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Clinical Trials Summaries

Phase II Study of 1,2,4-Triglycidyl Urasol (TGU) in Advanced Soft Tissue Sarcoma. A Trial of the EORTC Soft Tissue and Bone Sarcoma Cooperative Group

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TGU (1,2,4-triglycidyl uracil urasol, Henkes SIS 43 410, NSC 332488) is a triepoxide derivative. Compounds containing numbers of epoxide groups have only recently been evaluated for their antitumor activity and were found to be highly active [1, 2]. The first triepoxide to undergo extensive animal screening and clinical phase I study was TGT. TGU was selected as a successor to TGT because of its advantageous physicochemical properties, in particular its stability and solubility as well as its improved therapeutic index in animal experiments.

The exact mechanism by which TGU and other triepoxides exert their cytotoxic activity is unknown. By analogy with bifunctional epoxides such as DAG, TGU probably acts as an alkylating agent.

On the basis of three phase I studies [3–5], the recommended dosage was 800 mg/m^2 i.v. every 4 weeks for patients without prior treatment by chemotherapy and 600 mg/m^2 for pretreated patients.

Patients included in this study had histologically proven soft tissue sarcoma resistant to standard chemotherapy and either progressive advanced local disease or metastatic disease. The ages of the patients was between 19 and 69 years (median 51). All had normal cardiac, liver and kidney functions and had not been treated in the previous 4 weeks. The drug was administrated at a dose of 600 mg/m^2 i.v. every 4 weeks. It was given as a bolus i.v. injection in 10 min into a running infusion of 5% glucose. The drug administration was postponed by 1 week if there was no full hematologic recovery (WBC $> 4 \times 10^9$/l, platelets $> 100 \times 10^9$/l).

The dose adjustments were made according to the lowest values observed on day 15 in a previous course and according to the treatment delay due to myelosuppression. The dose was increased to 120% if leucocytes remained above 4000 and if platelets remained above 100,000. The dose was reduced to 75% if leucocytes at nadir were between 1 and 2×10^9/l or platelets were between 50 and 75×10^9/l. The dose was reduced to 50% if leucocytes were less than 1×10^9/l and platelets less than 50×10^9/l. If treatment was delayed because of myelosuppression at scheduled retreatment, drug doses were reduced to 75% if not already indicated by the nadir value in the previous course.

Twenty-one patients were entered into the study from September 1984 to April 1985, one was not eligible because of his pathology: radiation-

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Other participants included: P. Lucas, Centre Jean Godinot, Reims, France and J. Verweij, Rotterdam Cancer Institute, The Netherlands.

Table 1.

	Evaluable patients	WHO grade 1	2	3
Phlebitis	16	2		5
Nausea/vomiting	16	3	7	3
Diarrhea	16	1	1	
Cutaneous	16	2		
Cadiotoxicity*	16	1		
Consciousness	16	1		
Alopecia	16		1	2
Local pain (on site of injection	19	5	2	

*Supraventriculartachycardia, probably drug-unrelated.

induced sarcoma. Another was not evaluable because of missing measurable lesions. Nineteen patients were fully evaluable.

There were nine males and 10 females. All had been pretreated with chemotherapy, i.e. one with one drug, three with two drugs and 15 with a number of drugs ranging from 3 to 5. Two patients had only locoregional disease, seven only distant metastases and 10 locoregional as well as distant lesions. The histopathology of the tumors was: malignant fibrous histiocytoma (4), synovial sarcoma (4), leiomyosarcoma (4), fibrosarcoma (3), neurofibrosarcoma (2) and liposarcoma and rhabdomyosarcoma both one. All histologies were extramurally reviewed by our central pathology panel.

The median number of courses given was two with a range of 1–8 courses. In these courses, a median of 99% of the prescribed doses was administered (range 85–108%).

There was progressive disease in 16/19 cases and three had no change (during 11, 13 and 38 weeks), so no objective response was observed. Non-hematological toxicity is presented in Table 1; the major toxicity was local phlebitis.

The hematological toxicities were: leucopenia, leucocyte nadir was less than 2000 in one case and less than 3000 in six (the day nadir after last course: median 15, range 8–22); thrombocytopenia, platelets nadir was less than 75,000 in five patients (day nadir after last course; median 16, range 14–23). It is worthy of note that only 10 patients received more than one course.

From the data presented, it can be concluded that TGU has no effect on advanced soft tissue sarcomas and cannot be recommended for further use in this disease.

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