Eur J Cancer Clin Oncol, Vol. 21, No. 12, pp. 1557–1559, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Letter to the Editor

Phase II of ACNU for Non-small Cell Lung Cancer*

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ACNU (1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (Fig. 1), a water-soluble nitrosourea derivative, has been highly effective against L1210 leukemia [1, 2]. The results of an *in vitro* study of ACNU revealed the possibility that the drug is taken up into cells rapidly to exert its antitumor effect through alkylation of DNA and carbamoylation of proteins [3]. According to the report by the ACNU Phase I Study Group in Japan, the clinical maximal tolerable dose of ACNU was determined to be 100 mg/m^2 [4]. The total acceptable dose of ACNU was 300–600 mg, and the desirable interval between doses was 6–8 weeks. A preliminary broad phase II study showed ACNU to be effective against small cell lung cancer (SCLC), brain tumors, Hodgkin's disease and chronic myelocytic leukemia [5, 6]. However, the role of ACNU in the treatment of non-small cell lung cancer (NSCLC) has not yet been determined. In this study we report the results of a clinical phase II study of ACNU in 30 patients with NSCLC.

Thirty patients with NSCLC were entered into this study, and 21 patients were evaluable for tumor response against ACNU. The characteristics of the patients are summarized in Table 1. Sixteen patients with NSCLC received prior chemotherapy. No patient with NSCLC received prior chemotherapy with nitrosourea derivatives. Five patients with NSCLC were treated with radiotherapy previously. However, no patient received radiation therapy against the target tumor in this study. The median age of patients was 59 yr. The median performance status was 2 (range, 0–3). The diagnosis was confirmed by histology and/or cytology in every case. All patients had adequate

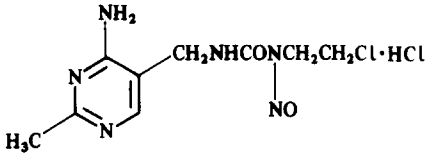

Fig. 1. Chemical structure of ACNU.

bone marrow, as examined by a white blood cell (WBC) count greater than 3000/mm^3 and a platelet count greater than 100,000/mm^3. Eligibility criteria included measurable lesions, a performance status ≦ 3, total bilirubin < 3 mg/dl, and glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) < 100 U/ml. All patients had a minimum interval of at least 4 weeks after prior chemotherapy. Informed consent was obtained from all patients and/or their

*Table 1. Characteristics of lung cancer patients treated with ACNU**

Characteristic	
Entered	30
Evaluable	21
Age in years	
Median	59
Range	31–74
Male:female	15:6
Performance status†	
0–1	6
2	6
3	9
Prior chemotherapy	
Yes	16
No	5
Prior radiotherapy	
Yes	5
No	16
Total dose of ACNU (mg)	
Median	180
Range	120–600
Stage	
III M_0	4
III M_1	17

*Unless otherwise indicated, values = No. of patients.
†Eastern Cooperative Oncology Group (ECOG) criteria.

Accepted 15 July 1985.
*This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health and Welfare and from the Comprehensive 10-year Strategy for Cancer Control.
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Table 2. Antitumor effect of ACNU against non-small cell lung cancer

Histology	No. of entered patients	No. of evaluable patients	Clinical response				
			CR	PR	MR	NC	PD
Adenocarcinoma	17	11				10	1
Squamous cell carcinoma	13	10				8	2
Total	30	21	0	0	0	18	3

families prior to initiation of therapy. ACNU was given intravenously at a dose of 67–100 mg/m^2 every 4–6 weeks, and the total dose of ACNU was 120–600 mg (median, 180 mg). The patients who received more than 100 mg/m^2 of ACNU in total dose were considered to be evaluable. Five patients could not receive ACNU at a total dose of more than 100 mg/m^2. Response to treatment was defined according to the standard criteria of WHO.

Twenty-one of 30 patients with NSCLC were evaluable for antitumor effects. Five patients were unevaluable because of the inappropriate dose of ACNU. Two patients had no measurable tumor. Two patients died within 4 weeks after initiation of ACNU administration. As shown in Table 2, no patient showed a complete, partial or minor response. No change was observed in ten patients with adenocarcinoma of the lung and eight patients with squamous cell carcinoma of the lung. Progressive disease was observed in one patient with adenocarcinoma of the lung and in two patients with squamous cell carcinoma of the lung. The toxic effects of ACNU are summarized in Table 3. The toxicities were evaluable in 23 patients with NSCLC. Leukocytopenia of less than 4000/mm^3 occurred in 12 of the 23 toxic-effect-evaluable patients (nadir, 41 ± 8 day). Four patients (17%) developed severe leukocytopenia of less than 2000/mm^3. Thrombocytopenia of less than 100,000/mm^3 occurred in 20 of the 23 toxic-effect-evaluable patients (nadir, 32 ± 6 day). Seven patients (30%) developed severe thrombocytopenia of less than 30,000/mm^3. Myelosuppression, especially thrombocytopenia, appears to be a dose-limiting factor. Elevation of serum GOT and GPT was observed in two of the 23 patients (9%). However, these hepatic disorders were mild and transient.

The present study failed to show any activity of ACNU against 21 evaluable patients with NSCLC. In National Cancer Center Hospital in Japan, the response rates for anticancer drugs against NSCLC were 18.9% (10/53) for mitomycin C, 0% (0/19) for adriamycin, 3.1% (1/31) for tegafur, 14.3% (3/21) for vindesine, 14.3% (6/42) for cisplatin, 0% (0/15) for 5′-DFUR and 0% (0/9) for MCNU [7–9]. Therefore the antitumor activity of ACNU against NSCLC is less than those of cisplatin, mitomycin C and vindesine. In addition, none of 14 adenocarcinoma patients without prior chemotherapy who were treated with ACNU (100 mg/m^2, every 5–6 weeks) and ftoraful (1000–1500 mg every day) experienced tumor regression (unpublished data). Concerning toxic effects, moderate-to-severe leukocytopenia and thrombocytopenia were frequently observed, the nadirs being 41 ± 8 and 32 ± 6 days after the initiation of chemotherapy, respectively. In conclusion, ACNU is not warranted for the treatment of NSCLC as one compartment of combination chemotherapy or single-agent chemotherapy, because of delayed severe myelosuppression and no antitumor activity.

Table 3. Toxicities of ACNU

Toxicity*	
Leukocytopenia: No. of patients with leukocytes/mm^3:	
Less than 1000	0
1000–2000	4
2000–3000	3
3000–4000	5
Total (%)	12 (52%)
Nadir†	41 ± 8
Thrombocytopenia: No. of patients with thrombocytes × 10^3/mm^3:	
Less than 10	4
10–30	3
30–50	2
50–70	6
70–100	5
Total (%)	20 (87%)
Nadir†	32 ± 6
Elevation of serum GOT and GPT	2 (9%)
Nausea	9 (39%)
Vomiting	8 (35%)
General fatigue	2 (9%)

*Toxicity was evaluable in 23 patients.
†Nadirs are expressed as days (mean ± S.D.) from start of ACNU administration.

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