Long-term survival following cladribine (2-chlorodeoxyadenosine) therapy in previously treated patients with chronic lymphocytic leukemia

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Summary

Purpose: To assess long-term survival following cladribine salvage treatment for previously treated patients with chronic lymphocytic leukemia.

Patients and methods: Fifty-two patients aged 39–84 years with previously treated CLL received cladribine 0.12 mg/kg/day in 2-hour infusions for 5 days in monthly courses. Two-thirds were refractory to previous therapy, and 8 had prior fludarabine.

Results: Sixteen (31%) patients achieved complete response (CR) and 14 (27%) partial remission (PR) according to consensus criteria. Response correlated with clinical stage, number of previous treatment regimes, blood lymphocyte count, and lymphocyte half-life following the first cladribine course. Toxicity included pneumonia (n = 9), herpes zoster (n = 7), and septicemia (n = 2). Four patients in CR underwent high-dose chemotherapy with autologous blood stem cell support, and 2 remain in CR 48 and 60 months from start of cladribine, and 2 had relapse at 42 and 48 months, respectively. Median progression-free survival (Kaplan–Meier analysis) for CR patients was 23 months from start of cladribine treatment, and for PR patients 16 months. The projected overall survival was 80% at 3 years for CR patients, and the median survival 28 months for PR patients and 4 months for non-responding patients.

Conclusions: Our previous finding of durable CRs from cladribine in advanced CLL is thus confirmed in a larger patient material, and follow-up indicate that long-term survival may be achieved.

Key words: autologous blood stem cell transplantation, 2-CdA, CLL, complete remission, fludarabine, nucleoside analogue, treatment

Introduction

Therapy of chronic lymphocytic leukemia (CLL) [1] has become an area of increasing interest due to the clinical introduction of a new group of chemotherapeutic agents, i.e., the halogenated purine nucleoside analogues [2], whose activity as anti-cancer agents was suggested 36 years ago [3]. Fludarabine [4] is now approved second-line therapy for CLL, and 2 randomized trials indicate an improved response rate [5, 6], although as yet no survival benefit is documented [5–7].

Cladribine (2-chloro-2'-deoxyadenosine, CdA) [8] is another halogenated purine analogue, with a clinical useful effect in a broad range of malignant and non-malignant disorders, such as hairy cell leukemia [9], B-cell [2, 10], and T-cell [11] lymphomas, Waldenström's macroglobulinemia [12], acute myeloid leukemia [13, 14], Langerhans cell histiocytosis [15], chronic progressive multiple sclerosis [16], and autoimmune hemolytic anemia [8].

In the report from the Scripp's Clinic, 4 of 90 (4%) previously treated patients with CLL achieved a CR from cladribine, and 36 (40%) had a PR [17]. The results in de novo patients are better, with 5 of 20 (25%) achieving CR [18] in the U.S. study, 9 of 19 (47%) in the Belgian study [19], and 9 of 32 (28%) in the Australian study [20]. In the interim analysis of our study of oral cladribine as primary therapy for CLL, 11 of 32 (34%) patients achieved CR, and 13 (41%) had PR [21]. In the updated analysis 24 of 63 (38%) patients had achieved CR, and 23 (37%) PR [22].

We previously reported a high response rate from cladribine also in previously treated CLL cases, with 7 of 18 patients (39%) achieving CR [23]. We here report an updated analysis of 52 patients, indicating a continuing high CR rate and durable responses.

Patients and methods

Patients

Fifty-two patients with symptomatic B-cell chronic lymphocytic leukemia according to standard criteria [24], including flow cytometry phenotyping, were included from May 1990 through February 1994. To be eligible for study patients had to have previous treatment for CLL, and ongoing active disease causing need for therapy. There were 38 males and 14 females. The mean (± SD) age
at start of cladribine therapy was 59 ± 12 years (range 39–84 years), and the disease duration 100 ± 48 months (range 27–224 months). The clinical stage according to Binet [25] was progressive stage A in 12 cases (23%), stage B in 13 cases (25%), and stage C in 27 cases (52%). All patients were previously treated; 21 (40%) had had 1 previous regime, 12 (23%) had 2, and 19 (37%) 3 or more previous regimes. Thirty-five patients (67%) had less than partial remission from the previous regime, and were considered to have resistant disease. Eight patients had previous fludarabine treatment, 1 of them had a relapse from PR whereas 7 failed fludarabine.

Cladribine source and treatment schedule

The cladribine was a generous gift from Dr. Ernest Beutler, La Jolla, CA, or purchased from Dr. Zygmunt Kazimierczuk, The Foundation for the Development of Diagnostics and Therapy, Warsaw, Poland. After analysis of chemical identity and purity a stock solution of 1 or 2 mg/ml in buffered saline was prepared by the pharmacy at Huddinge Hospital. All patients received 0.12 mg/kg body weight daily in 2-hour intravenous infusions during 5 consecutive days. The courses were repeated about monthly. Prophylactic antibiotics were not given routinely. Supported care included when appropriate filtered but not irradiated blood products. The study was approved by the FDA, initially under the IND of Dr. Beutler, and by the Swedish Medical Products Agency and the ethical committee at Huddinge Hospital.

Response criteria

The response criteria recommended by the National Cancer Institute-sponsored Working Group were used [24]. For complete remission, at least two months of hemoglobin >110 g/l, blood lymphocyte count less than 4 × 10^7/l, neutrophils more than 100 × 10^7/l, neutrophils more than 1.5 × 10^9/l, no constitutional symptoms, no organomegaly, and less than 30% lymphoid cells of the nucleated cells of the bone marrow with or without nodules were required. Nodules were disregarded, to allow comparability with other studies using the Working Group response criteria, and since nodules may be compatible with complete remission as indicated by flow cytometry, as well as lack of nodules are compatible with residual clonal cells.

Partial remission was indicated by a more than 50% decrease in the blood lymphocyte counts and organomegaly, and at least a 50% reduction of anemia, thrombocytopenia, and neutropenia. Routine bone marrow sampling for evaluation of remission duration was performed only in patients following stem cell transplantation, whereas progression in other patients was documented when indicated by blood counts or clinical findings during regular check-ups at least 3-monthly.

Statistical analysis

Parametric and non-parametric description of data, Student's t-test for independent samples, Kaplan–Meier plots and log-rank analyses were performed using the Statistica/Mac software (StatSoft, Tulsa, OK, U.S.A.).

Results

Response rate

Sixteen patients (31%) achieved CR, and 14 (27%) had a PR. CR patients received a mean of 5.1 ± 1.5 cladribine courses, PR patients 4.1 ± 1.3 courses and non-responding patients 1.9 ± 0.9 courses. Two-colour flow cytometry failed to identify CLL-cells in bone marrow aspirates from half of the patients with CR, including all patients who proceeded to stem cell harvest. Response rates according to clinical stage and number of previous regimes are shown in Table 1. Response was significantly associated with lower clinical stage (P < 0.01), lower lymphocyte count (P = 0.018), higher platelet count (P < 0.01), fewer previous treatment regimes (P < 0.01), previous response to therapy (P = 0.04) and lower serum creatinine (P = 0.04), whereas age, disease duration, hemoglobin, serum lactic dehydrogenase, albumin, uric acid, C-reactive protein and immunoglobulin levels were uninformative. There were significant correlations between the parameters stage, platelet count, number of previous regimes, and response to previous therapy (all P < 0.04), whereas the lymphocyte count was an independent prognostic factor. The median (range) lymphocyte halflife following the first cladribine course, defined as previously described [23], was 5 (1–38) days in CR patients, 18.5 (1–31) days in PR patients, and 28 (5–50) days in non-responding patients (CR + PR versus NR, P < 0.000001).

Remission duration

Median response duration was 20 months (quartile values, 14 and 25 months; Kaplan–Meier plot, patients with autologous or allogeneic transplants censored at time of transplant). CRs were more durable than PRs (Figure 1).

Survival

The projected median overall survival for all patients was 27 months (Figure 2 shows overall survival with patient censored at time for allogeneic transplant). Thirty-four patients (65%) have died, with a median survival of 14 months, and the median observation of surviving patients is 30 months. Kaplan–Meier plots of overall survival according to clinical stage and final re-

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Progression-free survival in months from start of cladribine therapy according to response to cladribine. CR, complete remission (n = 16); PR, partial remission (n = 14). Patients who underwent autologous or allogeneic transplant are censored at time of transplant.

Figure 1.

Overall survival in months according to Binet stage. A, n = 12; B, n = 13; C, n = 27. P = 0.008.

Figure 3.

Kaplan-Meier plot showing overall survival in months from start of cladribine treatment for all 52 patients. Patient with allogeneic transplant censored at time of transplant.

Figure 2.

Overall survival in months according to final response to cladribine. CR, n = 16; PR, n = 14; NR (no response), n = 22.

Figure 4.

Infections
Twenty-four patients (46%) had no infection during cladribine treatment and the subsequent observation until disease progression or change of therapy. Fourteen patients (27%) had moderate (not requiring intravenous treatment) and another 14 (27%) severe infections. There were 2 septicemias, 1 caused by *E. coli* and 1 by *N. meningitidis*, and 9 pneumonias, 4 of them with opportunistic agents, such as candida, aspergillus, and adenovirus, and 1 with pneumococci. Seven patients developed dermatomal herpes zoster, 1 had herpes simplex blisters, 1 elderly man had chickenpox, and 1 had an encephalitis thought to be caused by herpes virus. Two patients developed Richter transformation, and 1 had prolymphocytic transformation.

Hematologic toxicity
Most patients experienced hematologic toxicity. The mean nadir of platelet counts (including those with pre-
treatment thrombocytopenia) during the whole treatment period was $71 \pm 77 \times 10^9/l$. Forty-eight percent had WHO grade III–IV thrombocytopenia ($<50 \times 10^9/l$) at any time during therapy, and 26% grade I–II thrombocytopenia ($50–99 \times 10^9/l$). One fourth of the patients had a platelet nadir $<10 \times 10^9/l$, and one fourth had no platelet count below $100 \times 10^9/l$. The pretreatment platelet values corresponded to grade III–IV in 16%, and to grade I–II in 22%. Five of 22 patients (23%) with pretreatment platelet counts below $100 \times 10^9/l$ subsequently normalized their platelet counts, whereas 9 of 30 (33%) with pretreatment platelet counts over $100 \times 10^9/l$ developed a persistent or prolonged thrombocytopenia, not responding to steroid therapy.

The mean granulocyte nadir was $0.83 \pm 0.68 \times 10^9/l$. Granulocyte toxicity of grade IV at any time during treatment ($<0.5 \times 10^9/l$) was found in 40%, and grade III ($0.5–0.9 \times 10^9/l$) in 23%. Ten percent had a nadir of granulocyte counts at any time below $0.2 \times 10^9/l$. The granulocytopenias were usually brief and sporadic, and not associated to clinical symptoms.

One patient with a pretreatment positive Coomb's test developed a hemolytic crisis that responded to steroids, and could subsequently continue cladribine courses.

Sixteen patients had CD4-counts evaluated during treatment and follow-up (Figure 5). No correlation between CD4 counts and infectious complications was observed.

**Sequential purine analogues**

Twelve patients had both cladribine and fludarabine therapy, 8 of them with fludarabine prior to cladribine. Seven patients had failed fludarabine and received cladribine subsequently. Four of them are previously reported: One patient (no. 4 in ref. [26]) with progressive disease during 10 courses of fludarabine as third-line therapy achieved a complete remission from cladribine, subsequently underwent autologous stem cell harvest and transplantation (below) and is in continuous complete remission 53 months from start of cladribine. Patients 1 and 2 in ref. [26] had a PR duration of 20 and 25 months from start of cladribine, respectively, were retreated with cladribine [27] and died from progressive CLL with infections 44 and 41 months from start of initial cladribine, respectively. Patient 3 had a complete follow-up in the previous report [23]. One patient had fludarabine as primary treatment, and achieved partial remission of short duration. Cladribine was given as second-line therapy resulting in a more rapid response of a better quality than previously (Figure 6).

Four patients failed both fludarabine and cladribine; 3 heavily pretreated patients had fludarabine before cladribine, and 1 patient failed chlorambucil, cladribine, and fludarabine in that order.

One patient with cytopenia and no response to 2 courses of cladribine as sixth regime had a partial response to subsequent fludarabine given in 13 courses over 13 months, and he survived 23 months from start of fludarabine.

Two patients who responded to cladribine had fludarabine at relapse: 1 with relapse from CR 22 months from start of cladribine achieved PR from fludarabine, and 1 who progressed from PR at 18 months failed fludarabine.

Four additional patients who were retreated with cladribine following relapse from cladribine-induced responses are previously reported [27].

**Stem cell harvest and high-dose therapy with stem cell support**

Four patients in complete remission underwent stem cell harvest following cyclophosphamide (1–2 g/sqm)
and filgrastim (5 μg/kg daily) with or without additional bone marrow harvest and subsequently had high-dose therapy BEAM (carmustin, etoposide, cyto-
sin arabinoside, melphalan) and stem cell reinfusion. Multiple apheresis procedures were always required. Stem cell reinfusion was done 11, 13, 18 and 19 months from start of cladribine, respectively, following 6 or 7 courses of cladribine. Three patients had a quick initial recovery of blood counts, whereas 1 patient was transfusion-dependent for red cells and platelets for 1 year before having a normalized hemoglobin during erythropoietin treatment and becoming independent of platelet transfusions. Two patients are in continuous complete remission 29 and 50 months following stem cell transplantation without further treatment, whereas 2 have had relapse 28 and 29 months from transplant, respectively. One additional patient in CR was scheduled for autologous stem cell transplantation, but harvests yielded inadequate stem cell numbers.

A subsequent patient with minimal response to 2 courses cladribine had an allogeneic sibling marrow transplant 2 months from start of cladribine, and is also in continuous complete remission 18 months from transplant.

Discussion

In our previous evaluation of 18 previously treated CLL patients we found that the CR rate from intermittent infusion of cladribine was 39% [23], a higher response rate than in the U.S. study [17]. With an enlarged patient material we now confirm a CR rate of about one third in previously treated patients. Furthermore, with a longer follow-up we document that responses were durable, and survival prolonged for responding patients. On the other hand, one fifth of the patients died within 4 months, mostly due to progressive disease or recurrence of infections. Response and survival was expectedly related to predictive factors, such as clinical stage, number of previous treatment regimes, and response to previous therapy. We confirmed that the decrease rate of lymphocyte counts following the first cladribine course correlates with final response [23]; however, no such correlation to overall survival was found.

Patient selection and initial management of the CLL are probably significant causes of discrepancies between the results in different studies. In the Scripp's study almost all patients were refractory stage C patients [17]; however, the CR rate among our stage C patients was 25%, although some were not clearly refractory but progressing off therapy.

Of interest, the response duration in our study was not different from the 18 months overall response duration and 4-year CR duration following fludarabine as primary therapy [7]. However, as expected the response rates were higher from fludarabine in de novo patients than from cladribine in previously treated cases.

The present study enables the first reliable evaluation of overall survival following cladribine, since two thirds of the patients have been followed until death with a mean survival of 14 months, and the median observation time for surviving patients is 30 months. The overall survival, and survival according to Binet stage from cladribine treatment in our study seem to be as good as results in CLL patients following fludara-
biner therapy in the U.S. studies [4], when stratified for clinical stage and number of previous regimes. When survival of our patients is compared to that of previously treated patients in the European randomized trial between fludarabine and CAP (cyclophosphamide, doxorubicin, prednisone), the results are very similar to both the fludarabine and the CAP arm [28]. However, only a limited amount of an oral alkylating agent was allowed as previous treatment in the randomized trial, whereas most of our patients had had more intense previous therapy.

The four patients who underwent stem cell harvest with high-dose chemotherapy and stem cell reinfusion indicate firstly that cladribine-induced complete remissions may be of a high quality, and secondly, that the procedure is feasible following cladribine, similar to fludarabine-induced remissions in CLL [29, 30]. However, multiple harvests were always needed, and the stem cell yield was sometimes inadequate.

Long-term follow-up indicate that some patients may have a durable response to cladribine despite less than PR from preceeding fludarabine therapy [26, 31]. Some previously unpublished cases with divergent response to fludarabine and cladribine are presented here, including one patient with a clearly better response to fludarabine than to cladribine, and more such patients are reported (E. Beutler, personal communication). Unfortunately, previous studies documenting lack of response to cladribine in patients with fludarabine-failure have been unable to evaluate the existence of cross-resistance, since most patients (i) had other chemotherapy in between fludarabine and cladri-
bine, (ii) had significant tumor cell reduction by cladri-
bine, but (iii) were unable to tolerate repeated cladri-
bine courses (32). It is obvious that heavily pretreated patients are at great risk for bone marrow failure from nucleoside analogues, and the frequency of cross-resistance between fludarabine and cladribine has to be assessed in patients with early disease, such as in an ongoing U.S. study.

Toxicity in the current study was manageable, although most patients developed cytopenia and about half had some kind of infectious complication. It is important to be alert on early signs of toxicity, such as decreasing platelets and febrile episodes, and to avoid further treatment in such cases. It seems that the frequency of treatment-related severe cytopenia and fun-
gal pneumonia have decreased with such a strategy. However, we were in many cases able to continue suc-
cessful therapy in patients following recovery from certain complications, such as bacterial pneumonia, herpes zoster, and autoimmune hemolysis. Few patients had severe and fatal toxicity during the initial phase of therapy, whereas those with cladribine-refractory disease frequently developed severe infections, especially following salvage chemotherapy. Opportunistic infections were not found to be more common in patients who required steroid therapy for autoimmune hemolysis. Well-designed studies are required to evaluate the long-term risk for infectious complications due to the T-cell deficiency caused by the purine analogues (Figure 5, and refs. [7, 33, 34]). It is also important to assess whether the risk for Richter transformation or secondary cancers is increased.

In conclusion, our extended study of cladribine therapy to previously treated patients with CLL have resulted in an encouraging response rate, with a response duration and overall survival as good as those reported from fludarabine treatment. The optimal schedule for cladribine treatment is not yet known, and the search for improved regimes should preferably utilize the effective and simple subcutaneous or oral [21, 22, 35–37] routes of administration. Subsequently, a randomized trial comparing cladribine, fludarabine, and chlorambucil, with the evaluation of long-term toxicity and survival is warranted.

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