior to those of TGT. Furthermore, TGU has a generally higher experimental antitumor activity than TGT at equitoxic doses, with a consistently higher proportion of long-term survivors in P_{388} and L_{1210} leukemia. Therefore a phase I study was instituted within the Early Clinical Trials Group of the EORTC in a joint study by the Department of Chemotherapy, Finsen Institute, Copenhagen, Denmark and by the Department of Clinical Oncology, Ospedale San Giovanni, Bellinzona, Switzerland.

MATERIALS AND METHODS

Criteria for admission of patients into the trial included that the patient should have histologically confirmed solid tumor, not amenable to

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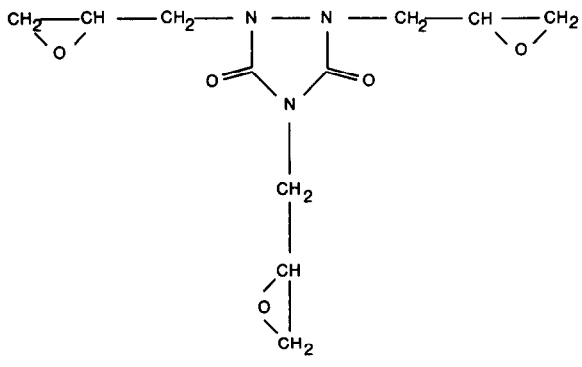

Fig. 1. Chemical structure of TGU.

known effective treatment, age below 75 yr, expected survival of at least 6 weeks, no anticancer treatment during the last 4 weeks (for nitrosoureas 6 weeks) and performance status according to WHO criteria below 3 [4]. Hematologic requirements consisted of WBC $\geq 4.0 \times 10^9/l$ and platelets $\geq 100 \times 10^9/l$. Furthermore, normal kidney and liver functions were required defined as serum creatinine < 120 μmol/l and/or Cr-EDTA-clearance of ≥ 60 ml/min/1.73 m² and *s*-bilirubin ≤ 17 μmol/l. Informed consent was obtined according to the Helsinki declaration.

TGU was supplied by ASTA-Werke AG, Bielefeld, F.R.G. in vials containing 100 mg TGU and 20 mg D-mannitol as lyophilized powder. The vials were stored refrigerated at 0-8°C before use. Before injection each vial was diluted in 5 ml sterile water. The drug was given as a push injection i.v. in 200 ml of dextrose 5% q 3 weeks. The starting dose in the trial of 30 mg/m² corresponded roughly to one-tenth of the LD_{10} (mg/m²) in mice. Doses of TGU were subsequently escalated with decreasing increments according to a modified Fibonacchii search scheme. It was planned to treat at least three patients on each non-toxic level, before the dose levels were escalated. At the toxic levels the number of patients were increased in order to discover whether prior treatment influenced the degree and the pattern of toxicity. A special dose level of 650 mg/m² was finally introduced when the results suggested that a lower dose level was needed for patients having received heavy prior treatment with chemotherapy and/or radiotherapy.

Before and during treatment the following examinations were performed weekly: clinical examination, serum (s)-creatinine, prothrombin, s-bilirubin, s-alkaline phosphatase, s-glutamic oxaloacetic transaminase, s-electrolytes, s-calcium, s-glucose and urinalysis. Complete blood cell counts were performed twice weekly during the first 6 weeks and then weekly while chest X-ray, electrocardiogram, performance status and body weight were performed evey 3 weeks. In patients with measurable or evaluable disease, tumor response was assessed according to the WHO criteria.

Table 1. Patient characteristics

No of patients entered	61
No. of patients excluded	4
Evaluable patients	57
Male	39
Female	18
Age (yr):	
median	55
range	29-72
Performance status:	
median	1
range	0-3
Tumor type:	
bronchogenic carcinoma	
epidermoid carcinoma	19
small cell carcinoma	5
adeno-carcinoma	10
large cell carcinoma	5
colon cancer	4
miscellaneous	14
Untreated	14
Previous treated:	43
chemotherapy	22
chemotherapy and radiotherapy	14
radiotherapy	7

RESULTS

Sixty-one patients entered the study, including 50 from Copenhagen and 11 from Bellinzona. Four patients died within the first 2 weeks after drug administration due to rapid tumor progression but without signs of toxicity. They were excluded from the analysis, leaving 57 evaluable patients. The characteristics of the patients are depicted in Table 1. It is noteworthy that 14 patients were untreated previously. Drug-induced side-effects consisted of phlebitis, gastrointestinal symptoms and hematologic toxicity (Tables 2 and 3). Local phlebitis was observed in 16 patients, occurring within 24 hr after injection. It was usually present directly at the site of injection but there were sometimes reactions along the veins on both the lower and upper arms. Discoloration of the veins, desquamation and local ulceration were observed in five patients. The phlebitis was observed at all dose levels. Gastrointestinal toxicity was clearly dose-related, with nausea and vomiting observed in the majority of the patients at the higher dose levels, usually of 6-8 hr duration.

No alopecia, kidney or cardiac toxicity was observed but in two patients treated at 1000 mg/m²

Table 2. Drug-induced non-hematologic toxicity

Dose (mg/m²)	No. of patients/ No. of courses	No. of patients with: phlebitis	nausea and/or vomiting	hepatotoxicity
30	3/6	1	0	0
60	3/2	0	0	0
90	6/22	1	2	0
140	3/5	0	1	0
250	3/11	1	3	0
350	3/3	2	2	0
450	4/15	2	4	0
600	3/9	1	3	0
650	10/18	1	10	0
800	17/33	4	17	0
1000	9/12	3	9	2

a transient elevation in s-GOT and alkaline phosphatase was observed 1 week after TGU injection with normalization of the values again after 2 weeks, suggesting reversible hepatic toxicity.

Dose-limiting toxicity of TGU was otherwise hematologic, observed first at 600 mg/m². It was clearly dose-related, being unacceptable at 1000 mg/m², at which dose level the median WBC $\times$ 10^9/l was 0.8 and the median value of thrombocytes 43 $\times$ 10^9/l. At 800 mg/m² 7/17 patients developed thrombocytopenia and/or leucopenia of grade III or IV according to WHO. One patient who had received prior radiotherapy and four cytostatic agents developed severe leucopenia of 0.6 $\times$ 10^9/l with septicemia. He expired in spite of the use of intensive antibiotic treatment. Further analysis of the toxicity revealed that the degree of toxicity was dependent on the amount of prior treatment the patient had received (Table 4). Only 2/9 patients who have received ≤ 3 cytostatic agents or only local radiotherapy developed hematologic toxicity grade III or IV, compared to 5/8 patients who had received >3 cytostatic agents and/or extensive radiotherapy.

Ten patients were treated at 650 mg/m² and seven of these had previously received >3 cytostatic agents and/or extensive radiotherapy. Only two patients had hematologic toxicity at this dose level. Both developed grade II toxicity and both were in the heavily pretreated group.

Cumulative hematologic side-effects were also observed among patients treated repeatedly at dose levels of 650 and 800 mg/m², with lower median values of both leucocytes and thrombocytes observed at the second course of TGU than in the first series (Figs 2 and 3). Only four patients have received more than two courses at 800 mg/m² and in two of these prolonged hematologic toxicity was seen. One patient had thrombocytopenia lasting 22 weeks, while the other had pancytopenia lasting 17 weeks. Bone marrow-aspiration, bone marrow culture in agar and chromosome analysis were performed, but no evidence of tumor infiltration of the bone marrow or preleukemia was observed. One patient died

Table 3. Hematologic toxicity secondary to TGU (NSC 332488)

Dose (mg/m²)	WBC $\times$ 10^9/l Median	Range	Platelets $\times$ 10^9/l Median	Range
30	9.0	5.8-15.1	325	190-359
60	6.7	6.2-7.3	318	383-354
90	6.8	4.7-10.2	307	180-478
140	9.1	4.9-10.3	188	185-370
250	6.3	3.4-12.5	344	258-447
350	8.2	4.7-11.3	180	111-265
450	4.9	3.5-5.5	186	145-511
600	3.6	2.8-4.9	268	168-274
650	6.0	2.3-7.5	289	77-696
800	2.3	0.4-9.0	100	13-295
1000	0.8	0.3-2.9	43	8-101

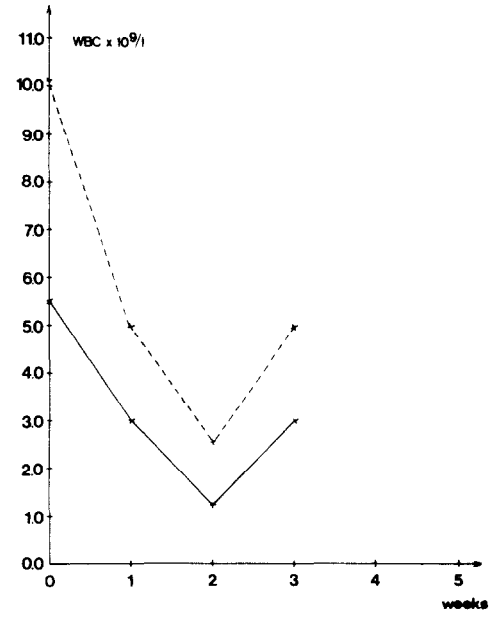

Fig. 2. WBC levels at 800 mg/m² with repeated TGU treatment, median values. – – – 17 patients, first series; —— 8 patients, second series.

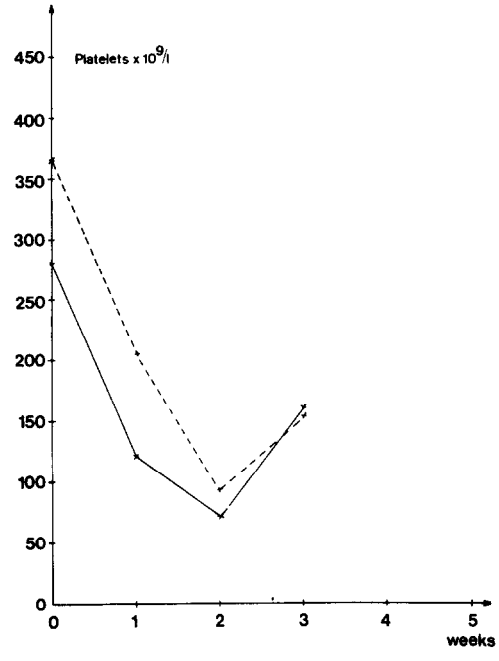

Fig. 3. Platelet levels at 800 mg/m² with repeated TGU treatment, median values. – – – 17 patients, first series; —— 8 patients, second series.

because of bleeding as a complication to pancytopenia. The other patient died due to tumor progression but the hematologic values had not returned to normal.

With respect to antineoplastic activity, tumor response was observed in three patients. Two of these had lung cancer of large cell and epidermoid carcinoma type. In one of these a total atelectasis of the left lung combined with pleural exudate cleared for a period of 2 months while in another patient an atelectasis of the inferior lobe on the right side was resolved for a period of 4 months. Both patients had re-evaluation of the primary tumor by fibro-bronchoscopy, and residual tumor masses were present. The third responding patient had a primary bladder cancer with biopsy-proven lymph node metastases at the neck and in the right axillary region. The lymph nodes decreased in size by more than 50% for a period of 4 months. The patient was still in partial remission when she died due to bleeding after prolonged pancytopenia (see above).

DISCUSSION

As suggested by the preclinical animal data, the hematological toxicity was also the dose-limiting factor in man. Leucopenia and thrombocytopenia occurred with nadirs 2 weeks after drug administration, usually with recovery to normal values after 4 weeks. The hematologic toxicity was clearly dose-related, with a relatively steep dose-toxicity curve. Our phase I study also suggests that cumulative hematological toxicity is characteristic for this compound, perhaps indicating that the hemopoietic stem cells in the marrow are severely damaged by this agent. Also of major clinical interest is the observation that the initial starting dose should be adjusted to the amount of prior therapy that the patients have received. Thus the recommended dosages in phase II trials for heavily pretreated patients are 650 vs 800 mg/m² i.v. q 4 weeks for less heavily pretreated or previously untreated patients. In addition to the hematologic toxicity, gastrointestinal toxicity with nausea and vomiting were observed in the majority of patients, while local phlebitis was seen in about one-third of all patients. It is conceivable that the use of isotonic NaCl instead of 5% dextrose as used in this study might decrease the tendency to local reactions [F. Stewart, personal communication].

The dose schedule in this trial tested an intermediate schedule given every 3–4 weeks, but also a 5-day schedule q 4 weeks has been tested in accordance with the preclinical data, showing that a slightly higher dose of TGU could be given with the fractionated dose schedule compared to the single-dose schedule in i.p. transplanted L_{1210} leukemia without losing therapeutic efficacy. However, preliminary clinical data do not indicate that this is the same under clinical conditions, and at present it appears that there is no advantage for the 5-day schedule as compared

Table 4. Hematologic toxicity of TGU according to prior treatment at 800 mg/m²

Toxicity WHO	No. of patients: No treatment WBC	No treatment Platelets	Local radiotherapy WBC	Local radiotherapy Platelets	Chemotherapy ≤3 drugs WBC	Chemotherapy ≤3 drugs Platelets	Chemotherapy >3 drugs WBC	Chemotherapy >3 drugs Platelets	Chemotherapy + radiotherapy WBC	Chemotherapy + radiotherapy Platelets
0	1	2	2	2	0	2	0	1	1	2
I	2	0	0	0	0	0	0	0	1	1
II	0	0	0	0	3	1	0	0	1	0
III	0	2	0	0	0	0	1	0	2	0
IV	1	0	0	0	0	0	1	1	1	3
Total No. of patients	4		2		3		2		6	

with the single schedule, with both schedules given every 4 weeks [5].

The clinical activity observed with this compound in a phase I trial is noteworthy and broad phase II trials within the ECTG have just been initiated. During these phase II trials it will not only be possible to retrieve information concerning the antitumor activity of the compound but also to get further information concerning the pharmacokinetic characteristics of the compound. A high-pressure liquid chromatographic method for the detection of TGU has been developed by Stewart *et al.* [6] and has shown that the plasma clearance of TGU in mice following the i.v. injection of a total dose of 6 mg per animal follows first-order kinetics with an initial half-life $t/2\alpha$ of 1.5 min and a $t/2\beta$ of 5 min. In addition, a new peak was detected on the TGU chromatogram, suggesting a metabolite as a result of hydrolytic degradation of the compound. Preliminary pharmacokinetic data from the human investigation also indicate a rapid, biexponential plasma decay, with a $t/2\alpha$ of 3.8 min and a $t/2\beta$ of 8.6 min [7].

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