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A Clinical and Pharmacokinetic Phase I Study of 1,2,4-Triglycidylurazol (TGU, NSC 332488)

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Abstract—*Twenty-six patients with advanced malignancies received TGU given as an intravenous (i.v.) bolus in physiological saline at* 3 *weekly intervals. The starting dose was* 30 mg/m^2 *with standard graded escalations to* 900 mg/m^2. *Myelosuppression occurred at* 800 mg/m^2, *with a mean nadir of* 2.0 ± 0.8 × 10^9/l *and a mean nadir platelet count of* 41 ± 31 × 10^9/l. *At* 800 *or* 900 mg/m^2 *nausea and vomiting was WHO grade* 0 *in* 5, *grade* I *in* 6, *grade* II *in* 11 *and grade* III *in* 10 *courses of therapy. Alopecia did not occur. TGU was given by i.v. infusion at* 800 mg/m^2 *in* 2 *patients, both of whom developed severe thrombophlebitis. Five patients given TGU by i.v. bolus developed mild phlebitis. No renal, hepatic or cardiac toxicity was noted. Two patients had partial responses; both had adenocarcinoma of unknown primary origin, one of whom had been resistant to prior therapy with FAM. An HPLC analytical method was developed with a sensitivity of* 250 ng/ml. *The data from* 7 *patients studied best fit a one compartment pharmacokinetic model with an exponential decay and a* $t_{\frac{1}{2}}$ *of only* 2.1 min.

In conclusion, the dose limiting toxicity of TGU appears to be myelosuppression and we would recommend a dose of 800 mg/m^2 *given as an intravenous bolus every* 4 weeks *for future phase* II *trials.*

INTRODUCTION

BIFUNCTIONAL alkylating drugs especially cyclophosphamide, chlorambucil and nitrogen mustard continue to be extensively used in the treatment of various cancers. The epoxides are recognised as effective alkylating agents, and it has been postulated that a tri-epoxide derivative might have measurably greater anti-cancer activity than either the mono, or the di-epoxide compounds such as treosulphan. Only within recent years has a stable tri-epoxide compound been prepared (TGT: 1,3,5 triglycidyl-s-trianzentrione) but formulation problems due to the drug's insolubility and instability resulted in local thrombophlebitis at injection sites and prevented the drug entering phase II trials [1,2]. This major pharmaceutical problem was resolved by re-synthesising the drug and developing TGU which is 1,2,4 triglycidyl urazol. In animal studies TGU was found to have activity in a wide variety of murine tumours, including cyclophosphamide-resistant leukaemia, which suggested that TGU might have clinically useful non-cross resistance with this class of alkylating agent [3]. The precise mechanism of action of TGU is unknown, but since it possesses epoxide groups it probably acts as an alkylating agent [3]. The LD_{50} and LD_{10} of TGU in mice were 80 mg/kg and 65 mg/kg. Therefore, the starting dose selected for this study was 30 mg/m^2 which is equivalent to approximately 10% of the LD_{10} dose.

The purpose of this study was to determine the maximum tolerated dose and dose limited toxicity of TGU in man, and to conduct a pharmacokinetic study of the drug.

PATIENTS AND METHODS

Patients

All patients had malignant disease for which no satisfactory, established treatment was available, or were refractory to conventional therapy. To be eligible for treatment with TGU patients had to fulfil the following criteria: life expectancy of at least 2 months, Karnofsky's performance status of 50% or better (ECOG 0,1,2,3), no chemotherapy or radiotherapy for at least 3 weeks prior to entry to the study (6 weeks for mitomycin-*c* and nitrosoureas), white cell count > 4 × 10^9/l, haemoglobin > 11 g/dl, platelets > 150,000 × 10^9/l,

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and normal hepatic and renal function. Informed consent was obtained from all patients.

Clinical monitoring

Prior to each course of TGU all patients had a full clinical examination, including documentation of relevant tumour masses. Also, the following estimations were performed: weekly full blood count and every 2 weeks serum urea, electrolytes, calcium, phosphate and uric acid were measured. Radiological investigations were performed as required.

Protocol for the administration of TGU

TGU is a white crystalline powder which was dissolved in 5 ml normal saline/100 mg drug and given as an i.v. bolus over 3–5 min. In the first two patients at 800 mg/m^2 because 40 ml of normal saline was required to dissolve the drug, it was administered by i.v. infusion over 15 min. This led to severe thrombophlebitis in both patients and we, therefore, reverted to the i.v. bolus technique. A starting dose of 30 mg/m^2 was selected and dose escalations of approximately 50% were proposed in the absence of significant toxicity. Treatment was repeated every 3–4 weeks and at least 2 patients were treated at each dose level.

Pharmacokinetic study

Venous blood samples were obtained at times zero, 5, 10, 15, 30 and 45 min, 1, 1½, 2, 3, 4, 6, 9, 12, 18, 24, 36 and 48 hr in 6 hourly aliquots. TGU was identified and measured in the plasma using high performance liquid chromatography (HPLC). The method has been described previously [4].

RESULTS

Twenty six patients (16 female, 10 male) with a mean age of 57.8 yr (range 34–74 yr) received 48 courses of TGU. All patients were evaluable for toxicity, but not all were evaluable for response to treatment (Table 1). Seventeen patients (65%) had previously received chemotherapy. Nine dose escalations were performed as follows: 30, 45, 75, 100, 150, 300, 400, 600, 800 and 900 mg/m^2. Two patients were treated at each escalation, up to and including 600 mg/m^2. Four patients underwent sequential dose escalations between 30 and 300 mg/m^2. A further four patients received one dose of TGU at 400 or 600 mg/m^2. Ten patients received chemotherapy at 800 mg/m^2 and 8 at 900 mg/m^2 and these 18 patients received a total of 32 courses of TGU.

Toxicity

No side effects of any kind were observed until 400 mg/m^2. At this dose, one patient with breast cancer who had received nine different cytotoxic drugs previously developed myelosuppression with a nadir white count of 1.9 × 10^9/l on day 15 after TGU which recovered by day 29. Her platelets remained in the normal range. At 600 mg/m^2 one of the two patients had a white count nadir of 2.5 on day 14 which recovered by day 28 after TGU. The platelets were normal. This patient had previously been treated with i.v. Treosulphan. Two patients, one at 400 mg/m^2 and one at 600 mg/m^2 had mild nausea and vomiting, WHO grade 2. The myelotoxicity for the patients who received TGU at a dose of 800 mg/m^2 and 900 mg/m^2 are summarised in Table 2. The haemoglobin concentration fell in 69% of patients; the pretreatment mean was 12.7 ±2 g/dl. Analysis of the influence of previous chemotherapy on the extent of myelosuppression is shown in Table 3. There did not appear to be any major differences between the different groups. Nausea and vomiting was grade 0 in 5, grade I in 6, grade II in 11 and grade III in 10. Mild thrombophlebitis was observed in five patients, but the two patients given TGU by i.v. infusion developed severe thrombophlebitis. In one patient extravasation of TGU led to severe tissue necrosis of the forearm. Alopecia did not occur and

Table 1. Site of primary tumour and category of assessable disease

Site of primary tumour	No. of patients	Category of assessable disease. No. of patients		
		Measurable	Evaluable	Non-evaluable
Colerectal	8	5	2	1
Adenocarcinoma of unknown primary origin	7	3	4	–
Breast	3	2	1	–
Ovary	4	2	1	1
Cervix	1	1	–	–
Lymphoma	1	1	–	–
Cholangiocarcinoma	1	1	–	–
Lung	1	1	–	–
Total	26	16	8	2

Table 2. White blood count and platelet count nadirs following TGU at 800 mg/m^2 *and* 900 mg/m^2 (32 *courses*)

Dose	WBC × 10^9/l		Nadir day		Recovery day	
	Median	Range	Mean	Range	Mean	Range
800 mg/m^2	2.3	0.7–7.6	17	10–24	35	21–62
900 mg/m^2	2.0	1.0–8.3	16	9–22	39	21–88
Dose	Platelet × 10^9/l		Nadir day		Recovery day	
	Medium	Range	Mean	Range	Mean	Range
800 mg/m^2	116	5 714	14	8–22	27	19– 41
900 mg/m^2	67	9–319	21	14–27	50	24–131

Table 3. Haematologic toxicity of TGU according to previous chemotherapy at 800 mg/m^2 *and* 900 mg/m^2 (32 *courses*)

Toxicity WHO	No previous treatment		Chemotherapy ≤ 3 drugs		Chemotherapy > 3 drugs		Radiotherapy	
	WCB	Platelets	WCB	Platelets	WCB	Platelets	WCB	Platelets
0	2	5	2	4	2	5	0	0
I	1	0	1	1	1	3	0	0
II	4	2	5	2	3	0	0	0
III	3	1	3	1	3	1	1	0
IV	0	2	1	4	0	0	0	1

there was no recorded liver or renal toxicity.

Pharmacokinetic study

Pharmacokinetics were performed on 7 patients given TGU at a dose of 800 mg/m^2 as an i.v. bolus. All patients had normal renal and hepatic function. The data best fits a one compartment model with an exponential decay and $t\frac{1}{2}$ of 2.1 min (Table 3 and Fig. 1). TGU was not found in any of the urine samples.

Response to TGU

Using standard WHO criteria [5] there were two partial responses. One was seen in a female patient with an adenocarcinoma of unknown primary origin. At laparotomy she had widespread intra-abdominal disease which was inoperable. She was initially treated with a combination of 5-fluorouracil, adriamycin and mitomycin-*c*, but did not respond. Before TGU she had a palpable mass measuring 10 × 10 cm and ascites which regressed completely after 3 pulses of TGU, but the ascites persisted. A further 2 pulses of TGU were given, but the mass recurred. The other response was seen in a man with adenocarcinoma of unknown primary origin who also presented with an abdominal mass. He had no prior chemotherapy. After 4 cycles of TGU there was a 50% reduction in the size of the tumour. The response lasted 4 months.

DISCUSSION

The dose limiting toxicity of TGU in this study occurred at 800 mg/m^2 and consisted of myelosuppression, which was reflected in all elements of the peripheral blood, but was particularly severe

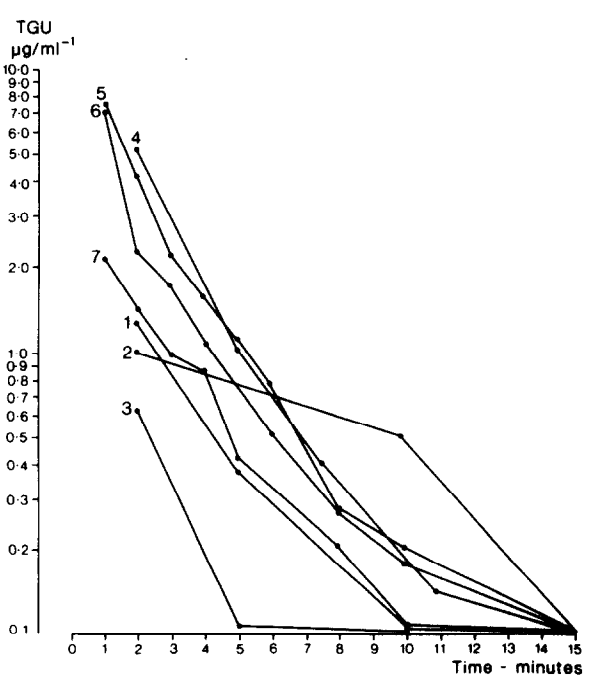

Fig. 1. Serum levels for 7 patients given TGU at a dose of 800 *mg/m^2.*

Table 4. Pharmacokinetic data for 7 patients treated at a dose of 800 mg/m^2 *TGU*

Patient	Sex	AUC (mg/ml × hr)	Clearance (ml/min)	Volume of distribution (litres)	$t_{\frac{1}{2}}$ (min)
1	F	7.26×10^{-5}	29384	847.2	2
2	F	4.796×10^{-5}	50046	1083.3	1.5
3	F	3.316×10^{-5}	65349	2828.99	3
4	F	1.959×10^{-4}	85091	196.7	1.6
5	F	2.642×10^{-4}	69391	190.45	1.9
6	M	2.025×10^{-4}	144848	460.25	2.2
7	M	1.073×10^{-4}	23609	817.6	2.4

with respect to leucopenia. Moreover, the time for full haematological recovery was often prolonged suggesting that this drug has the potential for cumulative myelosuppression if administered more frequently than every 4 weeks. The other toxicities of TGU consisted of nausea, vomiting and thrombophlebitis. At the higher dose levels the majority of patients experienced nausea and vomiting which, in general, was mild to moderate and usually responded to antiemetic therapy.

Thrombophlebitis was only a major problem in those 2 patients who received TGU as a short intravenous infusion. The thrombophlebitis which occurred when the drug was given by the intravenous bolus was mild and amounted to no more than superficial erythema. It is likely, therefore, that this is the most appropriate method for administration of the drug. Another important contributory factor to the development of thrombophlebitis appears to be the choice of solution for dissolving TGU. We used normal saline with apparent success, but others have used 5% dextrose which led to an increase in the incidence of thrombophlebitis, possibly by affecting the solubility of TGU, even when the drug was administered by an i.v. bolus technique [6]. Rozencweig *et al.* [7] have also completed a phase I study of TGU, giving the drug over 5 days and reported abolition of phlebitis when they converted from giving the drug as an i.v. infusion in 5% dextrose to an i.v. bolus in normal saline [7].

The clinical aspects of this study confirm those of a recently published phase I study of TGU [6]. One notable difference was that we did not encounter more severe myelosuppression in patients who had received previous chemotherapy. The cause for this is not clear. However, we would still consider it prudent to have a 25% dose modification for patients who have received previous chemotherapy in future phase II trials. The additional information in the current study on the pharmacokinetic profile of TGU, i.e. its rapid plasma clearance, coupled with the knowledge of myelosuppression as its dose limiting toxicity implies that this might be a useful agent to examine at high dose with autologous bone marrow rescue—especially if the drug is found to have significant anti-tumour activity in phase II clinical studies.

The anti-tumour activity exhibited by TGU in this phase I study is of interest and deserves further investigation. However, our results from a recently completed phase II study in small cell lung cancer were disappointing and showed virtually no activity of TGU in this tumour type [8]. Nevertheless, it is of interest that of the six responses so far reported, three were in-patients with adenocarcinoma of unknown primary origin [6,7] and it is possible that TGU should be examined in this tumour type rather than SCLC.

In conclusion, the toxicity and pharmacology of TGU is now being established and the recommended dose for phase II studies is 800 mg/m^2.

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