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Short communication

Phase II study of ACNU as second-line treatment in small-cell lung cancer*

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Summary. A total of 24 patients presenting with small-cell lung cancer either resistant to or relapsing within 3 months after first-line treatment were entered in a phase II study of 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU). ACNU was given i.v. at a dose of 75 mg/m^2 every 6 weeks. We observed a partial response of 7 months' duration in one patient and one case of stable disease that lasted for 6 months; all other subjects exhibited progressive disease. Two patients developed brain metastases during treatment. The toxicity of ACNU consisted mainly of bone marrow suppression, especially thrombocytopenia. At this dose and on this schedule, ACNU shows minimal activity as second-line treatment in small-cell lung cancer.

Introduction

ACNU [1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-(2-chloroethyl)-3-nitrosourea hydrochloride] is a water- and lipid-soluble nitrosourea derivative that was developed by Arakawa et al. in 1974 [1]. As an alkylating agent, it shows activity against transplanted human xenografts of GxF1 gastric cancer, MX1 breast cancer, and CO4 colon cancer in nude mice [7]. Pharmacology studies in humans demonstrated a plasma half-life of 35 min following i.v. administration. The drug is excreted via the bile and urine. In a phase I study performed in Japan [2], the dose-limiting toxicities consisted of granulocytopenia and thrombocytopenia; other toxicities observed included nausea, vomiting, and anorexia. Based on the results of this phase I study, a dose of 100 mg/m^2 given at intervals of 6–8 weeks was recommended.

The experience with ACNU in small-cell lung cancer is limited. In a phase II study conducted by Saijo and Niitani [6], 14 of 30 patients responded, whereas in a study carried out by the Swiss Group for Clinical Cancer Research (SAKK) in heavily pretreated patients, 3 of 34 subjects showed a partial response [3]. The Lung Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) decided to perform a phase II study in patients presenting with small-cell lung cancer that either was resistant to "standard" first-line treatment or progressed within 3 months after the cessation of first- or second-line chemotherapy.

Patients and methods

To be eligible in this study, patients were required to have histologically proven locally advanced or metastatic small-cell lung cancer and to exhibit measurable or evaluable lesions, documented disease progression following first-line chemotherapy or relapse within 3 months after the cessation of first- or second-line therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better, an age of <70 years, a WBC of >4.0 × 10^9/l, a platelet count of >100 × 10^9/l, creatinine clearance of >40 ml/min, and a serum bilirubin value of <2.5 mg/dl. All patients underwent a chest X-ray and, when indicated, a chest and/or abdominal computer-assisted tomography (CT) scan before the start of treatment. In all cases, full blood counts and estimations of renal and liver-function tests were obtained. During treatment, estimations of hemoglobin, WBC, and platelet counts were done weekly and liver and renal functions were evaluated every 6 weeks.

ACNU was given as a slow i.v. infusion at a dose of 75 mg/m^2 every 6 weeks. In case of bone marrow suppression, retreatment was delayed until hematologic recovery; a dose reduction of 25% was carried out in

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Table 1. Patients' characteristics and treatment results

Number of patients entered	24
Male : female	22 : 2
Median age (years)	61 (range, 47–68)
Median WHO performance status	1 (range, 0–2)
Limited disease	4
Distant metastases	20
Median number of courses given	1 (range, 1–4)
Nonevaluable patients	1
Evaluable patients	23
Responses:	
Complete response	0
Partial response	1
Stable disease	1
Progressive disease	21

patients exhibiting a WBC nadir of 1.0–2.0 × 10^9/l and/or a platelet nadir of 50–75 × 10^9/l. In subjects displaying a WBC nadir of <1.0 × 10^9/l and/or a platelet nadir of <50 × 10^9/l, the dose was reduced to 50% of the previous level. The response to treatment was assessed after every cycle. Response and toxicity criteria were applied according to WHO recommendations [8]; responses were reviewed extramurally.

Results

A total of 24 patients were entered in this study; their characteristics are summarized in Table 1. In all, 23 subjects were fully evaluable for response and toxicity; 1 death of unknown cause occurred on day 3 after the first ACNU administration. All patients were pretreated with EORTC "standard" first-line treatment consisting of Adriamycin, cyclophosphamide, and etoposide; two additional individuals also received ifosfamide and carboplatin as second-line treatment but had been accepted in this study because they were resistant to this treatment. None of the patients was pretreated with a nitrosourea derivative. Overall, 30 courses of ACNU were given, and the number was 1 course/patient (range, 1–4).

We observed a partial response by lung and bone metastases that lasted for 7 months in one subject (therapy had to be discontinued after 4 courses due to long-lasting bone marrow suppression) and stable disease that lasted for 6 months in a patient exhibiting local recurrence and bone metastases. All other patients displayed progressive disease. Two subjects developed brain metastases during treatment. The toxicity produced by this regimen was mild. The median leukocyte nadir was 4.6 × 10^9/l (range, 1.5–9.1 × 10^9/l), with only one patient developing grade 3 leukopenia. The platelet nadir was 84 × 10^9/l (range, 9–319 × 10^9/l), with two subjects developing grade 3 thrombocytopenia and three experiencing grade 4 toxicity. No patient required a platelet transfusion. WBC nadirs occurred at week 4 and platelet nadirs, at week 5, resulting in delays in the treatment of 3 of 5 subjects who advanced to a second or third course. Other toxicities observed were nausea and vomiting (grade 3 in four patients) and stomatitis (grade 1 in one individual).

Discussion

Although small-cell lung cancer is highly responsive to up-front chemotherapy, most patients unfortunately experience a relapse. In cases that relapse at >3 months after the completion of first-line treatment, a response can often be reinduced using the same regimen [5]. The outlook for patients whose disease either fails to respond to first-line treatment or relapses shortly after the cessation of such therapy is dismal. Such individuals are often offered investigational drugs. In the present study we treated refractory patients with ACNU in an attempt to confirm the positive results obtained by Japanese [6] and Swiss groups [3].

We observed only 1 partial response in 23 patients (response rate, 4%; 95% confidence limits 0–25%) and only 1 case of a stable disease. Saijo and Niitani [6] observed responses in 14 of 30 subjects (response rate, 46%; 95% confidence limits, 27%–64%) who had been given 101.8 mg/m^2 ACNU in combination with vincristine. The pretreatment status of these patients was not reported. In the SAKK study [3], ACNU was given as second-line therapy to 39 subjects, most of whom had been pretreated with >3 other cytostatics and 11 of whom had undergone pretreatment with other nitrosoureas. Of 34 evaluable patients, 3 achieved a partial response (response rate, 9%; 95% confidence limits, 2%–24%); this result is not significantly different from that obtained in the present study.

In the Japanese and SAKK investigations, a dose of 100 mg/m^2 was given as compared with the 75 mg/m^2 used in our study. The reason for this lower dose was the considerable hematologic toxicity we had encountered in pretreated patients in a previous trial of ACNU in non-small-cell lung cancer [4]. Because of this toxicity, we did not consider dose escalation in this poor-prognosis patient group. The high median nadir counts recorded for leukocytes and platelets in the present study may indicate that our dose of 75 mg/m^2 was too conservative. Two patients developed brain metastases during treatment despite the suggestion that ACNU might cross the blood-brain barrier and is thus likely to prevent the development of brain metastases. Toxicity was mainly hematologic. We have to conclude from these results that ACNU given at this dose and on this schedule is inactive against refractory small-cell lung cancer.

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