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Original Paper

Efficacy and Toxicity of 2-chlorodeoxyadenosine (Cladribine)—2 h Infusion for 5 Days—as First-line Treatment for Advanced Low Grade Non-Hodgkin's Lymphoma*

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2-Chlorodeoxyadenosine (Cladribine) is a new purine analogue with high activity in pretreated low grade non-Hodgkin's lymphoma (NHL). To evaluate the efficacy of this drug in untreated patients with advanced NHL, we performed a prospective multicentre trial. Cladribine (0.12 mg/kg) was administered intravenously daily for 5 consecutive days in an out-patient setting. The treatment was repeated every 28 days for four cycles. Included were patients with a histological diagnosis of low grade NHL according to the Kiel classification and stage III or IV disease. Stage II patients were included when radiotherapy had failed. 55 patients were entered into the study. 50 patients were evaluable. The remission rate was 44/50 (88%; 95% confidence interval 82–100%), including complete remissions (CR) in 14 (28%) patients. Only 2 patients showed progression while on Cladribine treatment. The estimated overall survival, and time to treatment failure (TTF) were 85% and 51%, respectively, after a median observation time of 92 weeks. 11 (22%) patients showed grade 3 or 4 toxicity according to the WHO grading. Haematological toxicity was responsible for 86% of the overall toxicity and 100% of grade 3 and 4 toxicity. 7 patients (14%) had an infection, two of which were opportunistic. 12 (24%) patients did not experience any toxicity during the treatment. The results of this study clearly demonstrate the safety and considerable activity of this regimen. Cladribine is very effective even at lower doses than have been used so far. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: lymphoma, low grade, intermediate grade, non-Hodgkin's, treatment, chemotherapy
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INTRODUCTION

LOW GRADE non-Hodgkin's lymphoma (NHL) usually has an indolent course. Asymptomatic patients show an excellent survival rate of 73% after 10 years, even if treatment is not started immediately. These patients develop symptoms after a median of 3 years and subsequently need therapy. Despite good response rates, patients in advanced stages are not curable with conventional chemotherapy [1]. Newer treatment strategies include high dose chemoradiotherapy with or without stem-cell support, biotechnological modifications or new drugs.

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2-Chlorodeoxyadenosine (Cladribine) is a new purine analogue that is toxic to lymphocytes because its active metabolite accumulates in the nucleus and inhibits DNA replication [2]. The exact mechanism of action of Cladribine is not known. It is suggested that DNA strands break, and rapid NAD consumption and ATP depletion lead to programmed cell death (apoptosis) [3]. In pretreated patients with low grade lymphoma, remissions could be achieved in approximately 40%; half of them complete. However, severe side-effects were observed in several heavily pretreated patients [4]. This could be because heavily pretreated patients with advanced disease tend to develop severe immune deficiency. The Austrian Working Group for Tumour Drug Treatment initiated a phase II trial to evaluate the remission rate and toxicity of Cladribine treatment in previously untreated patients with advanced low grade NHL and the results are reported herein.

PATIENTS AND METHODS

Inclusion criteria

Diagnosis was based on biopsy-proven low grade NHL according to the revised Kiel classification [5]. All slides were centrally reviewed by one of us.

Patients with stage III or IV disease were eligible for entry into the study. Patients with stage II disease were accepted if they had progressive disease after radiation therapy. All patients had to be between 18 and 80 years of age and had to fulfil at least one of the following criteria: symptomatic disease, tumour progression within the last 8 weeks, haemoglobin < 100 g/l or platelet count $< 100 \times 10^9$/l. All patients gave their written informed consent before registration.

Exclusion criteria

Patients with chronic lymphocytic leukaemia (CLL), immunocytoma (Waldenstrom macroglobulinaemia not excluded), hairy-cell leukaemia, cutaneous T-cell lymphoma, pretreatment with cytotoxic drugs, radiation within the last 6 weeks, central nervous system involvement, HIV-positive serology, Karnofsky index below 50% (WHO performance index > 2), > 70 years of age combined with a Karnofsky index $< 70\%$, a life expectancy shorter than 3 months without therapy, second malignancy, as well as pregnant and lactating women, were excluded.

Staging

All patients underwent a pretreatment history and physical examination. Furthermore, the following tests were performed: complete blood count with differential, chemistry panel with hepatic and renal function, LDH, β_2-microglobulin, albumin, quantitative immunoglobulin level, absolute CD4, CD8 count, HIV test, ultrasound examination of all lymph node regions, computed tomographic scans of the chest and abdomen, and a bone marrow biopsy. The entire staging procedure was repeated 4–8 weeks after the last Cladribine treatment and in case of progression. The physical examination, laboratory examination and ultrasound were repeated every third month for 2 years after treatment with Cladribine had been concluded.

Endpoints

The purpose of the study was to evaluate the rate of complete and partial remissions in untreated advanced progressive low grade NHL. Secondary endpoints were survival, time to treatment failure (TTF), time to relapse (TTR) [6], duration of immunosuppression, and toxicity of Cladribine therapy.

Treatment schedule

Cladribine was intravenously administered at a dosage of 0.12 mg/kg body weight as a 2 h infusion daily for 5 consecutive days. Cycles were repeated after 28–56 days. A total of four cycles were administered. No prophylactic antibiotic treatment was allowed. The trial was approved by the ethics committees of the participating centres.

Dose modifications

Before the next treatment cycle was started, the leucocyte count had to be ≥ 4.0 G/l (G = 10^9/l) (or the neutrophil count > 1.5 G/l) and platelet count ≥ 100 G/l in case of low leucocyte or platelet counts before therapy, the baseline counts had to be achieved. If these counts were not achieved, the next treatment cycle was delayed by 1 week. If these counts did not meet these criteria 8 weeks after the last treatment, the patient was withdrawn from the study. These patients were fully evaluable for the study and treated thereafter as deemed appropriate by the treating physician.

Response criteria

Complete remission was defined as the disappearance of all tumour manifestations at clinical examination, on ultrasound, computed tomography scan, bone marrow biopsy, bone marrow cytology, immunofixation, and a peripheral blood cell examination. Partial remission was defined as a $\geq 50\%$ regression of measurable tumour manifestations. No change was defined as a regression of measurable tumour manifestations of less than 50% without more than 25% progression at any tumour site. Progression was defined as an increase of any tumour manifestation by 25%.

Biostatistics

Survival and TTF were defined according to the criteria of Dixon and colleagues [6]. Briefly, survival includes all eligible patients and regards all deaths as events; TTF is the time from registration until relapse, progression, toxic death, withdrawal, or date last known to be alive, excluding deaths from unrelated causes. Survival, TTF and TTR were estimated according to the Kaplan–Meier method [7]. For assessing differences in response and toxic events the χ^2 test was used.

Toxicity criteria

The WHO toxicity grading was used [8]. In patients with abnormal haematological values before the treatment started, haematological toxicity was only reported if the values worsened during therapy.

RESULTS

55 patients were entered into a multicentre trial from June 1993 until January 1996. 4 patients were not eligible for the following reasons: revision of histological diagnosis after central review in 2 patients and 2 patients were previously not irradiated stage II disease. 1 patient was not evaluable because he was lost to follow-up after the first 5 days of treatment. Therefore, 50 patients were assessed.

Patients' ages ranged from 25 to 78 years; median age was 57 years. 23 patients were male, 27 female. 2 patients had relapsed with stage 2 disease after radiotherapy, 9 had stage III, and 39 had stage IV disease. 31 patients had B-symptoms. The distribution of patients in terms of different histological entities is shown in Table 1. 5 patients were in the low risk group, 20 in the low–intermediate, 20 in the high–intermediate, and 5 in the high risk group as assessed according to the International Non-Hodgkin's Lymphoma Prognostic Factors Project [10].

14 of 50 patients achieved complete remission (28%), 30 partial remission, and 4 patients achieved no change, which resulted in a remission rate of 88% (95% confidence interval 82–100%). Only 2 patients had a progressing lymphoma while on Cladribine treatment. Responses were seen in all subgroups of low grade lymphomas according to the Kiel classification [5] (Table 1). The median observation time was 92 weeks (range 5–192 weeks). Survival and TTF were 85% and 51%, respectively, after 92 weeks (21 months) (Figure 1). Of the 16 patients who have progressed to date, 6 showed evidence of transformation to a high grade lymphoma. 12 of 16 patients progressed in the site initially involved, while the remaining 4 progressed at an additional site. 7 patients died, all with progressing lymphoma, 6 with transformation to a high grade lymphoma. 1 patient died of pulmonary embolism.

Toxicity was primarily haematological (Table 2). Haematological toxicity accounted for 86% of all toxicities and 100% of all grade 3 and 4 toxicities. 8 patients had abnormal

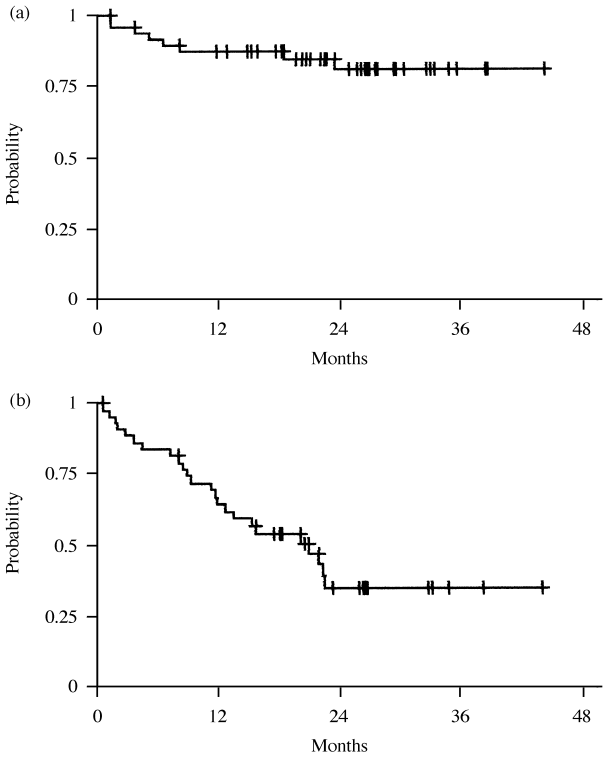

Figure 1. (a) Overall survival. (b) Time to treatment failure.

Table 1. *Histological subgroups and response to Cladribine treatment*

Kiel classification [5]	R.E.A.L. classification [9]	No. of patients	CR	PR	NC	PD
Centroblastic-centrocytic follicular ± diffuse	Follicular centre lymphoma grade 1 + 2	28	7	17	2	2
Lymphoplasmacytic immunocytoma with macroglobulinaemia (Waldenström disease)	Lymphoplasmacytic lymphoma with macroglobulinaemia (Waldenström disease)	10	1	8	1	0
B-lymphocytic	B-cell small lymphocytic lymphoma	1	0	0	1	0
Centrocytic	Mantle-cell	6	3	3	0	0
Centroblastic-centrocytic diffuse	Follicular centre lymphoma, diffuse, small cell	1	1	0	0	0
Prolymphocytic leukaemia B-cell	B-cell prolymphocytic leukaemia	2	1	1	0	0
Angioimmunoblastic	Angioimmunoblastic T-cell lymphoma	1	0	1	0	0
Lymphoepithelioid	Peripheral T-cell lymphoma	1	1	0	0	0

CR, complete remission; PR, partial remission; NC, no change; PD, progressive disease.

Table 2. *Toxicity of Cladribine*

	Highest toxicity (WHO)				
	0	1	2	3	4
Overall toxicity in 50 patients	12 (24%)	14 (28%)	13 (26%)	9 (18%)	2 (4%)
Overall toxicity in 180 cycles	87 (48.3%)	47 (26.1%)	27 (15%)	17 (9.4%)	2 (1.1%)
Haematological toxicity	100 (55.6%)	34 (18.9%)	27 (15.0%)	17 (9.5%)	2 (1.1%)
Anaemia	156 (86.7%)	14 (7.8%)	7 (3.9%)	3 (1.7%)	0
Leucopenia	113 (62.8%)	28 (15.5%)	21 (11.7%)	16 (8.9%)	2 (1.1%)
Thrombopenia	174 (96.7%)	3 (1.7%)	3 (1.7%)	0	0
Infection	173 (96.1%)	1 (0.6%)	4 (2.2%)	2 (1.1%)	0
Other toxicities	140 (77.8%)	35 (19.4%)	5 (2.8%)	0	0

Note that different toxicities occurred in the same cycle.

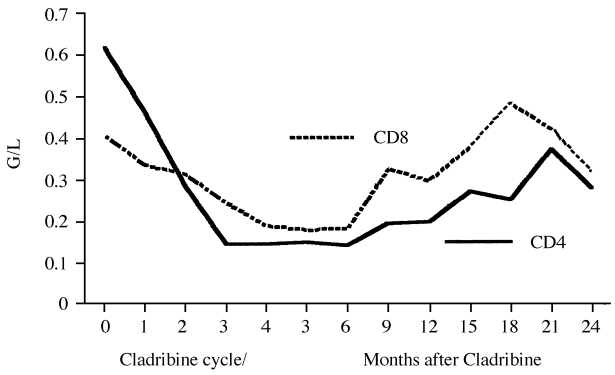

Figure 2. Median CD4 and CD8 counts during and after Cladribine treatment.

haematological values before treatment. Haematological toxicity for these patients was only reported if it worsened by at least one WHO grade during treatment. Leucopenia was the most frequent haematological toxicity (Table 2). All patients had a fast, substantial, and long-lasting reduction in CD4 counts. CD8 counts were less affected (Figure 2). There was no change in immunoglobulin levels during or after Cladribine therapy. Despite these severe and long-lasting suppressive effects on lymphocytes, only seven infections occurred during treatment with Cladribine (Table 2). Of these infections, four were found in the upper respiratory tract (one of them fungal), one bacterial pneumonia, one bacterial bronchitis, one herpes zoster. In addition, three periods of fever of unknown origin occurred in 2 patients. Because of the low infection rate, we could not find a correlation to leucopenia, CD4 count or immunoglobulin level. Toxicities other than haematological or infection were rare and mild (Table 3). 6 patients developed an infection in the observation period later than 28 days after the last Cladribine therapy was started. Three of these infections were due to herpes zoster virus, one bacterial pneumonia, one was a viral bronchitis, and one a Candida mucositis.

Table 3. Other toxicities during Clabribine treatment (number of patients is shown)

	WHO Grade	
Toxicity	1	2
Hair loss	4	1
Pain	3	0
Nausea	2	0
Allergic reaction	2	0
Confusion	2	0
Arthritis	1	1
Alkaline phosphatase	1	1
Creatinin increase	1	0
Dermal	1	0
Oral	1	0
Pulmonary	0	2
Polyneuropathy	1	0
Cardiac rhythm disturbance	1	0

DISCUSSION

Low grade NHL in advanced stages cannot be cured with conventional therapy. Palliation of symptoms depends on the rate of remissions and is inversely related to the duration and toxicity of treatment. With 4 months of Cladribine treatment, we achieved a remission rate of 88% in patients with previously untreated advanced low grade NHL, according to the Kiel classification [5]. However, in spite of the high remission rate, only 28% achieved complete remission. Other reports on purine analogue therapy in untreated follicular lymphomas had similar complete remission rates with 14% [11], 31% [12], and 37% [13], respectively. Complete remission is difficult to achieve in low grade lymphomas with conventional treatment. Two other reports achieved similar remission rates with a 7-day continuous infusion regimen. In these studies, Cladribine was used at a daily dose of 0.1 mg/kg, for either three cycles [14] or five cycles [11]. In a preliminary report of the CALGB trial 9153, the same results were achieved with a Cladribine dose of 0.14 mg/kg administered daily as a 2-h infusion for 5 days [12]. Compared with our regimen, the duration of treatment was longer and Cladribine doses were up to one-third higher. Remission rates were comparable. However, the long-term outcome has still to be assessed, as the observation period is not long enough in all reports. The median TTF of 22 months in our study was better than in other studies (10 months [14], 15.7 months [11] and 15 months [13]). Nine cycles of Fludarabine, another purine analogue, achieved a 65% remission rate in untreated follicular lymphomas and a median TTF of 18 months [13].

One of the concerns was the high toxicity rate described for purine analogues in heavily pretreated patients [15, 16]. One-hundred and seventy-three of 180 Cladribine cycles (96%) were performed without any infection. Therefore, the infection rate was extremely low with first-line treatment with Cladribine, despite the suppressive effect of Cladribine on CD4 lymphocyte counts, and although this CD4 lymphocyte suppression was long lasting. There was no evidence of a lower toxicity compared with regimens using higher doses [11, 12, 14]. However, the cost of treatment is substantially lower with our regimen.

6 patients had histological evidence of transformation to a higher grade lymphoma. Other authors observed similar transformation rates with Cladribine [17]. Approximately one-third of low grade lymphomas transform to high grade histology over time, irrespective of the alkylating treatment [1]. A longer follow-up is necessary to evaluate the risk of transformation after Cladribine therapy.

Remission rates of conventional treatment with chlorambucil, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), or CVP (cyclophosphamide, vincristine, prednisolone) vary widely between 36 and 86% and complete remission between 5 and 25% [18–20]. Comparison of different treatments is difficult because methods for assessment of remission have improved markedly since older trials were conducted and patient selection is not uniform. However, in spite of different remission and complete remission rates with single agent and combination chemotherapy, a survival benefit could not be demonstrated [19, 20]. We have demonstrated that Cladribine has at least as good remission and complete remission rates as the best conventional treatment, but lacks toxicities such as nausea and hair loss that are very inconvenient to most patients. Cladribine can be used in lower doses than previously described and conveniently administered as a 2-h infusion. Final conclusions regarding long-term outcome cannot be drawn yet, as the median survival for low grade NHL is 8–10 years [1].

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