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Phase II Study of 1,2,4-Triglycidylurazol (TGU) in Previously Untreated and Treated Patients With Small Cell Lung Cancer

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Abstract—*Six previously untreated poor prognosis patients and eight previously treated patients with small cell lung cancer (SCC) were treated with 1,2,4-triglycidylurazol (TGU, NSC-332488) 800 and 650 mg/m² every 4 weeks, respectively. No responses were observed. The survival time of the previously untreated patients was short, a median of 7 weeks (range 5–10 weeks). Myelosuppression was severe and prolonged with white blood count, WHO grade 3–4, in four previously untreated patients and in two previously patients, and with platelets, WHO grade 3–4, in both four previously untreated and in four previously treated patients. Gastrointestinal toxicity was mild to moderate. It is concluded that TGU is inactive in SCC.*

INTRODUCTION

PHASE II trials of chemotherapy sensitive tumors mainly or exclusively include patients with tumors resistant to conventional chemotherapy. Furthermore these patients are often characterized by other poor prognostic features such as low performance status, large tumor burdens and/or advanced disease. Since all these factors are related to lower response rates, conventional phase II trials imply a risk of overlooking an active agent. In fact, with tenoposide (VM-26) in small cell carcinoma of the lung (SCC), the response rates in patients previously treated with chemotherapy with or without etoposide (VP-16) were 5 and 25%, respectively, vs. 90% in previously untreated patients with good prognostic features [1, 2].

1,2,4-Triglycidylurazol (TGU, NSC-332488) is a triepoxide alkylating agent with high activity in animal tumor models [3]. In phase I studies the dose-limiting toxic effects were myelosuppression, dose-related gastrointestinal toxicity and local phlebitis of mild to moderate degree not related to the dose adminstered [4].

To minimize the risk of overlooking an active agent previously untreated patients with bone marrow metastases were included in a phase II study of TGU in patients with SCC. This was considered ethically acceptable, as the long-term prognosis in this group of patients is poor even with conventional chemotherapy [5].

MATERIALS AND METHODS

Previously untreated patients with biopsy-proven bone marrow metastasis at the time of diagnosis or patients with histologically proven SCC resistant to conventional combination chemotherapy were eligible. The patients had to have measurable or evaluable disease, Karnofsky performance status > 50, WBC count $\geq 4000/mm^3$, and platelet count $\geq 100{,}000/mm^3$ unless bone marrow involvement was documented. No prior chemotherapy during the previous 3 weeks (nitrosourea 6 weeks) and an unexpected survival exceeding 4 weeks was required.

Spoken informed consent was obtained from the patients.

Physical examination, chest X-ray, measurement of serum creatinine and bilirubin were performed at entry and every 4 weeks thereafter. Complete blood cell count, SGOT/SGPT and alkaline phosphatase were performed weekly for the first 8 weeks, thereafter every second week.

TGU was supplied by ASTA-Werke, F.R.G. as a lyophilized powder with 20 mg *d*-mannitol per 100 mg of the drug. It was reconstituted in water and given as a single push injection in 200 ml of isotonic saline.

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The starting dose was 800 mg/m^2 for patients previously untreated or patients who had received less than three cytostatic agents, and 650 mg/m^2 for patients previously treated with more than three cytostatic agents or extensive radiotherapy.

Treatment was given every 4 weeks if full hematological recovery had taken place, otherwise the treatment was postponed 1 week. Dose adjustments were made according to WBC and platelet nadirs. No hematological toxicity (WHO grade 0) required dose escalation by 20%. For grade 2 and 3 toxicities dose reduction to 75% and 50%, respectively, had to be made.

Response and toxicity evaluation was assessed according to WHO criteria [6]. Prior-treated patients had to receive at least two courses of treatment in order to be evaluable. Treatment was continued until objective evidence of disease progression or unacceptable toxicity occured. Prior untreated patients with no response after the first course or with partial response after three courses had the treatment changed to combination chemotherapy usually consisting of vincristine, cyclofosfamide, nitrosourea, and etoposide. If complete remission was obtained, combination chemotherapy might be initiated after a reevaluation.

Table 1. *Patient characteristics*

No. of patients included	19
No. of patients eligible	16
No. of patients prior treated/untreated	10/6
No. of patients evaluable for response	8/6
Median age (years)	62 (48–68)
Median performance status (Karnofsky)	80 (50–90)

Table 2. *Hematological toxicity of TGU*

	WHO grade				
	0	1	2	3	4
WBC × 10^9/l					
Prior untreated	0	1	1	2	2
Prior treated	3	4	1	1	1
Total	3	5	2	3	3
Platelets × 10^9/l					
Prior untreated	1	0	1	2	2
Prior treated	4	1	1	1	3
Total	5	1	2	3	5

RESULTS

Nineteen patients were initially selected for treatment. Three of these were excluded: one patient was lost to follow up, one did not have evaluable/measurable disease and one patient had an early death. Among the 16 eligible patients, 10 patients had already received from five to nine cytostatic agents while six previously untreated patients all had bone marrow metastases.

Of the previously treated patients, the response of two could not be evaluated, one due to the lack of supply of TGU and one patient with stable disease, who was incorrectly assessed as having progressive disease with subsequent change to combination chemotherapy after the first course. One patient could not be evaluated for toxicity in the first course. Of the previously untreated patients two could not be evaluated for toxicity in the second course.

Further details concerning patients' characteristics are listed in Table 1.

Among the six previously untreated patients two had progressive disease during the first treatment course and the remaining four progressed during the second course of TGU. The median survival of these six patients was 7 weeks (range 5–10 weeks). The performance status of the latter six patients after progression on TGU became so poor, that only one of these was fit to receive combination chemotherapy. This patient died within 14 days. Of the eight previously treated patients evaluable for response, five had tumor progression during the first course of TGU while the remaining three progressed after two courses of TGU. These patients received no further treatment. Their median survival was 7 weeks (range 6–45 weeks).

The hematological toxicity was severe and prolonged especially in the group of patients with bone marrow metastases (Table 2). No toxic deaths due to infection or bleeding were observed, but five patients died with thrombocytopenia of a duration from 2 to 7 weeks.

All patients experienced mild to moderate gastrointestinal toxicity. Only one case of moderate phlebitis was observed.

DISCUSSION

Effective first line treatment is available for patients with SCC but further therapeutic improvement is urgently needed, including identification of new active agents. The latter can only be tested up-front in previously untreated patients with a poor long-term prognosis on conventional therapy. This strategy gives the ability to discover an otherwise overlooked agent in phase II trials, particularly with regard to response rates, as has been documented for SCC with e.g. tenoposide and carboplatin (JM-8) [2, 7].

TGU showed, however, no responses in 14 evaluable patients with SCC, even though the agent was used as first line treatment in six of these patients. Furthermore, the median survival of these six pati-

ents was only 7 weeks, compared to 30 weeks in patients with bone marrow metastases treated with combination chemotherapy as first line treatment [5]. The number of patients is too small to conclude that the present strategy shortened their survival. However, it is important to consider for planning future phase II studies that if poor prognosis untreated patients are treated with an inactive agent they may die within one or two courses of treatment and will not be exposed to chemotherapy regimens with proven efficacy.

Cunningham *et al.* have also performed a phase II study of TGU in 14 patients with SCC. This study also showed that TGU is inactive in patients with SCC, even though two of the patients were previously untreated. Their survival time is not mentioned [8].

The hematological toxicity, especially thrombocytopenia, was severe and prolonged in the group of patients with bone marrow metastases. This might either be caused by the presence of bone marrow metastases or TGU *per se*, or a combination of these factors. Cunningham *et al.* have also reported prolonged thrombocytopenia with TGU [9].

The conclusion, therefore, is that TGU has no activity against SCC and that the strategy of inclusion of untreated poor prognosis patients in phase II trials must be further elucidated before being generally accepted.

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