Eur J Cancer Clin Oncol, Vol. 17, No. 12, pp. 1263–1266, 1981.
Printed in Great Britain.

0277-5379/81/121263-04$02.00/0
Pergamon Press Ltd.

Phase I Clinical Trial with Alpha 1,3,5-Triglycidyl-*s*-Triazinetrione (NSC-296934)*

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Abstract—1,3,5-*Triglycidyl-s-triazinetrione is a triepoxide derivative with attractive antitumor properties in mice. In this phase I trial, the drug was given as an i.v. infusion over 30 + min repeated every 2–3 weeks. The trial was initiated at a starting dose of 33 mg/m² and doses were escalated up to 2,000 mg/m². Local thrombophlebitis was dose-limiting and apparently dose-related. Other toxic effects were mild to moderate and consisted of nausea, vomiting, leukopenia and hair loss. More favorable formulations or schedules of administration are needed before testing this new agent in phase II trials.*

INTRODUCTION

1,3,5-TRIGLYCIDYL-*s*-TRIAZINETRIONE (TGT) is a new chemotherapeutic agent that was originally synthetized by Budnowski [1]. Its chemical structure is shown in Fig. 1. This triepoxide derivative appears to act through DNA cross-linking [2].

The α stereoisomer, which is 20 times more soluble than the β species, shows striking anticancer potential in experimental murine tumors [3]. αTGT is effective against P388 leukemia and against early and advanced L1210 leukemia; it also exerts moderate activity against intracerebrally implanted L1210. When given orally against i.v. or ascitic L1210 the drug retains significant efficacy at optimal doses that are 2.5–6 times higher than with the intraperitoneal route. In the Lewis lung carcinoma the drug noticeably inhibits the growth of the primary tumor and that of lung metastases. Pronounced schedule dependency may be demonstrated in the L1210 system with daily doses for 5 or 9 consecutive days, achieving increases in life span of greater than 600%, whereas single doses on day 1, days 1 and 9, or days 1, 5 and 9 produce increases in life span ranging from 87 to 153%. Also of interest, marked activity was found against a P388 cell line made resistant to cyclophosphamide.

The pharmacokinetics of the drug were determined in mice, using a gas–liquid chromatography assay [4]. Initial data indicated that, following single i.v. administration, the plasma disappearance curve was biphasic, with a terminal half-life of less than 2 min.

The rationale for introducing αTGT into clinical trials was based on its special chemical structure, its attractive anticancer properties in mice and the suggested lack of cross-resistance with cyclophosphamide. Our phase I study aimed at defining the maximum tolerated dose

Accepted 17 July 1981.
*This work was supported in part by grant No. 3.4535.79 of the "Fonds de la Recherche Scientifique Médicale" (FRMS-Belgium), and by contract NIH NOl/CM 53840 from the National Cancer Institute (Bethesda-Maryland).
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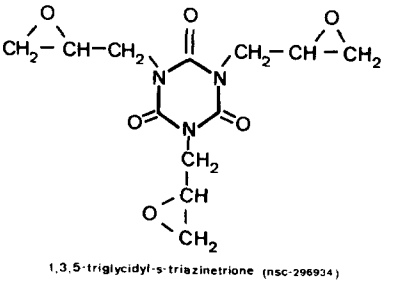

Fig. 1.

for single intermittent treatments. This study was undertaken as part of the new drug program of the Early Clinical Trials Group of the EORTC.

MATERIALS AND METHODS

All patients selected for this trial had histologically confirmed solid malignancies no longer suitable for conventional therapy. They had completely recovered from major toxic effects induced by prior treatments. All patients had white blood cell counts (WBC) of at least 4000/mm^3, platelet counts of 100,000/mm^3 or more, and maximum serum creatinine and bilirubin levels of 1.5 mg%. Expected survival upon entry into the trial was longer than 6 weeks.

Eighteen patients were treated with αTGT (Table 1). Among these there were 10 men and 8 women, aged between 34 and 73 years with a median of 62, with performance status on the Karnofsky scale ranging from 30 to 90 with a median of 60. Most patients had head and neck cancer, malignant melanoma or non-small cell carcinoma of the lung. All had received prior chemotherapy and a majority of patients had also been previously treated with radiotherapy.

The drug was supplied by Asta-Werke AG, Bielefeld, West Germany in vials containing 100 mg of αTGT as a dry substance. It was reconstituted with dextrose 5% for injection at a maximum concentration of 6.66 mg/ml. During the trial decreasing concentrations were used down to 1.66 mg/ml. Even at this lowest concentration, dissolution was very slow and required prolonged agitation of the preparation.

Table 1. *Patient characteristics*

Total number entered	18
Men : women	10 : 8
Age	
Median	62
Range	34–73
Performance status	
Median	60
Range	30–90
Primary tumors	
Head & neck	6
Melanoma	4
Lung (non-small cell)	3
Lung (small cell)	1
Breast	1
Vulva	1
Brain	1
Unknown	1
Previous treatment	
Chemotherapy only	5
Chemo- and radiotherapy	13

The drug was administered i.v. in no less that 30 min through filtration kit Satorius SM 16527. This filtration procedure was recommended by the manufacturer to ensure the sterility of the injected product. According to the manufacturer, αTGT was stable in dextrose 5% for at least 4 hr. αTGT was given as a single treatment repeated every 2–3 weeks. The trial was initiated at a dose corresponding to 1/10 of the LD_{10} (mg/m^2) in mice [4, 5]. Doses were escalated with decreasing increments. Patients were retreated at higher dose levels when no significant toxic effects were encountered in previous courses.

Three complete blood cell counts and one SMA12 chemistry panel were scheduled per week. In patients with measureable disease, tumor response was assessed according to conventional response criteria [6].

RESULTS

The starting dose was 33 mg/m^2 and doses were escalated up to 2000 mg/m^2 (Table 2). Two to five patients and 3–6 courses were evaluated per dose level. Ten patients received one course only, 7 patients received 2–4 courses and 1 patient received 7 courses for a total of 37 courses of αTGT. The dose-limiting factor was local thrombophlebitis, which usually became apparent at the injection site within a few days after drug administration and could develop regionally thereafter. This phenomenon was first noted at a dose of 600 mg/m^2 in 2 out of 3 patients. Its severity seemed to increase with higher dosages and it could not be reduced with smaller drug concentrations down to 1.66 mg/ml or a 2-hr post-hydration program to rinse the injected veins. At the highest dose levels αTGT was administered over 2–3 hr; two patients received the drug as a 24-hr continuous infusion. There was no clear relationship between duration of infusion and extent of phlebitis. Shorter infusions were not given because of the poor solubility of the drug and the large amount of fluids to be infused. Concomitant heparine, corticoids and/or isoproterenol did not prevent thrombophlebitis either.

Other toxic effects included nausea, vomiting, leukopenia and loss of hair. Mild to moderate gastrointestinal intolerance was seen at the initial dose level and inconsistently thereafter. Four patients experienced leukopenia. At the level of 130 mg/m^2, one patient had 3900 WBC/mm^3 in one course and 2000 WBC/mm^3 in his subsequent and last

Table 2. Drug-induced toxic effects

Dose (mg/m^2)	No. of patients/ No. of courses	No. of toxic patients	No. of patients with: Phlebitis	N & V	Leucopenia	Loss of hair
33	2/3	1	—	1	—	—
66	3/4	1	—	1	—	—
130	5/6	1	—	—	1	—
260	3/3	1	—	—	—	1
400	3/3	2	—	—	—	2
600	3/3	3	2	2	—	—
900	5/5	5	5	3	1	—
1350	4/5	4	4	3	—	—
2000	5/5	5	5	4	2	—

course. At 2000 mg/mm^2, two patients had very transient leukopenia with WBC nadirs of 1600 and 2900 respectively. Three patients had minimal loss of hair. Finally, there was one brief episode of minor, questionably drug-related, elevation of the serum creatinine level. No other toxic effects were identified.

Patients were also monitored to detect possible disease regression. There was no clinical evidence of antitumor activity in this trial.

DISCUSSION

In this phase I trial using single or intermittent administrations of αTGT, thrombophlebitis at the injection site was dose-limiting and, apparently, dose-related. Thrombophlebitis is not unusual with chemotherapy [7–10]: it may occasionally become dose-limiting, but it is generally circumvented by appropriate dilutions and infusion times. With αTGT there is little room left to modify these parameters because of the poor solubility of the drug and its probable short stability in solution. In addition to conventional measures we also investigated the effect of isoproterenol, which had been reported to prevent adriamycin-induced soft tissue necrosis in animals [11]. None of these manipulations appeared to clearly affect the occurrence of local problems produced by αTGT.

Overall, besides drug-induced thrombophlebitis, αTGT was remarkably well tolerated. Other toxic effects encountered in this trial had minimal clinical significance. In most cases vomiting was probably conditioned by prior cytotoxic therapy. Leukopenia was inconsistently found, conceivably in relation to large variations in performance status and extent of prior treatment in the population selected for this trial.

The starting dose in this study was based on 1/10 of the LD_{10} (mg/m^2) in mice and doses were escalated by 3 increments of 100% followed by increments of 50% for a total of 8 escalation steps. Based on past experience in phase I trials a recommendable dose for phase II trials should be reached for 95% of the drugs after such dose escalations [5], which was clearly not the case for αTGT. This puzzling observation was unlikely to result from drug loss, although crystals of undissolved drug might have been stopped in the filtration kit and drug degradation might possibly occur during prolonged drug preparation and administration.

A limited pharmacokinetic study of αTGT was conducted in our patients. Using a gas–liquid chromatography assay [4], preliminary studies revealed plasma concentrations of about 1 μg/ml during infusions of αTGT at doses of 2000 mg/m^2. Such drug levels showed that significant amounts of drug had been actually received. As reported in mice, the drug seemed to clear almost immediately from the plasma. These interim results must be interpreted with caution and firm conclusions on the pharmacokinetics of αTGT in humans must still await additional investigations.

Initial results in a soft agar clonogenic assay indicated that αTGT may achieve growth inhibition of freshly sampled human cancer cells [12]. No hints of antitumor activity could be documented in this clinical trial. However, all patients had far-advanced disease previously treated with at least one chemotherapy regimen. Moreover, in this expectedly refractory population few patients received adequate treatment with αTGT, as evidenced by the lack of major toxic effects other than thrombophlebitis. At the beginning of the trial doses were rapidly escalated within the same patients to allow most of these to receive the drug at potentially therapeutic dosages. Troubles at the injection site occurring subsequently account for the fact that, overall, a majority of patients received only one course of αTGT.

In conclusion, the method of drug administration selected for this study is clearly inadequate. Other formulations and possibly oral preparations should be explored. Fractionated daily i.v. administrations might also yield more favorable findings in man [13], in accordance to the schedule dependency demonstrated in animal models [3]. Finally, the Screening and Pharmacology Group of the EORTC has identified, in preclinical systems, new TGT derivatives that are more water-soluble than the parent compound and that deserve special consideration for further testing.

Acknowledgement—The authors acknowledge the secretarial help of Mrs G. Decoster in the preparation of this manuscript.

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