Eur J Cancer Clin Oncol, Vol. 23, No. 8, pp. 1207–1208, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

Clinical Trials Summaries

Phase II Evaluation of *Trans*-$N_3P_3Az_2(NHMe)_4$ (AZP) in Non-small Cell Lung Cancer

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Abstract—Trans-$N_3P_3Az_2(NHMe)_4$ (*AZP*), *an aziridinyl substituted cyclophosphazene, was evaluated in a phase II study in non-small cell lung cancer at a dose of* 33 mg/m^2 *i.v. bolus every* 3 *weeks. There were no tumor responses seen. Cumulative bone marrow toxicity, comparable to other cyclophosphazenes, was noted. AZP is not useful for the treatment of NSCLC.*

INTRODUCTION

Trans-$N_3P_3Az_2(NHMe)_4$ (AZP) is one of the aziridinyl substituted cyclophosphazenes. This group of agents has a wide spectrum of activity both *in vitro* and *in vivo* [1, 2].

In preclinical studies AZP showed activity against L1210, B16 melanoma, mouse osteosarcoma and human small cell lung cancer cell lines. Its mode of action was thought to be the production of interstrand DNA cross-links [3].

In a phase I study [4] cumulative bone marrow suppression was seen at doses of $\geq$ 50 mg/m^2. In 2 out of 8 patients with non-small cell lung cancer (NSCLC) a partial response was seen. The recommended dose for phase II studies was 33 mg/m^2 every 3 weeks.

PATIENTS AND METHODS

Fourteen patients (2 ♀, 12 ♂) with NSCLC were entered in the study. Patient characteristics are given in Table 1. Entry criteria included: histologically proven NSCLC, no previous chemotherapy, no curative radio- or surgical therapy possible, performance status (ECOG) < 3, measurable or evaluable disease outside previously irradiated areas, age < 75 years, serum creatinine levels < 120 μmol/l, informed consent.

Table 1. *Patient characteristics*

2♂ 12♀ Age median 60 years range 41–71
Histology: 10 squamous cell 4 large cell
Performance status ECOG
0 $n = 2$
1 $n = 8$
2 $n = 3$
3 $n = 1$
Site of disease:
only intrathoracic ± supraclavicular nodes 6
distant metastases 8
Prior surgery 4
Prior radiotherapy 2
Number of cycles
2 $n = 3$
3 $n = 6$
> 5 $n = 5$

AZP was administered at a dose of 33 mg/m^2 as an i.v. bolus infusion at 3 week intervals. Chemotherapy was postponed to a maximum of 6 week intervals, if at the day of the planned treatment leucocytes were $< 3.5 \times 10^9$/l or platelets $< 100 \times 10^9$/l. If recovery was not reached within that period the patient went off study.

All patients were evaluated for response after 2 courses. Complete response was defined as total disappearance of tumor for at least 4 weeks. A partial response was defined as a decrease of > 50% of the product of two perpendicular diameters for

Accepted 17 March 1987.
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Table 2. Toxicity (WHO grading [5])

	Grade 1	Grade 2	Grade 4
Nausea/vomiting	5	1	
Leucocytopenia			
Cycle 1 (n = 14)	1	—	
Cycle 2 (n = 14)	1	—	
Cycle 5 (n = 5)	1	—	
Cycle 6 (n = 2)	—	—	
Cycle 7 (n = 1)	1	—	
Thrombocytopenia			
Cycle 4 (n = 5)	1		
Cycle 5 (n = 5)	1	1	1
Cycle 6 (n = 2)	—	1	—

measurable lesions or a > 75% decrease of one diameter for evaluable lesions. Stable disease (SD) is a decrease of < 50% or increase of < 25% (for evaluable lesions < 75%, respectively, < 25%). Progressive disease (PD) was defined as occurrence of new tumor lesions or an increase of measurable lesions of > 25%.

RESULTS

Toxicity (*Table* 2) (*WHO-grading* [5])

Extra-medullary toxicity was mild. In 6 patients (43%) mild nausea was seen.

Bone marrow toxicity was minimal during the first 4 cycles. In 5 patients at least 5 courses were given; during the 5th cycle in 3 patients bone marrow toxicity was seen (grades 1, 2 and 4). In 1 patient bone marrow toxicity after 6 courses was the reason for stopping treatment.

Tumor response

There were no responses seen in this group of patients. After 2 courses 11 patients had SD, 6 of these patients had PD after 3 courses. Of the remaining 5 patients 3 had PD after 5 courses and 1 after 7 courses. In one patient treatment had to be stopped due to toxicity while the patient still had SD.

DISCUSSION

The observed activity of AZP against NSCLC during phase I evaluation [4] was not confirmed in this study. Overall toxicity was minimal but in the patients receiving 5 or more courses a tendency to cumulative bone marrow toxicity was noted as was seen with other aziridinyl substituted cyclophosphazenes [6]. In this study, however, this toxicity was reversible. It is our conclusion that AZP in this schedule is not useful in the treatment of NSCLC.

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