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Phase II Trial of Anaxirone (1,2,4-Triglycidylurazol, TGU) in Patients with Advanced Ovarian Carcinoma: an EORTC Gynecological Cancer Cooperative Group Study

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Abstract—*Sixteen patients with advanced ovarian carcinoma were treated with anaxirone (1,2,4-trigycidyl urazol, TGU), 600 mg/m² every 4 weeks. Anaxirone was the second or later line of therapy. All patients had evaluable tumors and evidence of failure of prior therapy. None of the patients responded. Two had stabilization of the disease for 4 months. In one patient WHO grade 4 leukopenia and grade 4 thrombocytopenia were observed after the second TGU cycle starting on day 41 and persisted until the patient died due to tumor progression (day 50). No patient experienced thrombophlebitis.*

INTRODUCTION

ANAXIRONE (1,2,4-triglycidylurazol, TGU) is a triepoxide alkylating anticancer agent. The activity of TGU was investigated by Atassi and Dumont [1] in a series of murine tumors. It was found to be active against L1210, L5222 and P388 leukemia as well as s.c. implanted colon 38 tumor and B_{16} melanoma. In the B_{16} melanoma they found a 98% increase in life span of mice inoculated with 2×10^6 cells i.p. on day 0 and treated with 12.5 mg/kg i.p. daily on days 1–9 [2]. Phase I clinical trial was undertaken by Early Clinical Trials Group of EORTC using either single dose schedule q 3–4 weeks or the daily × 5 q 3–4 weeks schedule. The dose-limiting toxicity at a MTD of 1000 mg was hematologic. Leucopenia and thrombocytopenia occurred with the nadir 10–12 days after drug administration, and recovery usually within 4 weeks. Further toxicity noted included local phlebitis and skin rash [3, 4].

The recommended dosage for phase II trials based on the phase I trials is 800 mg/m² i.v. every 4 weeks for patients with or without minimal treatment with chemotherapy and 600 mg/m² for pretreated patients. During the phase I studies partial responses were seen in four patients out of a total of 95 treated patients. Two patients had carcinoma of the lung (one large cell and the other squamous cell carcinoma) [2] and two patients had adenocarcinoma of unknown origin [5, 6].

This study was undertaken to determine if partial or complete responses can be achieved with TGU in advanced ovarian cancer and to further characterize the toxic effects of TGU in this group of patients.

MATERIALS AND METHODS

Six institutions of the EORTC Gynecological Cooperative Group participated in this trial. Patients with histologically confirmed advanced ovarian cancer were treated between January 1985 and January 1986. Eligibility criteria included the following:

—histologically verified ovarian carcinoma originating from the epithelial surface of the ovary according to the WHO classification [7],

—measurable or evaluable disease outside previously irradiated areas, and documented progression,

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—age < 75 yrs,
—WHO performance status < 3,
—no prior chemotherapy with nitrosoureas or mitomycin C,
—no prior radiotherapy, hormone therapy or chemotherapy within 4 weeks of start of protocol treatment and unresolved toxic manifestations of prior treatment.

At start of treatment:

- White blood cells (WBC): > 4000/mm^3
- Platelets (PLTS): > 100,000/mm^3
- Bilirubin: < 1.5 mg/dl (or < 26 mol/l.)
- Creatinine (SCr): < 1.5 gm/dl (or <132 mol/l.) and/or
- Creatinine clearance (CrCl): > 60 ml/min/1.73^2.

Because patients had been treated with multidrug chemotherapy regimens before they entered the present study, TGU was given in a dose of 600 mg/m^2 by bolus injection within 5 min into the tube of a running infusion of 200 ml of isotonic saline. The rest of the saline was given after the TGU injection in order to flush the needle properly. The tube was attached to a butterfly needle inserted into a large vein.

The dose was repeated at 28-day intervals.

TGU was supplied by Asta Werke, F.R.G. in vials containing 100 mg TGU and 20 mg D-mannitol as a sterile pyrogen-free lyophilized powder. Prior to use the drug was diluted in 5 ml sterile water for each vial.

Response was assessed according to the WHO criteria [7].

Drug administration was postponed by 1 week if there was no full hematologic recovery (WBC > 4000, platelets > 100,000) from the prior course at scheduled retreatment. The treatment could be postponed for 3 weeks; if there was still not full hematologic recovery the treatment was stopped.

Dosage adjustments were made according to the lowest value of WBC and platelets measured on days 8, 15, 22 in the previous course and according to treatment delay due to myelosuppression. Dosage adjustments due to other toxic effects were not anticipated.

A total of at least two courses had be given unless this was clearly not in the best interest of the patient, e.g. where there was a *rapid* progressive disease 4 weeks after the first treament cycle. These patients were considered as failures.

RESULTS

Seventeen patients were registered in the study. Due to one inevaluable case (lost to follow up), 16 patients are included in the analysis. The characteristics of the patients at entry are described in Table 1.

Five patients received one course, six received two courses, three received three courses and two received four courses.

Table 1. Patient characteristics

Number of patients	16
Age (years)	
Median	61
Range	30–69
Performance status:	
0	6
1	7
2	3
Prior therapy:	
Radiotherapy	4
Chemotherapy	16
Median number of regimen	2
Range	(1–4)
Histological type:	
Serous	4
Mucinous	4
Adenocarcinoma	4
Undifferentiated	3
Endometrioid	1

Table 2. Side effects

Nausea, vomiting:	
Grade 1	3 patients
Grade 2	8 patients
Grade 3	5 patients
Diarrhea:	
Grade 1	2 patients
Alopecia:	
Grade 1	2 patients

One patient had dose reduction while the rest received full doses and two had their treatment postponed for 2 weeks due to myelosuppression.

No dose escalations were undertaken.

No responses were seen. Two patients had stable disease for 4 months and 14 patients had progressive disease within 4–21 weeks (four early progression). The median white blood counts and platelet nadirs were 2300/mm^3 (600–3800) and 60,000/mm^3 (11,000–206,000).

In one patient WHO grade 4 leukopenia and grade 4 thrombocytopenia were observed after the second TGU cycle, starting on day 41 and persisting until the patient died due to tumor progression (day 50). During that period bleeding (grade 3) and infection (grade 2) occurred. Other toxicities are described in Table 2.

In contrast to other reports, none of our patients experienced phlebitis.

DISCUSSION

This trial failed to show any activity of TGU as

second (or more) line therapy in patients with advanced ovarian carcinoma. Toxicity was mild in general but prolonged and delayed myelosuppression was observed in one patient, supporting the data of other groups studying the same drug [8]. Toxicity was not negligible, with prolonged and delayed myelosuppression.

We therefore conclude that TGU has no activity in heavily pretreated patients with ovarian adenocarcinoma.

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