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Phase II Trial of Prednimustine (NSC-134087) in the Treatment of Small-cell Anaplastic Carcinoma of the Lung

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Summary. *In a phase II trial, the clinical activity of prednimustine, an ester of chlorambucil and prednisolone, was evaluated in 28 patients with small-cell anaplastic carcinoma of the lung. Prednimustine was given at dose levels ranging from 130 to 220 mg/m²/daily for 5 days every 3 weeks.*

Among 19 previously treated patients no responses were observed, while responses of 2, 2, and 3 months' duration were seen in three of nine previously untreated patients more than 70 years old. The toxicity took the form of mental disturbanes in six patients, while the hematologic toxicity was mild.

The therapeutic effectiveness of prednimustine in small-cell carcinoma of the lung is thus limited although some activity is observed in previously untreated patients.

Introduction

Prednimustine, an ester of prednisolone and chlorambucil, was synthesized so that the steroid molecule could be used as a carrier across the cellular membrane of tumor cells for the purpose of obtaining a higher antineoplastic effect with lower general toxicity [8].

Early clinical studies have shown activity against various types of leukemia [1–3] and non-Hodgkin lymphomas [9, 12]. Modest activity of prednimustine has been observed in bronchogenic carcinoma [4, 6], melanoma [6], ovarian cancer [10, 11], prostatic cancer [5], and carcinoma of the breast [13].

In previous trials in which patients with bronchogenic carcinoma were treated with prednimustine, the number of patients was limited. Catane et al. [4] saw no responses in two patients with small-cell carcinoma treated with 40 mg PO daily, and the EORTC Screening Co-operative Group treated 13 patients with carcinoma of the lung that was not subtyped, and recorded only one response [6].

The present phase II study was therefore undertaken to evaluate the effect of prednimustine in patients with small-cell anaplastic bronchogenic carcinoma.

Materials and Methods

All patients had histologically verified small-cell carcinoma of the lung. Pretreatment requirements consisted of white blood cell counts (WBC) $\geq 4{,}000/mm^3$ and platelet counts $\geq 100{,}000/mm^3$, unless lower counts were disease-related owing to bone-marrow infiltration by tumor cells demonstrated by bone-marrow examination. Furthermore, normal serum creatinine was required, and signs of systemic infections, diabetes mellitus, active tuberculosis, hypertension, or uncompensated heart disease constituted grounds for exclusion.

Chest roentgenograms and clinical evaluation including hematologic and biochemical parameters and blood-pressure measurements were performed at least every 3 weeks.

All patients included had measurable or evaluable disease as evidenced by chest X-ray and/or physical examination. Furthermore, informed consent from the patient was mandatory.

No other cytotoxic treatment or radiotherapy was administrated for at least 2 weeks, and for the nitrosoureas 6 weeks, prior to entry in the study.

Prednimustine[1] was administered as tablets of 20 and 100 mg with a starting dose of 130 mg/m²/daily PO for 5 days repeated every 3 weeks. As the hematologic and gastrointestinal toxicity was modest in the first patients, the dose was increased to 170 mg/m²/day, and subsequently to 220 mg/m²/day. A minimum of one course, consisting of 5 days' treatment followed by a 3-week observation period, was necessary for evaluation.

The hematologic toxicity was graded as follows: grade 0, no signs of change in WBC and/or platelets; grade 1, WBC between 2,000 and $4{,}000/mm^3$ and/or platelet count between 75,000 and $100{,}000/mm^3$; grade 2, WBC $\leq 2{,}000/mm^3$ and/or platelet count less than $75{,}000/mm^3$.

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1 Prednimustine (LEO 1031) was kindly supplied by AB LEO, Helsingborg, Sweden

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If hematologic toxicity occurred the prednimustine dose was modified as follows in the next series: grade 0, no change in drug dose; grade 1, 50% reduction of drug dose; grade 2, delay of treatment until recovery of hematologic values.

Partial response was defined as a decrease by more than 50% in the product of two perpendicular diameters of well-outlined lesions. Unequivocally marked changes of nonmeasurable, but evaluable chest roentgenographic lesions were also recorded as an objective response in the absence of progressive disease or the occurrence of new lesions elsewhere. When progression of disease was noted, defined as at least 25% increase in measurable diesease or the appearance of new lesions, treatment was discontinued.

Results

Thirty-two patients received prednimustine from September 1977 to December 1978. The median performance status was 60 (range 40–100). Eighteen patients had advanced and 14 patients had localized disease. Four patients were excluded because of death within the first 5 days of treatment, thus not having a full course of prednimustine. Of the evaluable patients, 5 were females and 23 males, with a median age of 65 years (range 39–76).

Nineteen patients had previously been treated with combination chemotherapy, including adriamycin, CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), cyclophosphamide, methotrexate, vincristine, and VP-16-213 (4′demethylepipodophyllotoxin 9-(4,6-0-ethylidene-β-D-glucopyranoside). Nine patients aged over 70 years were previously untreated. No patient had received irradiation to the primary tumor or the mediastinum.

Fifteen patients were treated with prednimustine at a dose of 130 mg/m^2, nine with 170 mg/m^2, and four with 220 mg/m^2 prednimustine PO daily for 5 days every 3 weeks. The median number of treatment cycles was 2 (range 1–7).

Partial responses of 2, 2, and 3 months' duration were observed in three previously untreated patients, two treated with the 130 mg/m^2 dose level and one with the 220 mg/m^2 level.

Of the 25 patients who did not respond to treatment, 14 had progressive disease within the first 3 weeks, and received only one course of prednimustine. Eleven patients had stable disease for a median of four cycles (2–7), followed by progression.

The hematologic toxicity was modest. A nadir WBC of 1,800/mm^3 was seen in two patients treated with 220 mg/m^2 and in two patients treated with 130 mg/m^2. Thrombocytopenia below 100,000/mm^3 was seen in six patients. The lowest platelet counts were 48,000/mm^3 and 30,000/mm^3, observed at the 130 and 170 mg/m^2 dose levels. Hemoglobin values below 7 mmol/liter (114 g/liter) were noted in six patients. No cases of sepsis or clinical bleeding were observed.

There was no record of any gastrointestinal disturbances, alopecia, diabetes mellitus, or hypertension in any patient. Mental disturbances occurred in six patients, with a median age of 69 years (range 57–76). The mental changes were observed in two of fifteen and two of four patients treated with 130 and 220 mg/m^2, respectively. The symptoms developed within the first 3–4 days of treatment, subsided within 1 week after discontinuation of treatment, and recurred when prednimustine was restarted. The mental disturbances consisted of hallucinations in three cases, and in four of less specific excitability, sleep disturbances and hypomania.

Discussion

In the present study, three of 28 patients (11%; 5% confidence limits 2%–28%) with small-cell carcinoma responded to treatment with prednimustine. The responses were of short duration and were observed only in three of nine previously untreated patients more than 70 years old, resulting in a response rate of 33%, which is equal to that for other alkylating agents [7].

In this study, we were unable to reproduce the findings of sensitivity to prednimustine in tumors otherwise resistant to alkylating agents. The findings in patients with breast cancer of activity of prednimustine after progression during therapy with alkylating agents has thus not been confirmed in small-cell carcinoma [13].

In this study with intermittent prednimustine treatment, the hematologic toxicity was very low in comparison with studies in which continuous treatment has been evaluated [13].

However, a major problem in the present study was the mental changes, including overt psychosis. These disturbances were provoked within a few days of the start of prednimustine treatment, but disappeared without sequelae within 1 week after treatment had been stopped.

On the basis of these results, further use of prednimustine in small-cell carcinoma does not appear to represent any advantage over other alkylating agents.

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