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Treatment of Chronic Lymphocytic Leukaemia and Well-differentiated Lymphocytic Lymphoma with Continuous Low- or Intermittent High-dose Prednimustine versus Chlorambucil/Prednisolone

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Abstract—*Prednimustine, a new antitumour drug, is a chlorambucil ester of prednisolone. The present prospective randomized study compares the effect of continuous low-dose (B) and intermittent high-dose (C) prednimustine in previously untreated patients with progressive CLL and WDLL. The control group received continuous chlorambucil/prednisolone therapy (A). One hundred and eighteen patients, 88 CLL and 30 WDLL, were evaluable. Response to therapy (> 50% improvement) was noted in 61, 55 and 57% in groups A, B and C respectively. The difference was not statistically significant. Time to response, response duration and survival did not show any differences between the groups. Responding patients survived longer than patients with stationary and progressive disease. Median survival time was 72 months from diagnosis and 52 months from start of therapy, with no differences between the treatment groups. Toxicity of prednimustine was usually mild and similar to that of the two constituents. Treatment schedule C showed a slight advantage with regard to frequency of side effects. In conclusion, in this study the therapeutic effect of prednimustine was equal to that of its constituents administrated separately.*

INTRODUCTION

PATIENTS with chronic lymphocytic leukaemia (CLL) and well-differentiated lymphocytic lymphoma (WDLL) show a highly variable clinical course. Therapy is usually not instituted until disease-related signs or symptoms appear [1]. Chloroambucil alone or in combination with prednisolone is extensively used and gives high response rates [2–4]. Administration of the drugs in an intermittent schedule is reported to have theoretical and clinical advantages [1, 4, 5].

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Cells from many human tissues have receptors for glucocorticoids, especially malignant myeloid and lymphoid cells [6–8]. Furthermore, the amount of glucocorticoid receptors was recently shown to vary between patients. The response to glucocorticoids was also shown to be related to the level of binding sites [9, 10].

Prednimustine, a new antitumour agent, is a chlorambucil ester of prednisolone (Fig. 1). The compound was synthesized with the aim of using the steroid as a carrier for the cytotoxic agent to facilitate the binding to tumour cells [11]. Clinical improvement after prednimustine treatment has been demonstrated in patients with various lymphoproliferative disorders [12–

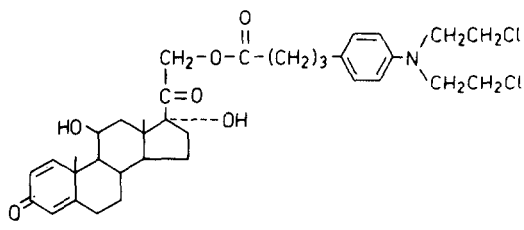

Fig. 1. The structural formula of prednimustine (LEO 1031).

16]. The aim of the present study was to compare the therapeutic effect of continuous and intermittent prednimustine administration to continuous treatment with its constituents, i.e. chlorambucil and prednisolone, in patients with progressive CLL and WDLL.

MATERIAL AND METHODS

Patients

One hundred and twenty-three previously untreated patients with CLL ($n = 92$) and WDLL ($n = 31$) from 5 different hospitals entered the study between October 1975 and October 1979. The evaluation was made in May 1980.

Five patients were lost during follow-up. Among the remaining 118 patients, 88 had CLL and 30 WDLL, 72 men and 46 women (ratio 1.6:1), with a mean age of 64.6 yr (range 39–84). The distribution according to age, sex and clinical stage was similar in the 3 treatment groups (Table 1).

Table 1. Patient characteristics in the three treatment groups

		Treatment group A ($n = 41$)	B ($n = 40$)	C ($n = 37$)
Stage				
CLL	I*	2	2	3
	II	3	2	1
	III	8	15	7
	IV	17	13	15
WDLL	III†	3	1	0
	IV	8	7	11
Sex ratio Male/female		24/17	23/17	25/12
Mean age (range)		65.0 (42–82)	65.1 (39–84)	63.2 (39–84)

*Rai classification.
†Ann Arbor classification.

All patients had active disease and fulfilled the criteria for treatment (see below). Disease was diagnosed at varying times before entering the study. Patients with a previous malignancy and patients with an absolute medical contradication for steroid therapy did not enter the study.

Diagnostic criteria

The diagnosis of CLL was based on a total blood lymphocyte count of $\geq 15 \times 10^9$/l and an infiltration of well-differentiated lymphocytes in the bone marrow. The Rai classification was used for a clinical staging [17]. The diagnosis of WDLL was based on a cytologic and histologic examination of lymph nodes and/or bone marrow, showing a major infiltration of well-differentiated lymphocytes according to the Rappaport classification [18]. Total blood lymphocyte count was $< 15 \times 10^9$/l. All WDLL patients had clinical stage III and IV according to the Ann Arbor system [19].

Clinical and laboratory investigation

Evaluation of patients before therapy included a thorough history and clinical examination. The following laboratory tests were performed: haemoglobin concentration, haematocrit, reticulocytes, WBC, differential count, platelet count, direct and indirect Coombs' tests, S-ASAT, S-ALAT, S-creatinine, S-uric acid, and serum and urine electrophoresis. X-ray examinations of the chest and abdomen were performed, as well as liver and spleen scans.

Haemoglobin concentration, WBC, differential count and platelet count were followed twice a week for the first six weeks. Later, blood tests were performed at varying time intervals but at least every six weeks, when a clinical examination was also done.

Indications for treatment

One or more of the following criteria had to be fulfilled for initiation of therapy: (1) anaemia (Hb $\leq$ 110 g/l) and/or thrombocytopoenia (platelets $\leq 100 \times 10^9$/l) due to progression of the disease; (2) symptoms related to enlargement of spleen and/or lymph nodes; and (3) severe and general symptoms (e.g. night sweats, weight loss, fever).

Treatment schedules

Patients were stratified for age, sex, diagnosis and hospital and then randomly assigned to 3 treatment protocols: (A) continuous administration of 5 mg chlorambucil twice daily and 10 mg prednisolone three times daily p.o.; (B)

continuous administration of 20 mg prednimustine p.o. twice daily; (C) intermittent administration of 100 mg prednimustine p.o. twice daily for three consecutive days, every two weeks.

When response (see below) was achieved, treatment was maintained for a further 6 months in most patients. The doses were modified according to a haematologic toxicity.

If no effect of therapy was obtained within 6 weeks, the dose(s) was increased by 50% of the initial dose(s). If still no effect was noticed after another 6 weeks, therapy was changed on an individual basis.

Criteria for response

The patients were considered to have a response to therapy (R) when the treatment criteria were improved according to the following definitions, with a duration of at least 6 weeks and with no new disease manifestations: (1) increase in haemoglobin concentration and platelet counts by at least 50% of the initial deviation from normal; (2) regression of the size of the spleen by more than 50% of the pretreatment extent below the left costal border and/or a 50% decrease of at least 2 enlarged lymph nodes; and (3) significant regression of general symptoms.

Stationary disease (SD) was defined as no improvement or improvement less than the above responses; progressive disease (PD) was defined as deterioration of desease related symptoms and laboratory parameters.

Statistical analysis

To detect differences in response between treatments, the χ^2 test for linear trend according to Armitage [20] was used. Duration of response and survival were defined as the period from start of treatment until observation of progressive disease or death respectively. Differences between treatments with regard to response duration and survival, as well as differences between responders and non-responders with regard to survival, were calculated using the generalized Wilcoxon test as described by Gehan [21].

RESULTS

Of the 118 evaluable patients (see Material and Methods) 68 (58%) responded to therapy: 61% in group A, 55% in group B and 57% in group C (Table 2). The response rates for the CLL patients were 70, 53 and 54% in groups A, B and C respectively (Table 2). These differences are not statistically significant. In all 3 groups median time to response was about 2 months (range, 1–12 months). The median response duration in the total material for responders was 22 months in group A, 16 months in group B and 18 months in group C (Fig. 2). Corresponding figures for CLL patients were 22 and 12 months in groups A and C respectively ($P < 0.05$). In group B the median response duration time was not reached at follow-up. However, the curve did

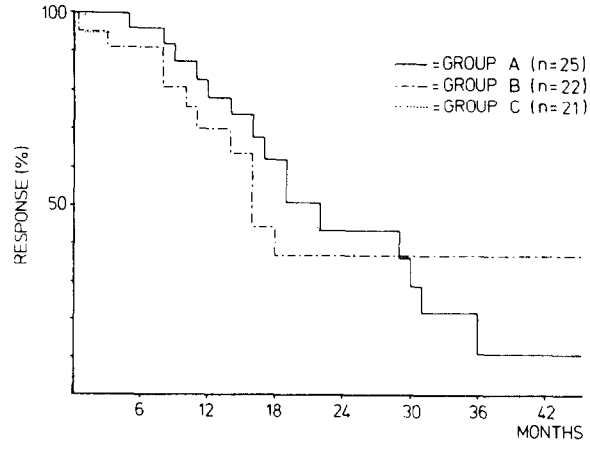

Fig. 2. Duration of response of the total patient material with regard to treatment schedule.

Table 2. Response to therapy in the three treatment groups

Diagnosis	Tratement group (*n*)	Response (%)	Stationary disease (%)	Progressive disease (%)
CLL + WDLL	A(41)	25(61)	9(22)	7(17)
	B(40)	22(55)	7(17)	11(28)
	C(37)	21(57)	9(24)	7(19)
	Total (118)	68(58)	25(21)	25(21)
CLL	A(30)	21(70)	5(17)	4(13)
	B(32)	17(53)	5(16)	10(31)
	C(26)	14(54)	5(19)	7(27)
	Total (88)	52(59)	15(17)	21(24)

not show any statistical difference from those of groups A and C (Fig. 3).

Median survival time of all patients was 72 months from diagnosis and 52 months from start of therapy. No statistically significant differences between the treatment groups were observed (Fig. 4). Responding patients had a longer survival than patients with stationary or progressive disease ($P < 0.001$) (Fig. 5). There was no difference in survival between patients with a long time from diagnosis to start of therapy and those with a short interval (Fig. 6). CLL patients had a median survival of 75 months from diagnosis and 52 months from start of therapy. Responders survived longer. Thus, median survival had not been reached at 50 months, compared to 24 months for non-responders ($P < 0.001$) (Fig. 7).

At follow-up 40 patients (31 CLL, 9 WDLL) had died. The causes of death are shown in

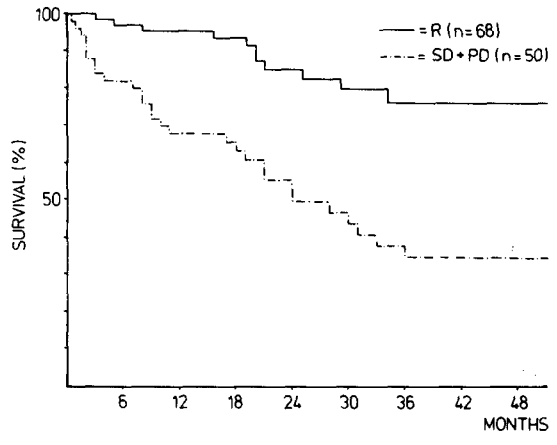

Fig. 5. Survival of the total patient material with regard to responding (R) and non-responding (SD + PD) patients.

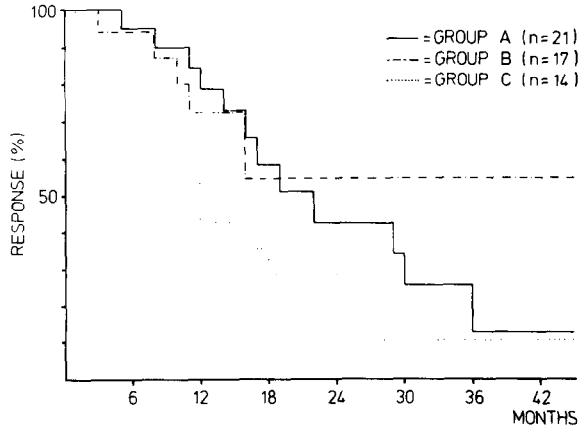

Fig. 3. Duration of response of the CLL patients with regard to treatment schedule.

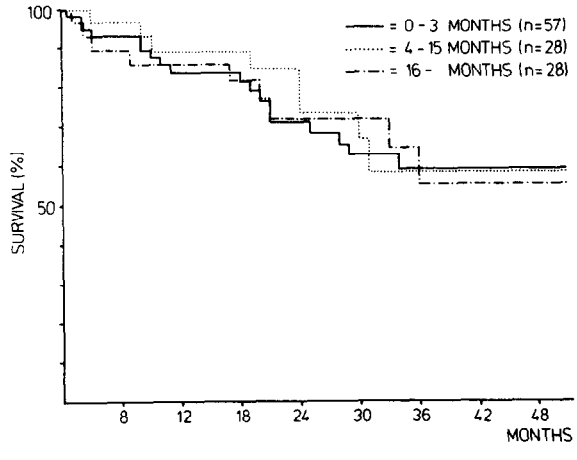

Fig. 6. Survival of the total patient material with regard to the interval between diagnosis and start of therapy.

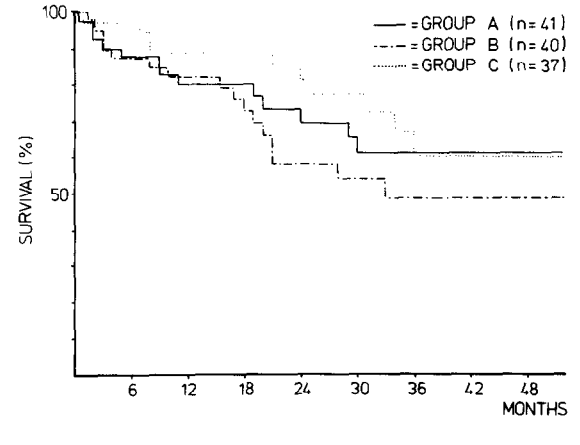

Fig. 4. Survival of the total patient material with regard to treatment schedule.

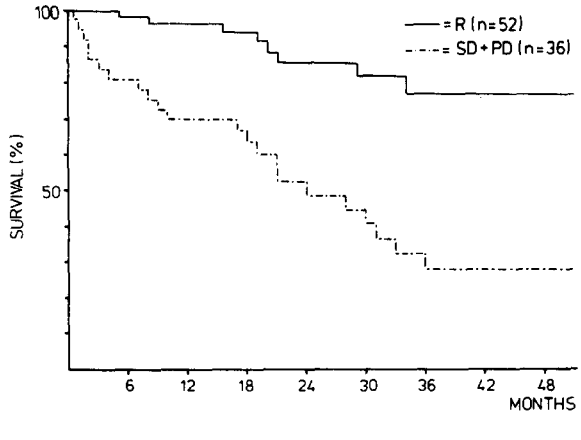

Fig. 7. Survival of responding (R) and non-responding (SD + PD) CLL patients.

Table 3. Haematologic toxicity effects are shown in Table 4. Significant myelodepression requiring dose reduction was noted in 31 patients. In 18 of these patients therapy was discontinued after a median treatment time of 2 months. Other drug-related side effects are summarized in Table 5. The treatment was discontinued because of the side effects in 8 patients (20%) in group A, 13 patients (33%) in group B and 5 patients (13%) in group C. This difference was not statistically significant. Infections have been reported as side effects only when seen in combination with leukopoenia and were observed in 3 patients. No severe steroid toxicity was seen in any of the treatment schedules.

Table 3. Cause of death in relation to treatment

Cause of death	Treatment group A	B	C
CLL and WDLL including infections and bleedings	12	9	6
Cardiovascular diseases	2	5	3
Other malignancies	0	2*	0
Suicide	0	0	1

*One patient with malignant melanoma, one with ovarian carcinoma.

Table 4. Haematological toxicity

Treatment group (*n*)	Number of patients with toxicity Grade 0	I*	II	III	IV
A(41)	31	0	2	2	6
B(40)	30	1	2	4	3
C(37)	27	3	3	3	1

*I = Leucopoenia 3–3.9 × 10^9/l and/or thrombocytopoenia 100–150 × 10^9/l; II = leucopoenia 2–2.9 × 10^9/l and/or thrombocytopoenia 50–99 × 10^9/l; III = leucopoenia 1–1.9 × 10^9/l and/or thrombocytopoenia 20–49 × 19^9/l; IV = leucopoenia < 1.0 × 10^9/l and/or thrombocytopoenia < 20 × 10^9/l.

DISCUSSION

The therapeutic effect of prednimustine, a new antitumour agent, has been evaluated in a prospective study including 88 CLL and 30 WDLL patients. Prednimustine was given either intermittently or continuously and was compared to its constituents, chlorambucil and prednisolone, given in a continuous treatment schedule. Prednimustine seems to provide an effective control of the disease, comparable to that of conventional combination therapy. No difference in survival was found between intermittent high-dose and continuous low-dose administration of prednimustine.

A daily dose of 40 mg prednimustine was chosen as this dose was established in a pre-

Table 5. Registered side effects

Side effect	Treatment group A (*n* = 41)	B (*n* = 40)	C (*n* = 37)
Myelosuppression	10 (6)*	10 (9)	10 (3)
Infection	2 (1)	1	0
Gastritis, ulcer	2 (1)	2	0
Nausea, vomiting, diarrhoea	0	6	1
Haematuria	0	0	1
Diabetes mellitus	1	1 (1)	2 (1)
Psychic disturbance	5	4 (2)	2 (1)
Insomnia	1	1 (1)	0
Photosensibility	0	0	1
Cushingoid habitus	2	0	0
Oedema	2	0	0
Tremor	1	0	0
Accentuated Parkinson tremor	0	0	1
Total numbers of patients where therapy was discontinued	8	13	5
Numbers of patients without side effects	23	21	20

*Figures in parenthesis indicate the number of patients where the side effect prompted discontinuation of therapy.

vious pilot study as having a good therapeutic effect with minimal toxicity (unpublished results). Chlorambucil and prednisolone were given in doses commonly used. The high dose of prednimustine in the intermittent schedule is the sum of the daily low dose of prednimustine during a 2-week period.

The overall response rate was 59% in patients with progressive CLL. No statistically significant difference was observed between the treatment groups. These results are consistent with previous reports using a combination of chlorambucil and prednisolone [4]. The response rate of prednimustine in previous trials of treated and untreated CLL patients varied between 30 and 60% [12, 22].

WDLL patients showed a somewhat lower response rate (50%) than that reported by others using prednimustine [15, 23]. The difference is probably not statistically significant. With aggressive multiple chemotherapy schedules, complete responses have been seen in 60% of the patients with WDLL [24].

The median time to response was short (2 months) and the response duration was rather long. The lack of difference between intermittent and continuous therapy is in contrast to some other studies. Using only chlorambucil intermittently, a long induction phase was required to obtain response [3]. Moreover, a shorter response duration was noticed when the cytostatic drug was given continuously as compared to intermittent administration [4].

Response to therapy may significantly influence the survival in CLL and other chronic malignant lymphoproliferative disorders [1, 25–28]. The present study confirms these findings, i.e. that responding patients survive longer than non-responders.

The toxicity was usually mild. Side effects of prednimustine, mainly myelosuppression (Table 4), has been reported with higher frequences in other studies [15, 16]. However, it should be pointed out that a majority of those patients had had previous therapy, which makes the bone marrow more vulnerable to myelosuppressive agents. The incidence and type of other side effects (Table 5) were comparable to those of other reports. As expected, discontinuation of therapy due to toxicity was more common in the continuous administration of prednimustine than in the intermittent one.

In conclusion, prednimustine given as intermittent or continuous therapy, offers an effective therapeutic control of CLL and WDLL. Considering the absence of improvement of response rate and survival with prednimustine compared to the combinations of chlorambucil and prednisolone, the hypothesis of a specific transport or binding mechanism for prednimustine is not confirmed by this clinical study. Thus, the question of a possible theoretical advantage of this drug still remains open, and may not be fully answered unless information regarding amounts of glucocorticoid binding sites in individual patients is provided.

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