Eur J Cancer Clin Oncol, Vol. 22, No. 6, pp. 697–699, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Primary Resistance of Renal Adenocarcinoma to 1,2,4-Triglycidylurazol (TGU, NSC 332488), a New Triexpoxide Cytostatic Agent — A Phase II Study of the EORTC Early Clinical Trials Group

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Abstract—*Fourteen patients with metastatic renal adenocarcinoma without prior chemotherapy were treated with* 1,2,4-*triglycidylurazol* (*TGU, NSC*-332488), *a new triepoxide alkylating agent. TGU was chosen for this study among other triepoxides because of its high antitumour activity in animal models, its relatively good water solubility and the expected favourable therapeutic index. The starting dose was* 800 mg/m^2 *i.v.* (600 mg/m^2 *for patients with prior extensive radiotherapy*) *every* 4 weeks. *No objective tumour regression was seen in this favourable group of patients. Leuko- and thrombocytopenia were the most important side-effects. Severe cumulative and prolonged thrombocytopenia was seen. Other toxicities observed were nausea with or without vomiting in all patients and local phlebitis in some.*

INTRODUCTION

A LARGE number of chemotherapeutic agents has been tested in metastatic renal adenocarcinoma, as summarized in several reviews [1–5]. Among these agents vinblastin appears to be the most active drug. Reviewing the literature Hrushesky and Murphy [2] thus found 33 reported responses among 135 patients: a 25% response rate. For all other agents tested in a sufficient number of evaluable patients the quoted reviews reveal response rates below 10%. Progesterone and other hormonal agents were also claimed to be active but subsequent studies have demonstrated their ineffectiveness [2,5]. 1,2,4-Triglycidylurazol (TGU, NSC-332488) is a triepoxide alkylating antitumour agent developed by Asta-Werke, West Germany (Fig. 1). It was found active in a number of murine tumours, including a cyclophosphamide resistant P 388 strain, B16 melanoma and the s.c. implanted colon 38 tumour in mice. TGU was selected for clinical screening among other triepoxides for this activity in animal models, its expected favourable therapeutic index and its relatively good water solubility [6–8].

Two phase I studies were performed by the Early Clinical Trials Group of the EORTC and by Soukop *et al.* using a single dose schedule very 3–4 weeks [9,10]. In another study a fractionated schedule over 5 days every 4 weeks was used [11]. Myelosuppression was dose limiting, with a steep dose-toxicity curve. Other toxicities included local phlebitis as well as nausea and vomiting in most patients. Partial remissions were observed in two patients with 'non small cell' carcinoma of the lung, one bladder cancer [9] and in one adenocarcinoma of unknown origin [10].

MATERIALS AND METHODS

Ten members of the Early Clinical Trials Group participated in this trial. The lowest limit of interest for clinical activity was set at a response rate of 20%. Therefore 14 patients were to be entered in the first stage and further patients were only to be included if objective responses were documented among these 14 patients. This procedure ensures — with an error below 5% — that the drug is rejected if its activity is below 20%.

Accepted 2 December 1985.
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Patients were informed about the experimental nature of the drug and were free to withdraw from the study at any time. Criteria for eligibility included histologically confirmed renal adenocarcinoma with progression during the previous two months, lesions measurable in at least one diameter, performance status < 3 according to the WHO-scale, a life expectancy greater than 3 months, and normal renal, liver, and bone marrow functions. No prior chemotherapy was allowed.

TGU was supplied by Asta-Werke, Germany, as a lyophilized powder with 20 mg D-mannitol per 100 mg of the drug. It was reconstituted in water and given as a short i.v. infusion (5 min) in 200 ml of 5% glucose. The starting dose was 800 mg/m^2 for patients without prior extensive radiotherapy and 600 mg/m^2 for this latter group. Treatment was to be repeated every 4 weeks if full hematological recovery had taken place, otherwise it was to be postponed by 1 week. Dose adjustments were made according to WBC and platelet nadirs. With no hematological toxicity (WHO grade 0) dose escalation by 20% was planned. For grade 2 and 3 toxicities dose reductions to 75% and 50% respectively, had to be made.

Response was assessed according to the WHO criteria [12]. The treatment protocol required at least 2 courses of therapy for the patient to be evaluable. Patients who fulfilled the criteria of progressive disease after one treatment cycle — i.e. the occurrence of new lesions or an increase of > 25% in the size of at least one lesion — were classified as 'early progression'.

RESULTS

Starting in March 1984, 18 patients were entered within 12 months. One patient was ineligible because of prior chemotherapy and was excluded from further analysis. Three patients were considered unevaluable for the following reasons: death within 3 weeks due to malignant disease without signs of drug toxicity (1 patient), development of symptoms from unrecognized brain metastases (1 patient), development of renal insufficiency unrelated to treatment (1 patient).

The characteristics of the 14 patients are given in Table 1. Twelve patients started treatment on the full dose of 800 mg/m^2, while two patients received only 600 mg/m^2 because of prior radiotherapy to the primary tumour area. Dose escalation for the second cycle was possible in only one patient, whereas four patients needed dose reductions. None of the 14 evaluable patients showed an objective response to TGU therapy. Two patients had no change of their lung metastases after three and four cycles, respectively. The latter one had shown some response after two cycles but criteria for partial remission were never met and the disease progressed thereafter. The other 12 patients had progressive disease. One patient showed a more than 50% increase of the volume of his skin metastases within 4 weeks, another patient rapidly developed a new lung lesion.

Table 1. Characteristics of evaluable patients

Number of evaluable patients		14
Male/female		10/4
Age (years)	median	55
	range	(27–69)
WHO performance status	0	4
	1	6
	2	4
Prior chemotherapy		0
Extensive prior radiotherapy		2
Indicator lesions		
lung		11
lymph nodes		3
others		4

TOXICITY

As expected from phase I data myelosuppression was the most important toxicity [9–11]. Nadir values for leukocytes and thrombocytes as well as length of myelosuppression are given in Table 2. Considering all 32 treatment cycles given, WHO grade 3 or 4 leukopenia was seen in eight courses and grade 3 or 4 thrombocytopenia during four courses. In two instances protocol violations occurred and drug doses were not reduced after low nadir values. Both patients developed severe and prolonged thrombocytopenia for more than 6 and 12 weeks, respectively. As the protocol requested

Table 2. Toxicity of TGU treatment

		WBC (× 10^3)	platelets (× 10^3)
Nadir 1. cycle —	median	2.2	167
	range	(1.3–6.6)	(32–489)
Day of 1. nadir —	mean	16	17
	range	(7–23)	(8–30)
Time to recovery —	mean	23	26
	range	(19–30)	(22–29)
Nadir all cycles —	median	2.0	114
	range	(0.8–3.0)	(11–115)
Nausea and vomiting WHO	grade	0	0 pts.
	grade	1	3 pts.
	grade	2	8 pts.
	grade	3	3 pts.

dose adjustment on the basis of hematological toxicity interpretation of the data is difficult but apparently rather marked cumulative platelet toxicity can occur when TGU is given every 4 weeks.

Nonhematological toxicity was generally mild but a number of patients developed severe thrombophlebitis of the infused veins. This apparently was not dose related. The exact incidence cannot be given as central venous lines were used for an unknown number of courses. Acute gastrointestinal toxicity was observed in all patients. Table 2 presents the most severe episode recorded during each patient's treatment. Again the intensity of this side effect is probably underestimated as antiemetics were usually given in subsequent courses.

DISCUSSION

In 14 evaluable patients with renal adenocarcinoma who had not received any prior chemotherapy no therapeutic response to TGU, a new triepoxide alkylating agent, was observed. Selection of patients was favourable for an early phase II study (Table 1). Also, as 11 of the 14 patients had measurable lung metastases, evaluation of response was not a problem. The starting dose chosen also seemed appropriate as hematological toxicity allowed dose escalation in only one patient whereas four patients had required dose reductions for the second treatment cycle.

In conclusion, TGU given at the maximal tolerable dose every 4 weeks, is ineffective in renal cell adenocarcinoma.

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