CLINICAL TRIALS AND OBSERVATIONS

Clinical characteristics and long-term outcome of young hairy cell leukemia patients treated with cladribine: a single-institution series

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Key Points

- HCL patients ≤40 years at diagnosis treated with cladribine obtain complete and durable responses, but ultimately relapse.
- There was no increased risk of second primary malignancies in young hairy cell leukemia patients followed for protracted periods.

Hairy cell leukemia (HCL) is a rare, indolent B-cell disorder in which single courses of cladribine induce high rates of complete responses. We report on 88 young HCL patients (≤40 years of age at diagnosis) treated with cladribine from the Scripps Clinic HCL Database, of whom 83 were evaluable for response. Seventy-three patients (88%) achieved an initial complete response and 10 (12%) a partial response, with a median response duration of 57 months. Forty-eight patients (58%) relapsed, with a median time to first relapse for all responders of 54 months. Eight patients developed 11 second primary malignancies with an excess frequency of 1.60 (95% confidence interval, 0.80-2.89). Thirteen (15%) patients died with a mortality ratio compared with age-matched normals of 1.85 (95% confidence interval, 1.07-3.18). Median overall survival for all patients following the first cladribine course was 231 months, and 251 months from diagnosis. Single courses of cladribine induce high rates of complete and durable responses in the majority of young HCL patients and are therefore recommended for HCL patients regardless of age. (*Blood*. 2014;123(2):177-183)

Introduction

Hairy cell leukemia (HCL) is an uncommon chronic B-cell lymphoproliferative disorder originally described by Bouroncle[1] in 1958 and characterized by circulating B cells with cytoplasmic projections, pancytopenia, splenomegaly, and recurrent infections. HCL expresses CD11c, CD25, and CD103 surface antigens in addition to the pan B-cell antigens CD19, CD20, and CD22. More recently, whole-exome gene sequencing has identified the BRAF V600E mutation in the majority of HCL patients, suggesting disease-specific oncogene dependence.[2] Though indolent, HCL remains an incurable disease. Splenectomy was historically the treatment of choice. Quesada et al were the first to describe responses induced by interferon α in HCL patients, though subsequent studies revealed a disappointingly low complete response (CR) rate and short response duration.[3,4] Subsequently, 2 nucleoside analogs, 2′-deoxycoformycin (pentostatin) and 2-chlorodeoxyadenosine (cladribine) were found to induce long-lasting complete remissions in the majority of HCL patients.[4-6] Rituximab has modest single-agent activity in patients with relapsed HCL, though increased response rates and more durable remissions are seen when combined with purine nucleoside analogs.[7,8] Most recently, the BRAF inhibitor, vemurafenib, demonstrated efficacy in a single, highly refractory HCL patient.[9]

In 1990, investigators at Scripps Clinic first reported the promising activity of cladribine in HCL patients.[10] Of 12 patients treated, 11 achieved a CR, with 1 achieving a partial response (PR). Saven et al demonstrated long-lasting CRs in the majority of 349 evaluable patients following a single course of cladribine.[11] There is limited information about the specific clinical characteristics and outcomes of young patients following cladribine therapy for HCL. Prior therapeutic trials reported outcomes in patients with a median age in their sixth decade. We report here on a retrospective study of 88 young HCL patients, ≤40 years of age at diagnosis from the Scripps Clinic HCL Database, who all received cladribine, and update their outcomes documenting their response rates and duration, retreatment results, time-to-treatment failure (TTF) rates, survival rates, and incidence of second malignancies.

Patients and methods

Patient population and methods

Patients were identified from the Scripps Clinic HCL Database, an observational database of 394 consecutive HCL patients treated at Scripps Clinic with cladribine, beginning in 1986. Patients required a diagnosis of HCL on the basis of a review of the peripheral blood, bone marrow, and/or splenic tissue in splenectomized patients, as reviewed by hematopathologists at Scripps Clinic. Most of the patients in this database received cladribine before US Food and Drug Administration approval in 1993 and were enrolled in a clinical trial with stringent follow-up assessments being required. A total of 88 patients had a diagnosis of HCL at or before the age of 40 years. Though treatment was not always administered before 40 years of age, each patient received cladribine during his or her disease course. The Scripps Clinic Institutional Review Board approved this retrospective

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analysis. Informed consent was obtained in accordance with the Declaration of Helsinki. Patients only received cladribine therapy for an absolute neutrophil count $<1.0 \times 10^9$/L, hemoglobin concentration <10 g/dL, platelets $<100 \times 10^9$/L, and/or symptomatic splenomegaly.

A second primary malignancy was defined as any invasive malignancy, with the exception of nonmelanoma-localized skin (squamous or basal) cancer.

Drug therapy and supportive care

Cladribine was given as a 7-day continuous intravenous infusion at a dose of 0.1 mg/kg per day.

Response criteria and relapse definition

Complete response (CR) to cladribine was defined as the disappearance of all evidence of disease. The complete blood count was required to have $\geq 1.5 \times 10^9$ neutrophils/L, ≥12.0 g/dL of hemoglobin, $\geq 100 \times 10^9$ platelets/L, and the absence of any hairy cells on peripheral blood smear. Morphologic absence of disease on marrow aspiration and biopsy specimens was required. Physical examination showed no palpable lymphadenopathy or hepatosplenomegaly. In those patients with baseline lymphadenopathy on chest radiograph and/or computed tomography scans of the abdomen and pelvis, follow-up imaging studies showed all lymph nodes to be ≤2 cm in diameter. Peripheral blood immunophenotypic analysis, tartrate-resistant acid phosphatase staining, and marrow immunohistochemical staining (L26 and DBA.44) were not included in the definition of CR.

PR to cladribine required >50% reduction in the absolute hairy cell count in the peripheral blood and bone marrow, >50% improvement of all cytopenias, and >50% reduction in abnormal lymphadenopathy or hepatosplenomegaly.

Complete hematologic response (CHR) to cladribine required blood count normalization although no evaluation of the bone marrow was performed to document hairy cell status.

Patients not meeting any of these criteria were classified as nonresponders

Posttreatment assessments were not uniform for all patients. The first 76 patients, treated on the original cladribine study, generally had peripheral blood counts and bone marrow evaluations performed at 3, 6, 12, and 24 months after treatment.[11] Subsequently, peripheral blood counts were obtained yearly and bone marrow biopsies were repeated only for evaluation of cytopenias. The other 12 patients treated with cladribine had their peripheral blood counts monitored as outlined previously, with bone marrow biopsies repeated to assess their first response to cladribine, and only thereafter to evaluate subsequent development of cytopenias or splenomegaly.

Immunophenotyping was not routinely collected and was not included in response determinations

Relapse after CR to cladribine was defined as the reappearance of hairy cells in the peripheral blood smear and/or bone marrow (regardless of the degree of infiltration), development of peripheral blood cytopenias, and/or splenomegaly on physical examination. Relapse after PR was a greater than 50% increase of residual hairy cells in the marrow, development of cytopenias, splenomegaly on physical examination insufficient to qualify as a PR, or reappearance of hairy cells in the bone marrow of those patients classified as partial responders based on residual splenomegaly only.

Statistical analysis

TTF was calculated for each patient achieving a PR or CR as the time from first treatment with cladribine to first relapse or death from any cause (event) or last contact (censored). Overall survival (OS) was calculated as the time from diagnosis to death (event) or last contact (censored). Kaplan-Meier curves were constructed for TTF and OS for the overall cohort as well as patients with CR and those with PR, respectively. Survival and TTF curves of patients with CR were compared with those with PR by the 2-sided log-rank test.

Standardized mortality ratio was calculated by dividing the observed number of deaths by the expected numbers of deaths calculated from sex- and age-specific (in 10-year categories) mortality rates, as reported by the National Center for Health Statistics,[12] multiplied by the observed number of person-years at risk following the diagnosis of HCL. The standardized incidence ratio for second malignancies was calculated by dividing the observed number of malignancies following the diagnosis of HCL by the expected number of malignancies (excluding squamous and basal cell skin cancers) calculated from sex- and age-specific (in 5-year categories) cancer incidence rates,[13] obtained from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, multiplied by person-years at risk. Confidence intervals for both the standardized mortality ratio and the standardized incidence ratio for second malignancies were calculated assuming a Poisson distribution for the observed numbers.

Statistical analyses were conducted using the Prism 5 (GraphPad Software, La Jolla, CA).

Results

Patients

For all 88 patients, an attempt was made to obtain current health information on their HCL status, subsequent therapy, and possible development of secondary neoplasms. Eighty-one of these patients were treated on a prospective cladribine study, whereas 7 were treated off-study after US Food and Drug Administration approval of cladribine.[9,10] Nineteen patients could not be located for an updated status. The median follow-up for all 88 patients was 251 months (range, 42 to 484 months), and for the 19 patients whose status could not be updated was 241 months (range, 42-297 months).

There were 63 men (72%) and 25 women (28%), with a median age of 36 years (range, 20-40 years). Before receiving cladribine, 42 patients (48%) were previously untreated, 28 (32%) had undergone splenectomy, and 39 (44%) had received prior systemic therapy. Thirty-seven patients (42%) had received interferon, 4 (4%) received chlorambucil, 2 (2%) received 2′-deoxycoformycin, and 1 (1%) received an unknown systemic therapy. These therapies were given in varying combinations and sequences. The median duration from diagnosis from HCL to the first cladribine course was 16 months (range, 2 days to 470 months). The patient characteristics at first treatment of cladribine are listed in Table 1.

Response

Of 88 patients receiving a single course of cladribine, 83 were evaluable for response determination. Seventy-three (88%) patients achieved a CR and 10 (12%) achieved a PR; hence, the overall response rate was 100%. Five (6%) of the 88 patients did not undergo a repeat bone marrow examination, although they achieved normalization of their blood counts (CHR). Median response duration for the complete responders was 57 months (range, 7-246 months), and median response duration for partial responders was 20 months (range, 7-108 months). Median response duration for all responders was 57 months (range, 7-246 months).

Relapse and retreatment results

Forty-five of 83 (54%) evaluable patients who achieved a response ultimately relapsed; 37 of 73 (51%) complete responders relapsed at a median of 54 months (range, 7-246 months), and 8 of 10 (80%) partial responders relapsed at a median of 20 months (range, 7-108 months). Three of the 5 patients who achieved an initial CHR later

Table 1. Young HCL patient demographics at first treatment of cladribine

No. of patients	88
Male/female	63/25 (72%/28%)
Age, y	
Median	36 y
Range	20-40 y
Prior therapy	
None	42
Splenectomy alone	7
Interferon alone	17
Splenectomy, interferon	15
Splenectomy, interferon, 2′-deoxycoformycin	2
Chlorambucil, splenectomy	1
Chlorambucil, interferon, splenectomy	3
Other regimens	1
Duration from diagnosis of HCL to the first cladribine course	
Median	16 mo
Range	2 d to 470 mo
Peripheral blood hematologic parameters	
Absolute neutrophil count ($\times 10^9$/L)	
Median (range)	0.6 (0.1-2.7)
White blood cell count ($\times 10^9$/L)	
Median (range)	2.8 (0.3-30.3)
Hemoglobin level (g/dL)	
Median (range)	10.7 (3.2-16.1)
Platelets ($\times 10^9$/L)	
Median (range)	63 (11-136)

relapsed. Median time to first relapse for all responders was 54 months (range, 7-246 months).

Of the 48 patients who relapsed, 11 (23%) did not receive additional therapy, 31 (65%) were retreated with a second cladribine course, 5 (10%) received single-agent rituximab, and 1 (2%) received cladribine in combination with rituximab. The other patients who relapsed did not receive additional therapy because they had no significant cytopenias, no transfusion requirements, no constitutional symptoms, and no massive splenomegaly.

Response information following a second cladribine course was available for 27 of the 31 (87%) who were retreated. Of these 27 patients, 12 (44%) achieved a CR, 6 (22%) a PR, 8 (30%) a CHR, and 1 (4%) patient had no response. The median second response duration to cladribine for all responders was 30 months (range, 3-182 months). The median response duration to any second-line therapy was 27 months (range, 3-182 months). Patients with a prior CR had a median second response to cladribine of 35 months (range, 8-182 months), whereas those who had a prior PR had a median second response duration to cladribine of 30 months (range, 3-57 months), which was not statistically significant ($P = .66$; Wilcoxon rank-sum test). Table 2 outlines patient characteristics, prior therapies, and response to first and second courses of cladribine in relapsed patients.

Five patients who relapsed after receiving their first course of cladribine were treated with rituximab; 2 achieved a CHR, 2 had no response, and 1 patient's response was unknown. The 2 non-responders to rituximab subsequently received cladribine and both achieved a CHR. One patient who relapsed after the first course of cladribine received combination treatment with cladribine and rituximab and achieved a CHR.

Fourteen (45%) patients experienced a second relapse after 2 prior courses of cladribine. Of these patients, 5 (36%) receved a third course of cladribine: 1 patient achieved a CR and 4 patients achieved a PR. Four of 14 (29%) patients who relapsed after 2 courses of cladribine were treated with interferon or rituximab; 3 received single-agent rituximab, with 2 patients having no response and 1 response was unknown. One patient received rituximab alone (no response) followed by 2′-deoxycoformycin, which induced a CHR. One patient received interferon initially with an unknown response, but obtained a CR to subsequent 2′-deoxycoformycin.

Two patients received a fourth course of cladribine. One patient achieved a CR and subsequently relapsed 3 months later. He received a fifth course of cladribine and again achieved a CR. The other patient had no response to his fourth course of cladribine.

Second primary malignancies

After cladribine therapy, 8 patients developed 11 primary malignancies: 2 adenocarcinomas of the colon, 2 non-Hodgkin lymphomas, 2 adenocarcinomas of the prostate, 1 clear-cell carcinoma of kidney,

Table 2. Young HCL patients at first relapse after receiving cladribine

Number	48
Age	
Median (y)	38
Range	31-55
Sex	
Male	36
Female	12
Disease duration before cladribine	
Median (mo)	15
Range	0-668
Treatment before cladribine	
None	29
Splenectomy alone	3
Interferon alone	6
Splenectomy, interferon	6
Splenectomy, interferon, 2′-deoxycoformycin	2
Chlorambucil, splenectomy	1
Other regimens	1
First response to cladribine	
CR	37
PR	8
Unknown	3
Peripheral blood hematologic parameters at first relapse	
Absolute neutrophil count ($\times 10^9$/L)	
Median (range)	1.4 (0.6-6.0)
Hemoglobin level (g/dL)	
Median (range)	14.2 (8.7-17.5)
Platelets ($\times 10^9$/L)	
Median (range)	135 (4-403)
Duration to first relapse from cladribine therapy	
Median (mo)	54
Range	7-246
Treatment at relapse	
None	11
Cladribine	31
Rituximab	5
Cladribine + rituximab	1
Response to second course of cladribine (31 patients)	
CR	12
PR	6
CHR	8
No response	1
Unknown	4

Table 3. Second malignancies in young HCL patients after cladribine treatment

Patient	Second cancer	HCL therapy before cladribine	Age (y) at diagnosis of second cancer	Time (mo) from diagnosis of HCL to second cancer	Time (mo) from cladribine to second cancer	Survival (mo) from diagnosis of HCL	Survival (mo) after diagnosis of second cancer	Status
1	Adenocarcinoma, colon	Splenectomy	53	178	1	284	106	Alive
2	Adenocarcinoma, prostate	Splenectomy, interferon, chlorambucil	64	314	122	385	71	Dead
2	Adenocarcinoma, colon	Splenectomy, interferon, chlorambucil	61	281	89	385	104	Dead
2	Adenocarcinoma, pancreas	Splenectomy, interferon, chlorambucil	69	375	183	385	11	Dead
3	Non-Hodgkin lymphoma	IFN, G-CSF	65	301	236	337	37	Alive
4	Metastatic renal cell carcinoma	Splenectomy, IFN, chlorambucil, prednisone	59	353	206	354	1	Dead
5	CML	None	49	163	136	277	115	Alive
5	Non-Hodgkin lymphoma (follicular)	None	54	223	196	277	55	Alive
6	Adenocarcinoma, prostate	None	58	243	239	244	1	Alive
7	Acute myeloid leukemia – FAB M2	IFN, prednisone	60	327	63	334	7	Dead
8	Acute myeloid leukemia	Splenectomy, chlorambucil	61	395	247	402	7	Dead

CML, chronic myelogenous leukemia; G-CSF, granulocyte colony-stimulating factor; IFN, interferon.

1 adenocarcinoma of the pancreas, 1 chronic myeloid leukemia, and 2 acute myeloid leukemia (Table 3). No instances of myelodysplastic syndrome were observed. Of these 8 patients, 2 were previously untreated before cladribine therapy. Four patients were previously treated with interferon, 4 had prior splenectomies, and 3 had received prior chlorambucil. The median age at diagnosis of the second malignancy was 60 years (range, 49-73 years), median time from diagnosis of HCL to the second cancer was 301 months (range, 178-395 months), median time from cladribine administration to the second cancer was 183 months (range, 1-247 months), median survival time from diagnosis of HCL was 337 months (range, 244-402 months), and median survival time from diagnosis of the second cancer was 37 months (range, 1-115 months).

The expected number of second primary malignancies in this group of 88 patients is 6.86, based on calculations derived from the National Cancer Institute's SEER data. Since 11 cancers were observed in 8 patients, the excess frequency (observed-to-expected ratio) of developing a second primary malignancy was 1.60 (95% confidence interval, 0.80-2.89). This excess in secondary malignancies is not statistically significant ($P = .11$).

Of interest, 4 patients (median age 31; range, 24-35 years) had an antecedent diagnosis of malignancy before the diagnosis of HCL; 1 infiltrating carcinoma of the breast, 1 bladder cancer, 1 thyroid cancer, and 1 testicular cancer, despite their young age. Median time from the diagnosis of the antecedent malignancy to HCL diagnosis was 65 months (range, 35-159 months).

Deaths

Of the 88 young HCL patients, 13 (16%) have died. Of these 13 patients, 9 had experienced a prior CR and 4 a PR. These 13 patients died at a median of 109 months (range, 57-256 months) after their first cladribine course. The causes of death were 2 acute myeloid leukemia, 1 kidney cancer, 1 pancreatic cancer, 1 refractory HCL, 1 probable sepsis after retreatment of refractory HCL, and 7 unknown. Only 3 of these 13 patients did not have a documented relapse of HCL before death. The expected number of deaths in this group of 88 patients is 7.03 based on calculations from data from the National Center for Health Statistics. With 13 patient deaths in this series of patients, the standardized mortality ratio (observed-to-expected) ratio was 1.85 (95% confidence interval, 1.07-3.18), representing a small, but statistically significant increase in the risk of death ($P = .04$).

TTF and OS

The median TTF for the 88 patients was 56 months (range, 3-295 months) (Figure 1A). Median TTF for complete responders was 57 months (range, 7-246 months), whereas the median TTF or death for partial responders was 20 months (range, 6-108 months), which was statistically significant ($P = .001$) (Figure 1B). The median OS for all 88 patients from the time of their HCL diagnosis was 251 months (range, 42-484 months) (Figure 2A). Median survival from diagnosis for complete responders was 260 months (range, 42-441 months), whereas the median survival for partial responders was 199 months (range, 82-334 months), which was statistically significant ($P < .0001$) (Figure 2B). The median OS for all 88 patients after their first administration of cladribine was 231 months (range, 13-295 months) (Figure 3A). Median survival for complete responders from their first course of cladribine was 238 months (range, 13-295 months), whereas the median survival for partial responders from their first cladribine course was 122 months (range, 71-270 months), also statistically significant ($P = .0008$) (Figure 3B).

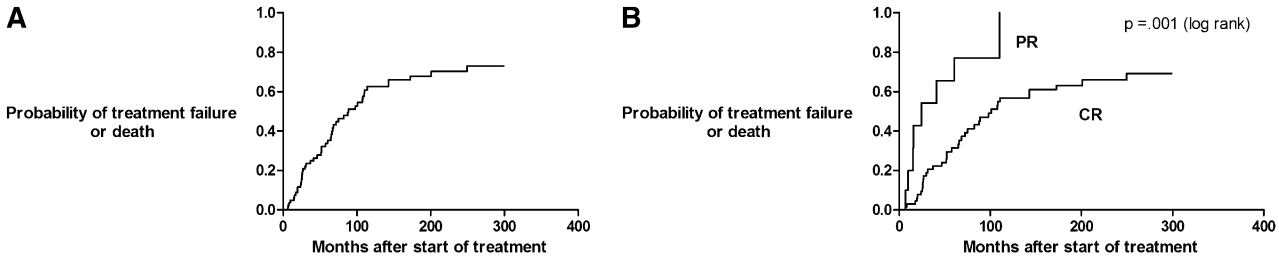

Figure 1. Time-to-treatment failure or death. (A) All 88 patients who achieved a response and (B) patients achieving a CR or PR.

Discussion

This study describes the characteristics and outcomes of 88 HCL patients, ≤40 years old at diagnosis, who were treated with cladribine between April 1986 and July 2011 at Scripps Clinic. These results confirm prior observations seen in older HCL patient populations that single courses of cladribine induce very high response rates, the majority of which are complete and durable, but with a risk of late relapse.[10,11,14,15] Salvage rates with second courses of cladribine in young HCL patients remain high, as has been documented in older HCL patients. A small, but increased incidence of second primary malignancies was observed in this young patient population; however, this was not statistically significant. There was, however, a small, but statistically significant, increase in the risk of death compared with the general population in this group of young HCL patients.

In 2003, Goodman et al reported the extended follow-up of 209 HCL patients, without age restriction, treated with cladribine, and at least 7 years of follow-up, selected from a dataset of 379 consecutive HCL patients treated at Scripps Clinic.[6] Of these 209 patients, 207 were evaluable for a response—achieving a 95% CR rate, whereas 5% achieved a PR—after a single course of cladribine. The median first response duration for all responders was 98 months. A total of 37% of patients relapsed after their first course of cladribine, with a median time to first relapse of 42 months. Of the 59 evaluable patients who received a second course of cladribine after having relapsed, 75% achieved a CR, 17% achieved a PR, and 8% failed to respond. In 379 consecutive HCL patients, 22% developed second primary malignancies with an observed-to-expected ratio of 2.03 using National Cancer Institute SEER data. The OS rate was 97% at 108 months.

Other groups have reported similar response rates in HCL patients with a median age in the sixth decade of life, with CRs demonstrated in 76% to 98% of evaluable patients.[14-17] Northwestern University has reported similar outcomes, with an OS rate of 87% at 12 years in HCL patients receiving a single course of cladribine.[17]

In this report, 88 HCL patients were ≤40 years of age at diagnosis, with a median age of 36 years. This represents a younger patient population than previously published studies, whose patient population was approximately 2 decades older.[7,15] The outcome of this young group was similarly outstanding. The initial response rate after the first course of cladribine was 100%, with the majority of responses being complete (88%). As in prior studies, responses were maintained for protracted periods, with a median 57-month duration of response for patients following their first course of cladribine. The median TTF for first relapse was 56 months; patients who had achieved a prior CR had a longer TTF than patients who achieved a PR (57 vs 20 months).

These patients also had high salvage rates with subsequent administrations of cladribine, demonstrating its efficacy in relapsed young HCL patients. Although each successive administration of cladribine yielded a lower CR rate and a shorter response duration, it was still efficacious in the majority of patients with a CR. There was no significant difference in median response duration between the first and second course of cladribine, 57 vs 30 months, respectively ($P = .22$). However, the large variability in response duration and the relatively small number of patients resulted in a very low power to find statistically significant differences between the 2 groups. This young cohort of HCL patients experienced survivals approximating that of healthy individuals. The median OS from diagnosis and after the first cladribine course was 251 and 231 months, respectively. Patients who achieved a CR after their first cladribine course had longer survivals compared with the partial responders: 260 vs 199 months, respectively.

The median response duration following a single course of cladribine in this cohort of young HCL patients was 57 months (range, 7-246 months). In the previously reported Scripps Clinic HCL population without age restrictions, the median response duration was 98 months, namely, 41 months longer than the young HCL population

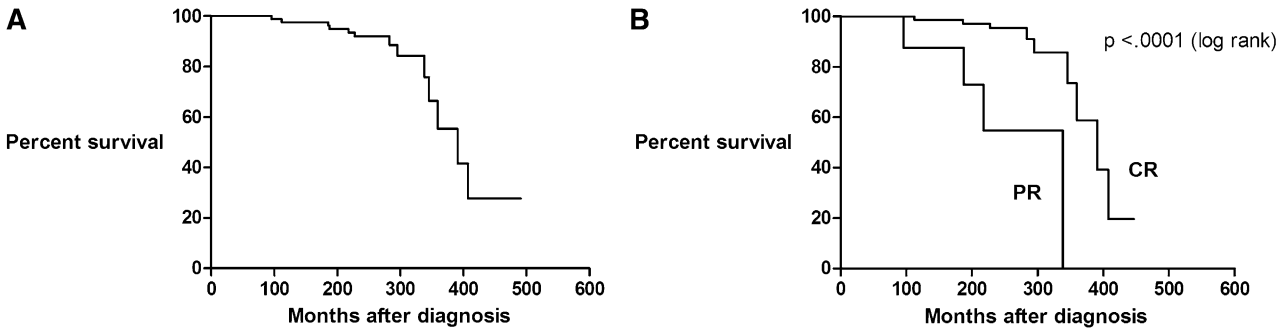

Figure 2. Overall survival from date of diagnosis. (A) All 88 treated patients and (B) for patients achieving a CR or PR.

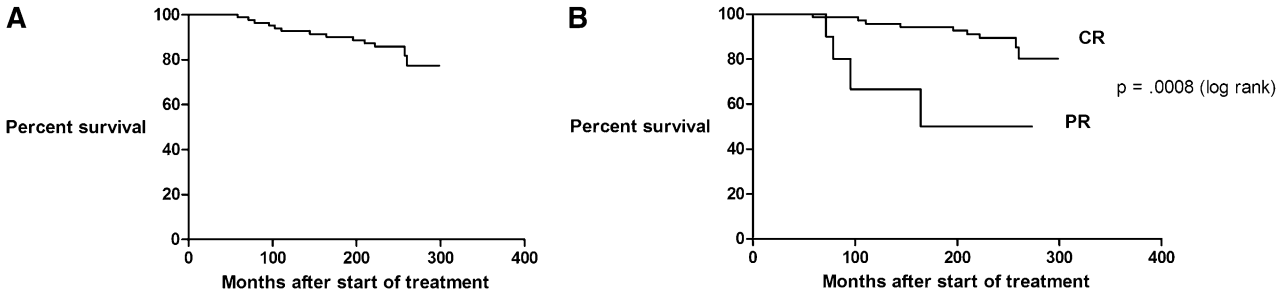

Figure 3. Overall survival from first cladribine administration. (A) All 88 patients and (B) for patients achieving a CR or PR.

(Table 4).[6] Furthermore, 58% of these young HCL patients were found to have relapsed after their first cladribine course, compared with only 37% without age restrictions.[6] When evaluating only those patients who relapsed in both Scripps studies, young patients relapsed 12 months later (54 vs 42 months, respectively) than the population without age restriction.[6] This result would appear to be counterintuitive. Potential explanations for this include nonstandardization of follow-up bone marrows, potential inaccuracies in the censoring of time intervals (including some patients who could not have their disease status updated), limitations of retrospective analyses, and intrinsic biologic differences between young and old HCL patients. Further investigations into the biology of young HCL patients' hairy cells, such as BRAF mutational status and cell-surface antigen expression, may provide insights and potentially indicate whether combination therapy with a purine nucleoside analog would be more efficacious in a young HCL populations.

Sigal et al[18] previously reported that in 19 HCL patients who received a single course of cladribine treatment and were in continuous and CHR at a median of 16 years, 9 (47%) had no evidence of minimal residual disease on bone marrow examination, whereas 10 (53%) had either minimal residual disease or frank morphologic evidence of HCL. This study demonstrated that the presence of minimal residual disease did not necessarily correlate with clinical hematologic relapse. Other studies, however, demonstrated a statistically significant association between the presence of minimal residual disease and HCL relapse.[19,20] It is therefore reasonable to predict that over time, the majority of patients will relapse following an initial response to cladribine.

Eleven second primary malignancies were documented in 8 (9%) of the young HCL patients treated with cladribine, representing a low and statistically insignificant (1.60-fold) increased risk of developing second primary cancers. Four of these second malignancies were hematologic. Earlier reports documented second malignancies in 8% to 22% of HCL patients following cladribine.[6,11,15-17] Using National Cancer Institute SEER data, investigators at Scripps Clinic have previously reported an observed-to-expected ratio of developing a second primary malignancy following cladribine treatment from 1.88 to 2.03, both representing a relatively small but statistically significant increased risk.[6,11] This is reassuring given the young age of these HCL patients and the initial concerns that cladribine-induced immunosuppression might be associated with the late development of second primary malignancies.

There are limitations to this report. It is retrospective, not all HCL patients were followed uniformly, and subsequent therapies were not standardized. Also, some second primary malignancies may not have been recorded and, in some cases, the cause of death could not be obtained. Nineteen patients could not be located to update their clinical status. These factors could have influenced the death and secondary malignancy rates reported. However, these 19 patients did have extended follow-up, with a median of 241 months (range, 42-297 months) from diagnosis of HCL to date of last contact. Furthermore, they were censored at the date of last contact for survival analysis.

In conclusion, this analysis of HCL patients demonstrates that cladribine is an effective treatment choice for young HCL patients. The majority of patients obtained CR to their first course of cladribine therapy, and these remissions were long-lasting. Furthermore, these patients could often be successfully salvaged with cladribine retreatment upon relapse. This is the largest report of young HCL patients treated with cladribine. These results indicate that cladribine remains an excellent therapeutic approach for HCL patients, even if diagnosed at a young age.

Table 4. Clinical outcomes according to age at diagnosis of HCL

	≤40 y of age (n = 88)	All patients (n = 209)[6]
Median age (range)	36 y (20-40)	50 y (28-79)
Response rate	100%	100%
Complete	88%	95%
Partial	12%	5%
Median response duration (mo)	57 (range, 7-246 mo)	98 (range, 8-172 mo)
Relapse rate	58%	37%
Median time to relapse (mo)	54 (range, 7-246 mo)	42 (range, 8-118 mo)
Observed-to-expected ratio of developing a second malignancy	1.60 (95% CI, 0.80-2.89)	2.03 (95% CI, 1.49-2.71)

CI, confidence interval.

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Authorship

Contribution: J.D.R. analyzed the data; J.D.R. and A.S. wrote the manuscript and designed and performed the research; C.B. organized the data; J.W. performed the statistical analysis; and all authors were involved in manuscript preparation.

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