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Retrospective Evaluation of Hairy Cell Leukemia Patients: Analysis of a Long-Term Single Center Data

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ABSTRACT

Background: Hairy cell leukemia (HCL) is a distinct lymphoproliferative disorder with unique circulating lymphocyte morphology. It is now regarded as an indolent disease yet treatable with purine analogs. We are going to present a complete long-term clinical and prognostic report of our HCL patients as a large cohort in Iran.

Materials and Methods: All patients diagnosed with HCL, according to the World Health Organization (WHO) criteria, were enrolled in this study. They were referred to our academic center between 1995 and 2020. Treatment with a daily cladribine regimen was initiated as indicated and patients were followed. Survival data and clinical outcomes of patients were calculated.

Results: A total of 50 patients were studied (76% male). The median time to treatment was 4.8 months and complete remission was achieved in 92% of patients. Nine patients (18%) experienced relapse with a median time to relapse of 47 months. After a median follow-up of 51 months, the median OS was not reached and after 234 months, the overall survival rate was 86%. Survival was worse in patients with non-classic HCL (vHCL) compared to classic HCL.

Conclusion: Our long-term follow-up data confirmed the favorable outcomes of Iranian HCL patients with cladribine and provide a useful viewpoint of the disease.

Keywords: Hairy cell leukemia; Leukemia; Survival

INTRODUCTION

Hairy cell leukemia (HCL) is an unusual type of the broad spectrum of lymphoproliferative disorders accounting for less than 2% of leukemia cases [1]. It has distinct morphologic characteristics with the most common manifestations of pancytopenia and splenomegaly. HCL is well known for circulating lymphocytes with explicit cytoplasmic projections resembling tiny hair strands [2,3]. While pathologic assessment of the bone marrow specimen is still considered the mainstay for diagnosis, immunophenotyping has led to a better identification of HCL by elucidating unique expression of CD markers on the so-called hairy cells, which are CD11c, CD25, CD103, and CD123[4,5]. Overexpression of CD19, CD20 and other B cell markers may also be helpful.

HCL is usually known as a slow progressing disease[3]. Interferon-α (IFN) was the first drug used in treatment of HCL, leading only to partial responses among patients and improving survival by nearly 6

years[6]. The introduction of purine nucleoside analogs, namely 2-chlorodeoxyadenosine (2-CDA or cladribine), resulted in much better remission rates up to 98% following only a single course of treatment[7]. Although, IFN might be an appropriate and beneficial treatment in selected patients[8,9], cladribine and its equally effective counterpart, pentostatin, are now considered the preferred therapeutic agents for HCL [10, 11], and the disease is now regarded as a truly treatable leukemia with favorable survival rates.

The outcome of HCL in different centers and organizations is heterogeneous [2-4, 7]. In this paper, we presented the first complete report of our academic center experience in treatment of HCL and provided the long-term follow-up of patients during a 25-year period. This would probably help clinicians choose better treatment schedules and predict outcomes more precisely.

MATERIALS AND METHODS

In this retrospective study, all patients with the diagnosis of hairy cell leukemia, who have been evaluated and treated in the Shariati hospital (Tehran, Iran) from September 1995 to October 2020, were included in the study. In other words, the inclusion criterion was the confirmed diagnosis of HCL based on bone marrow aspiration results and clinician judgment. Patients with previous history of hematologic malignancies or solid tumors were excluded from the study. Moreover, any patient receiving corticosteroid or immunosuppressives for other diagnoses such as collagen vascular diseases were excluded. Informed consent was taken from all participants. The study protocol was approved by Research and Ethics Committee of Tehran University of Medical Sciences, Iran (No. 14-761).

For all patients, peripheral blood smear was obtained, and bone marrow aspiration and biopsy were done. Histopathologic assessment was performed using Geimsa staining. Three-color flow cytometry was used to assess the presence of CD11c, CD19, CD20, CD25, and CD103 in bone marrow aspirates. At least, 6000 cells were analyzed in FC500® Flow Cytometer (Beckman Coulter) with control samples to confirm the positivity of antigens. HCL diagnosis was confirmed according to the World Health Organization (WHO) criteria [12]. The following definitions were used for cytopenia: Neutropenia (ANC <1 x 10^9/L), anemia (Hb <10 g/dL), and thrombocytopenia (plt <100 x 10^9/L). Patients with either forms of cytopenia or symptomatic splenomegaly were considered eligible for chemotherapy. Indication of treatment was independent from patients' age and amount of bone marrow infiltration with malignant cells. For relapsed cases, the same criteria were implemented.

Patients were treated with cladribine intravenously as 1 hour bolus dose of 0.09 mg/Kg/d for 7 days [13]. In patients with renal dysfunction (CrCl < 60 mL/min), IFN alpha 2b was injected subcutaneously at a dose of 2 million U/m^2 three times a week for 12 weeks [13]. No patient was hospitalized for treatment. Complete blood count was performed weekly for 8 weeks, then monthly for 3 months, and then every 3-6 months. Bone marrow examination was scheduled for 3 months after completion of each course of treatment. In case of any unexplained occurrence of cytopenia or splenomegaly, bone marrow aspiration and biopsy were repeated to evaluate the possibility of relapse. Morphologic assessment of peripheral blood smear and bone marrow specimens along with immunephenotyping characteristics (3 months after completion of treatment) were used for response assessment according to Consensus Resolution[13]. Complete remission (CR) required disappearance of hairy cells from blood and bone marrow, resolution of splenomegaly and no evidence of cytopenia (ANC >1.5 x 10^9/L, Hb >11 g/dL, plt >100 x 10^9/L)[6,13]. If cytopenia was resolved with at least 50% decrease in spleen size and infiltration of bone marrow with hairy cells, and circulating leukemic cells were less than 5%, partial response (PR) was confirmed. Relapse after CR was considered if any of the following occurred: re-emergence of hairy cells in the peripheral blood or bone marrow, return of cytopenia, new splenomegaly[13]. A minimum of 50% increase in marrow leukemic cells or spleen size was also considered a relapse in case of previous PR. Relapse-free survival was determined from the onset of therapy to any form of relapse, and overall survival (OS) was calculated as time from the day of the diagnosis to death from any cause. The effect of patients' characteristics on OS was also examined.

Statistical analysis

Statistical analyses were done using SPSS version 21.0 (Chicago, IL, USA). Descriptive statistics are reported as mean ± standard deviation (SD) or percentage frequencies. The univariate Kaplan–Meier analysis was implemented for survival analysis and two-sided log rank tests for parameters effects on survival. The statistical significance level was defined as p-value less than 0.05**.**

RESULTS

A total of 50 patients were included in the study. The median age of the participants was 56 years (range 26-85), and 42 (84%) patients were under 65 years old. There were 38 (76%) male and 12 (24%) female patients. Most of the patients were diagnosed with classical HCL (84%), and only 8 (16%) had variant HCL. Table 1 shows the main characteristics of patients, and initial laboratory results are given in Table 2.

42 patients had an indication for treatment, and the median duration from diagnosis of HCL to initial therapy was 4.8 months (range, 1-36 months). In 90% of patients (38 out of 42), cladribine (2-CDA) was the initial treatment, and only four patients received interferon. Seven patients died during treatment, two because of pulmonary infection and one because of a heart attack. Four patients died due to disease progression, of whom two had variant HCL.

Complete remission was achieved in 38 patients (90%) treated with cladribine, 4 patients (10%) showed a PR, and no patient was unresponsive (overall response rate 100%). Three patients who received interferon achieved CR, and one experienced PR. From these interferon-treated patients, only one experienced a recurrence during the follow-up period who had an initial CR. From partially responsive patients to cladribine, only two experienced a relapse: one after 17 months and the other after 24 months. Both of these patients were treated with cladribine again and were alive and relapse-free at the time of analysis.

Nine patients (21%) relapsed after the initial cladribine treatment; of whom 8 had previously achieved CR and one PR. The median time to relapse was 47 months, mean time to relapse (TTR) was 40 and 3 months in patients with achievement of prior CR and PR, respectively (P=0.14). Cladribine was used in all patients with relapse and only one of them failed to achieve CR. No second relapse was recorded during follow-up.

The follow-up range was between 3 to 234 months. Within the median follow-up of 51 months, the median OS has not been reached in the whole cohort. No comparison was performed between 2-CDA and interferon, given that only four patients were treated with the latter. The overall survival rate of participants at 234 months was 86% (Figure 1). 5- and 10-year survivals from the initial cladribine use were 90% and 88%, respectively (Figure 2). There was a shorter survival reported in patients with non-classic HCL (vHCL) compared to patients with the classical type, but the difference was not significant (P=0.09) (Figure 3). Overall survival was also not significantly different regarding patients' sex (P=0.33).

In multivariate analysis, our data did not show any effect of hemoglobin level (p= 0.46), platelet count (P= 0.64), or age (P=0.54) on treatment failure. However, patients with higher WBC count were more likely to experience disease recurrence (P<0.01) (Table 3). Splenomegaly or pancytopenia were not correlated with relapse rates.

In terms of adverse events and mortality, three patients died of causes other than disease progression. Infectious complications were seen in 22% of patients with pneumonia being the most common (n=6). A second malignancy was developed in just one patient (lung adenocarcinoma) with median time from HCL diagnosis to the second malignancy being 33 months.

Table 1. Main characteristics of patients

Feature	n (%)
Gender	
Male	38 (76)
Female	12 (24)
Age (years)	
Median	56
Range	26-85
Type	
Classic	42 (84)
Variant	8 (16)
Splenomegaly	39 (78)
Cytopenia	45 (90)

Table 2. Initial lab results

Parameter	Median (range)
WBC (x 10^6/L)	2700 (600-40000)
Hemoglobin (g/dL)	10 (3.5-14.6)
Platelet (x 10^6/L)	57500 (22000-142000)
CD markers	n (%)
CD11c	46 (92)
CD19	47 (94)
CD20	47 (94)
CD25	43 (86)
CD103	46 (92)
DBA-44 positivity	30 (60)

WBC: White Blood Cell

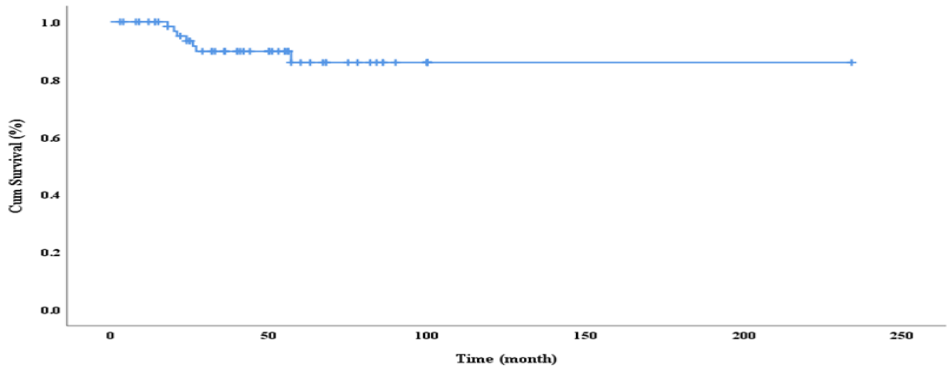

Figure 1. Survival function of all participants

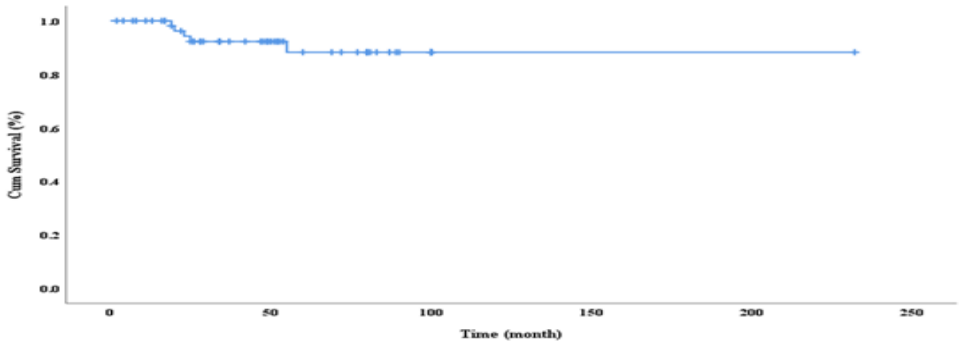

Figure 2. Overall survival after cladribine treatment

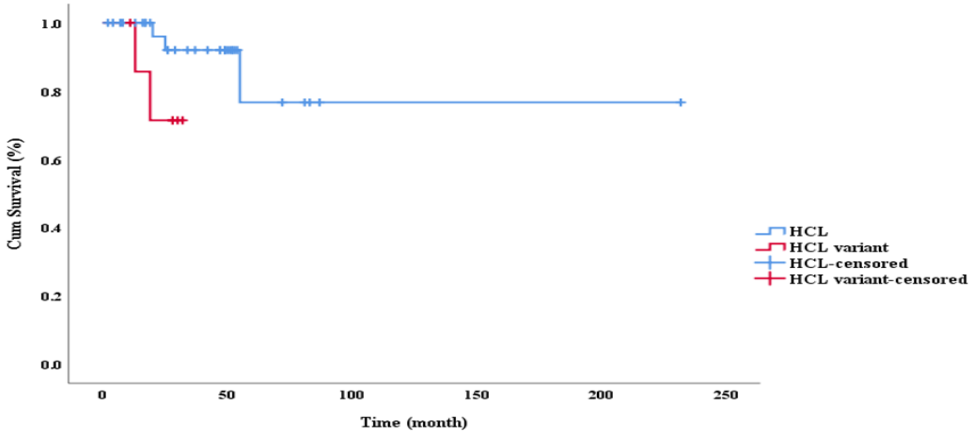

Figure 3. Survival comparison between classic and variant HCL

Table 3. Correlation of food count with relapse rate

Variable	Mean (SD)		P
	Relapse	No relapse	
Age (years)	54.6 (13.4)	51.1 (15.1)	0.54
WBC (x 10^6/L)	14100 (5500)	4300 (5100)	0.002
Hemoglobin (g/dL)	8.9 (2.7)	9.6 (2.1)	0.46
Platelet (x 10^6/L)	57000 (26000)	62000 (29000)	0.64

DISCUSSION

This study was conducted to reveal the long-term follow up of hairy cell leukemia (HCL) patients in an academic tertiary center. The main shortcoming in HCL is that the nature of HCL is not yet well understood, and providing data regarding disease spectrum and long-term data will be informative and elucidating[14]. Although innovations in flow cytometry and blood immunophenotyping have facilitated the diagnosis[15,16], different outcome perspectives have been pictured by various studies using an array of drugs in treating HCL [6-10]. Hence, we report a 20-year follow-up of HCL patients, Iranian population, in an academic hospital setting. We found similar clinical course of HCL in Iranian population, revealing a good prognosis and presenting long-term status of their clinical scenario. With regard to overall response rate (ORR), the current article including HCL patients treated with cladribine in a non-western community, revealed a 100% ORR with 92% achieving complete response. This is in accordance with former reports of favorable response to cladribine in HCL [4, 17-21]. In this study, interferon was administered only to 3 patients, and our data is not sufficient for response assessment. Nevertheless, previous experience with

IFN shows lower response rate with this drug compared to purine analogs, which is mainly attributed to pharmacodynamics of the drug enhancing cytotoxic abilities of white blood cells, while cladribine mainly interfere with DNA synthesis cycle resulting in more robust effect [4, 8, 9].

In this study, the 5-year OS of patients was calculated as 90% from the start of treatment. The overall survival (OS) of HCL patients treated with cladribine is reported to be in the range of 75 to 87%. These patients received 0.08 to 0.1 mg/Kg/d cladribine by continuous intravenous infusion for 7 days. Another study encompassing 86 consecutive HCL patients treated with the same protocol reported a 79% response rate [22]. This might be attributed to the earlier diagnosis possible today and better care provided to these patients during chemotherapy, for the mentioned articles are conducted before 2000. A study performed in Turkey in 2015 followed HCL patients and reported a 5-year OS of 96% [7]. While some previous researchers have shown worse survival in older patients with HCL [23, 24], as our participants were mostly younger than 60 years, we could not evaluate this factor`s effect on survival.

Furthermore, like many previous reports, our patients were mostly men [5, 10, 25, 26]. Though one of the studies has shown a better outcome in women[5], our observation did not reveal any difference; this might be due to some unknown hormonal effect of sex chromosome imprinting. Thus, no conclusion can be made regarding sex effect on HCL patients' survival. We report a non-significant though remarkably shorter survival in patients with variant HCL (P=0.09), which agrees with the result of the previous study in Turkish population [7].

Eighteen percent of our patients experienced relapse with the median time to relapse of 47 months. This result is in accord with the result of previous studies reporting relapse rate of 16.6% to 31% [7, 18, 27]. All of these studies also confirmed that CR rate after relapse is less likely to occur. Response to treatment has been associated with various factors in literature. Presence of leukocytosis was significantly correlated with disease recurrence in our study as reported by Hacioglu et al. [7]. Nonetheless, we did not find any association with other blood count measures, splenomegaly or age which is contrast to some prior reports [28-30].

One recognized complication of HCL patients is an increased risk of developing second malignancies. However, in our patients, only one patient treated with cladribine was diagnosed with lung cancer. The increased probability of malignancy has been attributed to advanced age of these patients and the use of drugs including purine analogs [27, 31-33], as it was the case in our results, while others considered this as just a coincidence [34-36].

The retrospective design, patients' unwillingness to bone marrow examination during follow-up, and therefore the lack of precise data regarding relapse status and minimal residual disease might have confounded the results of this study. On the other hand, our relatively large number of patients and long-term follow up period may be considered as this study's strength.

CONCLUSION

In conclusion, our data reveal the similar clinical course of HCL in a non-western population confirming a favorable survival status as well as providing an informative long-lasting perspective of their clinical features and prognosis. Longer follow-up could better guide our decisions regarding possible long-term adverse effects of cladribine in HCL patients.

CONFLICT OF INTERESTS

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