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Prednimustine in Adult Acute Myeloid Leukaemia

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Summary. *In 23 patients with acute myeloid leukaemia (AML) and over the age of 64, four remissions (17%) were obtained with Prednimustine as a single drug. The daily dose was 24–60 mg orally. In 14 patients aged between 35 and 64 years who were treated with Prednimustine 60–80 mg daily and vincristine 2.5 mg i.v. every 7–10 days, six remissions were obtained (43%). Upon remission, patients were given 20–40 mg of Prednimustine daily as maintenance therapy. Drug-induced pancytopenia preceding remission was not recorded in any patient. There were no side effects of major importance during maintenance therapy, and the median duration of remission was 8 months. It is concluded that the low toxicity of Prednimustine in normal bone marrow cells is of value, especially in elderly patients with AML.*

Introduction

Prednimustine is a chlorambucil ester of prednisolone [14] (Fig. 1). Data on the antitumour properties, the toxicity and the pharmacokinetics of the drug have been published previously [7, 8, 10, 13, 14, 24]. Clinical studies have demonstrated activity of Prednimustine in various haematological disorders [4, 9, 12, 18, 19] and in solid tumours [5, 15, 16].

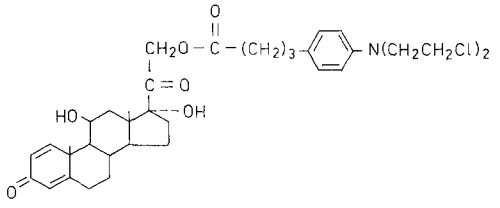

Fig. 1. Formula of Prednimustine

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Preliminary results [3] have indicated that Prednimustine as a single drug or in combination with vincristine can induce remissions in adult acute myeloid leukaemia (AML) without serious toxic side effects. We present results from a study of 37 AML patients, in which Prednimustine was given (1) as a single drug, to 23 patients aged 65 years or over, and (2) combined with vincristine to 14 patients aged 35–64 years.

Patients and Methods

A consecutive series of 37 previously untreated AML patients aged 35 years or over were studied. Patients with acute myeloblastic, promyelocytic, myelomonocytic, and monocytic leukaemia were included in the study. The FAB (French-American-British Co-operative Group) criteria [1] were followed for classification of the leukaemias. In appropriate circumstances Sudan Black B staining was used to exclude patients with acute lymphoblastic leukaemia. In all patients studied the bone marrow was rich in cells and the proportion of blast cells was 20%–90% (mean 67%). The patients were divided into two groups:

Group I consisted of 23 patients aged 65 years or over (median 71 years), who were given a daily dose of 24–60 mg of Prednimustine. It was considered that chemotherapy was indicated when one or more of the following criteria were fulfilled: (1) anaemia, requiring frequent transfusions, (2) granulocytopenia with infections, and (3) thrombocytopenia with a tendency to bleeding. The first patients who entered the study were given the lower dose, but in cases where the toxicity of the drug at this dose was negligible the daily dose was increased to 60 mg.

Group II consisted of 14 patients aged 35–64 years (median 51 years), who received a daily oral dose of 60–80 mg Prednimustine and 2.5 mg vincristine i.v. every 7–10 days. Treatment was started immediately after the diagnosis of AML.

Blood transfusions were given to all patients as required and platelet concentrates were given to patients with severe thrombocytopenia and a tendency to bleeding. Infections were treated with various combinations of antibiotics without following any fixed schedule. Patients were considered to be in remission if their bone marrow contained no more than 5% blast cells and if their blood granulocyte

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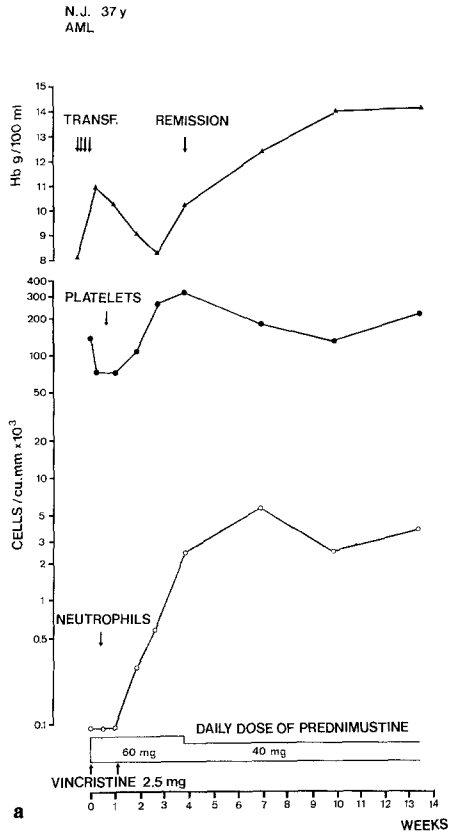

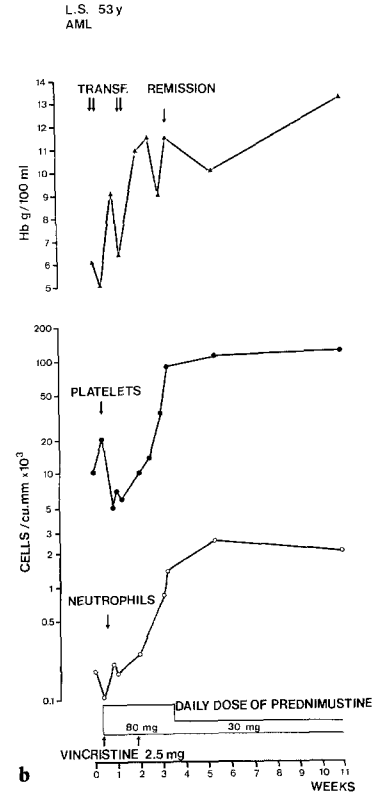

Fig. 2a and b. Haematologic data from the remission induction period in two patients treated with Prednimustine and vincristine

count and platelet count were at least 1,500/μl and 100,000/μl, respectively.

Patients who attained remission were given 20–40 mg of Prednimustine daily as maintenance therapy.

Results

Remission was attained in 4 of 23 elderly patients (17%) aged 65 years or over. All patients who attained remission were classified as acute myeloblastic leukaemia with 40%–90% blast cells in the bone marrow. The two oldest patients with remission were 71 and 74 years old. Drug-induced neutropenia or thrombocytopenia did not precede remission in any patient. Low toxicity was especially notable in the oldest patients. Thus, 9 of the 14 patients (64%) who were more than 70 years old (median 79 years) survived for six weeks or more, and the median survival time for all patients more than 70 years old was three months.

Remission was attained in 6 of the 14 patients (43%) aged 35–64 years. In no case was the remission preceded by drug-induced bone marrow aplasia. Haematological data from the remission induction period in two patients are given in Fig. 2. Paraesthesia as a symptom of neurotoxicity was observed in most patients, and was in all probability due to the administration of vincristine.

The median duration of remission in both groups was eight months. During the maintenance therapy with Prednimustine no side effects were noted.

Discussion

The results of the present study confirm preliminary results [3] suggesting that Prednimustine is effective as a single drug or in combination with vincristine for remission induction therapy in adult AML. The frequencies of remission in the age groups studied seem to be comparable to those obtained with several other treatment schedules. Thus, Bodey et al. [2] reported remissions in 12 of 68 patients (18%) aged 65 years or over, who were treated with various schedules of cytarabine and COAP. Of our 23 elderly patients in the same age group, four (17%) attained remission. Bodey et al. [2] obtained remission in 56 of 160 (35%) patients aged 35–64 years, which may be comparable with the remission frequency of 43% induced by Prednimustine plus vincristine. The limited bone marrow toxicity of Prednimustine found in the present study may be an advantage especially in the treatment of elderly AML patients. More than one-third of adults with AML are 70 years old or older [20]. When cytarabine and daunorubicin are used for the treatment of these patients only about 15% have been

reported to survive for 6 weeks or longer [22]. In the present study, 64% of the patients more than 70 years old survived for a similar period. The median survival time of three months in these elderly patients compares favourably with the median survivals of less than six weeks [22] and two months [21] reported when cytarabine and daunorubicin are used. The low toxicity of the drug is supported by the findings in the patients 35–64 years old, as the remissions obtained in this age group were never preceded by a drug-induced phase of pancytopenia. It is possible, however, that thrombocytopenia and neutropenia in the nonresponding patients were due at least in part to the treatment.

The possible role of Prednimustine for maintenance therapy after the induction of remission must await further evaluation. The median duration of the ten remissions induced in the present study was eight months, which may be comparable with the duration of 5–12 months obtained with daunorubicin or cytarabine [23].

It has been stated that it is rare for AML patients to attain remission without going through a period of usually marked bone marrow hypoplasia [11]. There are, however, indications that remission may be attained without a preceding phase of drug-induced hypoplasia [17]. The present results in two groups of patients with relatively high median ages (51 and 71 years) emphasize that it is possible to avoid drug-induced pancytopenia while retaining a reasonable remission frequency. This may be beneficial especially to elderly patients, who are notoriously susceptible to the side effects of aggressive chemotherapy.

In the present study Prednimustine was given continuously for relatively long periods of time. Intermittent administration of the drug in high daily doses has been found to be effective and well tolerated in patients with non-Hodgkin's lymphoma [6]. It may therefore be justified to study whether intermittent treatment with considerably higher doses than those used in the present study might be of value in AML.

In AML, Prednimustine has up to now been tested only in pilot studies as a single drug or in combination with vincristine. Its capacity to induce remissions and its low toxicity indicate that the drug deserves to be included as a part of various treatment schedules in future controlled studies.

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