Annals of Oncology 9: 721–726, 1998.

Original article

Reduced dose of subcutaneous cladribine induces identical response rates but decreased toxicity in pretreated chronic lymphocytic leukaemia

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Summary

Purpose: To study the efficacy and the safety of cladribine (2-chlorodeoxyadenosine, 2-CDA) administered as 24-hour infusions or as subcutaneous bolus injections at two different doses to patients with relapsing or refractory chronic lymphocytic leukaemia (CLL).

Patients and methods: In this non randomised 2-cohort study, 20 patients with pretreated CLL received cladribine at a dose of 0.7 mg/kg/cycle as continuous i.v. infusions over seven days (group 1) and 35 patients were treated at a reduced dose of 0.5 mg/kg/cycle given as s.c. bolus injections for five days (group 2). After two cycles of four week duration, response was assessed. In the case of progressive disease, therapy was discontinued, otherwise a maximum of four additional cycles were administered until best response.

Results: A total of 130 cycles were administered (group 1: 41, group 2: 89). Patient characteristics in both groups were comparable. The median dose intensities were 0.172 mg/kg per week and 0.123 mg/kg per week for groups 1 and 2, respectively ($P \leq 0.0001$). The overall response rate for all 55 patients was 38% (95% confidence interval (95% CI): 25%–52%), with 5% CR and 33% PR. Response was similar in both patient groups (35% in group 1, 40% in group 2). No association between cladribine dose intensity and response rate was found, and there was no difference between patients relapsing after or refractory to previous therapies (11 of 24 vs. 10 of 31). Median remission duration was six months in both groups. Toxicity, in particular infections (all WHO grades, 34% in group 1 *versus* 7% in group 2) and myelosuppression (grade 1–4 neutropenia, 72% *versus* 41% of cladribine cycles) were statistically significantly more frequent in group 1.

Conclusion: Cladribine is active in heavily pretreated patients with chronic lymphocytic leukaemias. Dose reduction by 29% led to similar response and remission duration, but to a significant decrease of myelotoxicity and risk of infection. Cladribine administered as s.c. bolus injections at 0.5 mg/kg per cycle is safe and this dose level should not be exceeded in this patient population.

Key words: cladribine, 2-chlorodeoxyadenosine, chronic lymphocytic leukaemia, infection, myelotoxicity, remission duration

Introduction

The cornerstones of treatment in advanced chronic lymphocytic leukaemia (CLL) are alkylators, in particular chlorambucil and cyclophosphamide, with or without the addition of corticosteroids. In the early 1980s purine analogs were introduced into clinical research and showed striking activity in relapsing as well as refractory CLL. Both fludarabine phosphate [1] and cladribine (2-chlorodeoxyadenosine) [2] show response rates varying between 30% to 70% depending on the patient selection [3–9]. Data on remission durations are scarce; in four studies [6–9] it varies between four to 20 months.

Cladribine was first reported to be active in CLL by Piro et al. in 1988 [7]. Patients received a cladribine dose of 0.7 mg/kg/cycle as continuous i.v. infusions over seven days. At present, data are available on more than 300 previously treated patients as well as about 100 previously untreated patients who received cladribine either at 0.1 mg/kg/day by continuous infusions for seven consecutive days or by two-hour infusions usually at a dose of 0.14 mg/kg/day for five consecutive days [6–15]. Despite the high rate of responses, the routine use of cladribine was dampered by its marked side effects, in particular infections and myelosuppression [2, 16, 17]. In addition, the rather complicated way of its administration (daily infusions) renders this therapy rather cumbersome especially in elderly patients. To find a simpler way of cladribine administration, we tested the subcutaneous route of cladribine administration which is associated with a different plasma cladribine concentration-time profile and the mean residence time when compared with continuous intravenous administration [18].

In this two-cohort study we compared the activity and toxicity of cladribine administered intravenously as 24-hour infusions over seven days *versus* subcutaneous bolus injections over five days. In the attempt to decrease

the side effects, the dose intensity of cladribine was reduced by 29% in patients receiving the subcutaneous schedule.

Patients and methods

Study design

This study includes two consecutive prospective multicentre phase II trials in Switzerland: first trial from June 1992 to May 1993 (group 1), second trial from June 1993 to October 1995 (group 2). Due to a high incidence of infections seen in group 1, the cladribine dose was reduced by 29% in group 2. The protocols were approved by the local ethic's committee of each participating centre. The study was performed in keeping with good clinical practice regulations and informed consent was given by all patients.

Eligibility criteria

Patients were required to have CLL of B-cell type of International stage B or C. Immunophaenotyping was performed to confirm the diagnosis. Patients were required to have undergone prior conventional treatment, including at least one alkylating agent and either failed to respond or developed progressive disease after an initial response. Patients had to be free of prior therapy for four or more weeks. All patients were older than 18 years. No upper age limit was specified. However, a performance status of ≤ 2 and a life expectancy of > 3 months were required as well as absence of active infection, and adequate cardiac, renal and hepatic function. Exclusion criteria were prior malignancy (other than non-melanomatous skin cancer or adequately treated stage I *in situ* cervical cancer), or peripheral blood cytopenia (leucocyte count $< 3.0 \times 10^9$/l, neutrophil count $< 1.0 \times 10^9$/l or thrombocyte count $< 100 \times 10^9$/l) unless this was clearly related to bone marrow infiltration by CLL.

Pretreatment investigations

The diagnosis of CLL was confirmed before start of treatment. The extent of disease was determined by standardised staging evaluation, which included CT scanning of the chest, abdomen and pelvis, and bone marrow aspiration and trephine biopsy. Kidney function and liver enzymes were measured.

Drug therapy

Patients were treated with cladribine (provided by Dr. Z. Kazimierczuk et al. [19] and by Lipomed, Basel, Switzerland) at a daily dose of 0.1 mg/kg/day diluted in 0.9% saline solution. In group 1, cladribine was given as continuous i.v. infusions over seven days. In group 2, the drug was self-administered by the majority of patients as s.c. bolus injections over five days mostly on an outpatient basis. Cladribine cycles were repeated at ≥ 4 week intervals. After two cycles staging was performed, and therapy was discontinued in case of progressive disease. In responders, therapy was continued at physician's request until best response, but for a maximum of six cycles. If patients received one 2-CDA course only, due to toxicity or further treatment refusal by the patient, response was assessed four weeks after 2-CDA start. Weekly blood cell counts including granulocytes were performed. Treatment was delayed if the neutrophil count was less than 1.0×10^9/l and/or the platelet count was less than 100×10^9/l, unless the cause was clearly due to infiltration of the bone marrow by CLL. No routine antimicrobial prophylaxis was given, and no concomitant therapy such as antiemetics or steroids were administered.

Response criteria

All responses were reviewed by two of us (DCB, DR) using the response criteria recommended by the National Cancer Institute-sponsored Working Group [20]. Peripheral lymph node enlargements were documented after each cladribine cycle. Sites of disease not assessable by clinical examination (mediastinal and retroperitoneal lymphadenopathy, bone marrow infiltration) were examined by chest X-ray, CT scan and/or bone marrow examination after two cycles as well as at completion of cladribine therapy. Duration of remission was assessed through clinical and radiological (where appropriate) examinations as well as blood cell counts at three month intervals until relapse.

Toxicity criteria

Toxicity was evaluated according to World Health Organisation (WHO) criteria [21]. Physical examination and full blood count including differential were done weekly.

Statistical analyses

All patients were evaluated for toxicity, response, time to treatment failure and response duration. Time to treatment failure was calculated from date of enrollment to either disease progression/relapse, discontinuation of treatment for toxicity or death due to CLL, whichever occurred first. Remission duration was calculated from the date of response until relapse, progression or death due to CLL. Survival curves were compared using the log-rank test. Contingency tables were analysed by Fisher's exact test, while continuous variables were analysed by the Wilcoxon rank sums test. Due to relatively small sample size, all P-values should be interpreted with caution; e.g., the statistical power is low and significant trends may be missed.

Results

Study population

We report on 55 patients with previously treated CLL who were treated with cladribine therapy between June 1992 and October 1995 in two cohorts. Twenty patients received infusional cladribine (group 1: 0.7 mg/kg/cycle as continuous i.v. infusions over seven days). A further 35 patients were administered cladribine subcutaneously as bolus injections (group 2: 0.5 mg/kg/cycle over five days). The median age was 68 years, ranging from 43 to 79 years. Two patients had International stage B disease, and 53 patients had stage C. Patient characteristics are shown in Table 1. All patients are evaluable for toxicity and response. Both patient groups are well balanced with respect to CLL prognostic factors (gender, age, performance status, lymphocyte count and disease status; refractory to or relapsing after standard therapy). The number of different pretreatments (group 1 vs. group 2: median 3 vs. 2, $P = 0.04$) appeared to be greater in group 1.

Therapy

Overall, 130 cycles of cladribine were administered. The median number of cycles was 2 (range 1–5, in group 1; and 1–6 in group 2) in both groups. Responders of group

Table 1. Patient characteristics and cladribine therapy.

	Group 1	Group 2	*P*-value
Number of patients	20 (36%)	35 (64%)	
Gender			0.61
Male	15 (75%)	24 (69%)	
Female	5 (25%)	11 (31%)	
Age (in years)			0.06
Median	70	66	
Range	52–76	43–79	
Years since diagnosis			0.18
Median	4.7	3.2	
Range	0.2–11.3	0.03–21.9	
Stage of disease (international stage)			0.13
A	0	0	
B	2	0	
C	18	35	
Performance status			0.93
0	8	13	
1	10	16	
2	1	4	
3	1	2	
Number of pretreatments			0.04
Median	3	2	
Range	1–7	1–5	
Status after pretreatment			1.00
In relapse	9	15	
Refractory	11	20	
Blood values at study entry			
Hb (g/l)			0.57
Median	107	112	
Range	57–114	70–166	
Lymphocytes ($\times 10^9$/l)			0.29
Median	46	39	
Range	0.9–32	0.5–754	
Platelets ($\times 10^9$/l)			0.55
Median	115	108	
Range	10–279	7–362	
Number of cladribine cycles			0.10
Median	2	2	
Range	1–5	1–6	
Total of cladribine cycles	41	89	
Number of patients with ≥ 3 cycles	5 (of 20)	17 (of 35)	0.15
Total dose per patient (mg/kg)			0.96
Median	1.4	1.0	
Range	0.7–3.5	0.5–3.0	
Dose intensity (according to study design, in mg/kg/wk)			<0.0001
Median	0.172	0.123	
Range	0.085–0.179	0.054–0.127	

1 and 2 received two (median, range one to four) and three (one to six) cladribine cycles, respectively. Twenty-two patients received ≥ 3 cycles (group 1, n = 5 of 20; group 2, n = 17 of 35; P = 0.15). The total cladribine dose administered in both groups was similar (median: 1.4 *versus* 1.0 mg/kg, P = 0.96). The median dose-intensity for patients in group 1 with higher dose 2-CDA was 0.172 mg/kg/week (range 0.085–0.179 mg/kg/week). As expected from the study design, the dose intensity was

Table 2. Response rate, remission duration and time to treatment failure.

a) Response rate, remission duration and time to treatment failure according to cladribine dose and route of administration

	Group 1	Group 2	*P*-value
Response rate (CR + PR)	35%	40%	0.78
95% confidence interval	15%–59%	24%–58%	
Response			
CR	1	2	
PR	6	12	
NC	10	17	
PD	3	4	
Remission duration (months)	6	6	0.88
Time to treatment failure (months)	4.5	3.8	0.74

b) response rate according to blood values at start of therapy

	CR + PR	NC + PD	*P*-value
Hb (g/l)			0.04
Median	123	105	
Range	57–166	70–163	
Lymphocytes ($\times 10^9$/l)			0.23
Median	41	39	
Range	1–174	1.5–152	
Platelets ($\times 10^9$/l)			0.004
Median	168	83	
Range	16–353	7–362	

Abbreviations: CR – complete remission; PR – partial remission; NC – no change; PD – progressive disease.

reduced by 29% in group 2 (0.123, 0.054–0.127, $P <$ 0.0001, Table 1). In 15 patients (group 1/2 = 8/7) cladribine therapy was discontinued because of CLL progression (n = 4), infections (n = 4), autoimmune-haemolytic anaemia (n = 1), and patient refusal (n = 6) before administration of the second cycle.

Response to therapy

The overall response rate of the 55 patients was 38% (95% confidence interval (95% CI): 25%–52%), with a CR rate of 5% (95% CI: 1%–15%) and a PR rate of 33% (95% CI: 21%–47%) (Table 2a). Stable disease was obtained in further 16 patients (29%) who were progressing under previous therapy. There was no difference in the response rates between the two study groups (response in group 1 and 2: 35% vs. 40%) and no association between cladribine dose intensity and response rate was found. In a univariate analysis, separately performed in each group, the response rate did not depend on prognostic factors such as age, gender, duration of disease, lymphocyte count at study entry, and number of different pretreatments. More importantly, in both study groups the response rates were independent of whether patients relapsed after or were refractory to previous chemotherapy (46% *versus* 32%). Response, however, was associated with a higher platelet and

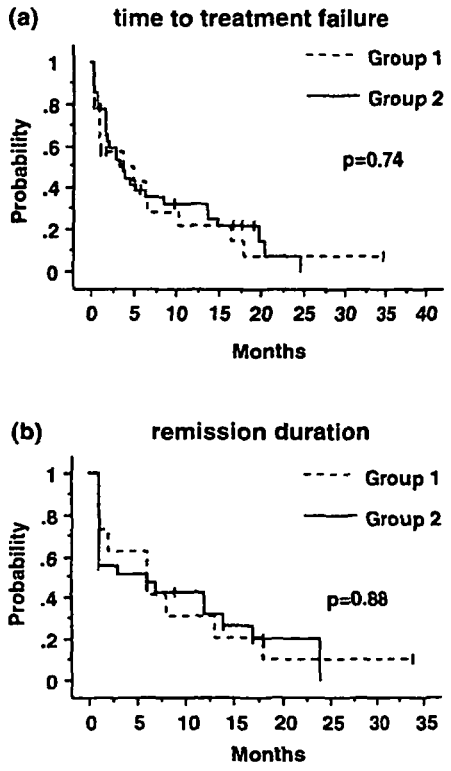

Figure 1. Time to treatment failure for group 1 and 2 (a), and (b) remission duration for group 1 and 2.

haemoglobin count before cladribine initiation ($P \leq 0.04$, Table 2b).

Tumour load reduction of $> 50\%$ as assessed by lymph node, liver and spleen measurements as well as lymphocyte count decrease of $> 50\%$ was seen in 23 patients in which the response criteria according to the blood counts did not reach the strict criteria for response. In three patients, no tumour was detectable (including bone marrow biopsy and CT scans), haemoglobin and platelet count however did not completely recover. This observation was independent of patient groups (group 1: 10 of 20, group 2: 13 of 35).

Follow-up

After the last cladribine cycle, the patients were observed without receiving further therapy until relapse or progression. The median time to treatment failure was 4.5 months and 3.8 months in group 1 and 2, respectively (Figure 1a). Median follow-up time was 19.3 months, while median overall remission duration was six months in both groups (Figure 1b).

Toxicity

Non-haematologic toxicity was mild. Overall, three of 20 patients (15%) in group 1 had no side effects compared with 16 of 35 patients (46%) in group 2 ($P = 0.04$). Nausea (grade 2) was seen in one patient, but vomiting did not occur. No patient had mucositis, alopecia, and pulmonary, cardiac or renal toxicities. Moderate skin exanthema and induration were occasionally seen at the injection sites in group 2. Three patients of group 1 developed moderate phlebitis. Treatment was discontinued in nine patients due to toxicity, in eight patients because of severe infections (group 1: seven patients, group 2: one patient), and in one patient due to autoimmune-haemolytic anaemia (group 2) acquired during treatment.

Myelotoxicity and immunosuppression with opportunistic infections were the most important side effects. Twenty-six of 36 cycles (72%) of cladribine administered to patients in group 1 were associated with grade 1–4 neutropenia. With dose reduction in group 2 this high incidence was reduced to 28 of 68 cycles (41%). Decrease of platelets $< 100 \times 10^9/l$ was seen in 18 of 37 cycles in group 1 (49%) and in 29 of 79 cycles in group 2 (37%). One patient in group 2 developed an immune haemolytic anaemia after the first cycle which was successfully treated with steroids.

Infectious complications were the most important adverse event in group 1. Infections occurred in 14 out of 41 cycles (34%) given to 10 of 20 patients (50%). The incidence was much lower in group 2: seven of 89 cycles administered were complicated by infections (8%), and seven of 35 patients (20%) suffered from infection ($P = 0.03$, by patient). This was also true for infections of grade ≥ 2 (10 of 41 vs. two of 89 by cycle, and nine of 20 vs. two of 35 by patient, $P = 0.0009$). All infections occurred within 40 days after the start of any cladribine cycle. The infectious agents are listed in Table 3. In a univariate analysis, infections of grade ≥ 2 (both groups together) were independent of age, performance status, disease duration, number of pretreatments, and lymphocyte count as well as status of disease. Neutrophil count before start of therapy was associated with infection risk ($P = 0.008$).

Discussion

Cladribine at a dose of 0.6–0.7 mg/kg/cycle has been given intravenously to more than 400 patients with CLL leading to responses varying between 20% to 70% [6–15]. As in the present study, a large number of these patients were heavily pretreated, refractory to previous therapy and/or progressive. Our response rate of 38% is in the range of other studies using the same response criteria [24]. It is of interest that a $> 50\%$ tumour load reduction as assessed by measurements of lymph node/liver/spleen enlargements and lymphocyte count was observed in another 35% of patients. However, the blood cell counts (in particular platelets) did not reach normal values, and thus, these patients did not fulfil the International Criteria for response [24]. It is, however, possible that long-lasting myelotoxicity after several cytostatic therapies including cladribine was the cause for this persistent cytopenia. Indeed, we have recently reported persistent thrombocytopenia in previously untreated fol-

Table 3. Type of infections.

	Group 1 WHO grade					Group 2 WHO grade				
	All	1	2	3	4	All	1	2	3	4
Skin infections										
Herpes simplex (labialis, genitalis)	1	1	–	–	–	1	1	–	–	–
Herpes zoster	1	–	–	–	1	–	–	–	–	–
Abscess of unknown origin	1	–	1	–	–	1	–	–	1	–
Fungal infections	1	1	–	–	–	1	1	–	–	–
Bronchopneumonia	6	2	–	3	1[a]	–	–	–	–	–
Septicaemia										
Proteus vulgaris	–	–	–	–	–	1	–	–	1	–
Staph. aureus	1	–	–	1	–	–	–	–	–	–
Miscellaneous										
Cholecystitis acuta	1	–	–	1	–	–	–	–	–	–
Sinusitis/otitis media	1	–	1	–	–	2	2	–	–	–
Flu	1	–	1	–	–	1	1	–	–	–
Total	14	4	3	5	2	7	5	–	2	–
Total cycles with infections	14/41					7/89				
Percentage of cycles with infections	34%					8%				

[a] Lethal.

licular lymphomas after cladribine [16]. Taken together, cladribine is highly active in pretreated CLL, with a total response of 67% when refractory and progressive patients, who reached clinical stabilisation under cladribine, are also included. The remission duration and time to treatment failure, similar in both groups, are in agreement with reported data of four to 20 months [6–9].

The high response rate together with durable remissions (median of six months in our study) makes cladribine a suitable drug for refractory or relapsing CLL patients. However, toxicity (myelotoxicity and infections, mainly of opportunistic type [12, 22–24]) and its rather complicated way of administration are reasons to withhold the drug. We therefore aimed to simplify cladribine administration and to decrease the side effects by dose reduction. Our results show that i.v. infusions (over 24 hours) give no advantage and that subcutaneous cladribine bolus injections are feasible on an outpatient basis. Indeed, most patients were able to inject the daily dose themselves and were seen in the oncology departments only once every four weeks. Furthermore, the dose reduction by 29% led to a clear decrease in the incidence of side effects, in particular less neutropenias and perhaps more importantly, to a diminished risk of infections ($P = 0.03$), especially of severe grades (≥ 2, $P = 0.0009$). Conversely, the response rate was apparently not influenced by the dose reduction ($P = 0.78$).

The present study is not a randomised trial. However, all participating physicians were informed about the increased risk of infections in group 1 before the dose was reduced. At this time it was decided by the participating physicians not to administer a prophylactic antimicrobial therapy, but to reduce the dose. Special attention was therefore directed by the physicians to the occurrence of infections and myelotoxicity in group 2. This is perhaps one of the explanations of why the frequency of grade 1 infections (in particular *Herpes simplex*) were similar in both groups. Our results therefore indicate strongly that the diminution of infection risk in group 2 is real and due to the reduced cladribine dose intensity.

There remains the question as to which purine nucleoside should be used for CLL, since both fludarabine and cladribine are highly active in this disease [3]. A randomised study comparing response rate, durability of response, and toxicity profile after fludarabine, chlorambucil or cladribine therapy has been recently started by G. Juliusson et al. in previously untreated CLL patients.

In conclusion our study shows that cladribine is an effective salvage therapy in CLL and that cladribine can be administered safely as s.c. bolus injections on an outpatient basis. A 29% reduction from standard dose resulted in a significant decrease in infection rate together with a comparable response rate. Further trials with relatively larger sample sizes should confirm these findings in order to establish the optimum dose for cladribine in patients with CLL.

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Received 9 January 1998; accepted 29 April 1998.

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