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Outcome of Hairy Cell Leukemia: A Single-center Study

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Abstract:

BACKGROUND: Hairy cell leukemia (HCL) is a rare chronic B-cell lymphoproliferative disorder. Modern therapy with purine analogs and immunotherapy can provide long-term remission, but the risk of recurrence remains about 40%–50%. The aim of this study was to evaluate the outcome of patients with HCL who received treatment in Nanakali Hospital.

PATIENTS AND METHODS: A retrospective cross-sectional study was carried out on 50 patients of HCL diagnosed from 2004 to 2022 in Nanakali Hospital in Erbil City, Kurdistan Region, Iraq. Demographics, clinical presentation, treatment data, complications, response, recurrence, and survival data were collected from medical records. The results were presented with descriptive statistics. Variables were compared by Chi-square analysis.

RESULTS: The mean age was 52.64 ± 12.37 years, and 84% were male. The most common presenting symptoms were splenomegaly (18%) and fatigue (14%). The majority (69.6%) received cladribine; the response rate was 73.9%, with a complete remission (67.4%). 47.8% had recurrent disease. The most common adverse effects were febrile neutropenia (58.7%) and Grade III and IV hematologic toxicity (41.3%). The results were significantly associated with ANC pretreatment (P = 0.019), comorbidity (P = 0.001), and treatment response (P = 0.004). Cladribine–rituximab combination resulted in complete remission (100%). Ten-year overall survival was 70%.

CONCLUSIONS: The results were broadly consistent with literature reports, demonstrating the efficacy and safety of cladribine with/without rituximab as first-line therapy for HCL but with a 30% mortality of concern. Further studies should identify modifiable factors that affect poor prognosis in subgroups to guide improvements in risk management of HCL.

Keywords:

Hairy cell leukemia, outcome, survival

Introduction

Hairy cell leukemia (HCL) is a rare, slow-growing, mature B-cell lymphoproliferative disorder.[1-3] Its name originates from the "hair-like" cytoplasmic projections on its cell surface membrane.[4] The median age of diagnosis for HCL ranges from 41 to 55 years, with a male predominance (male-to-female ratio 4:1). The disorder is marked by abnormal hairy lymphocyte infiltration of the bone marrow and spleen, causing cytopenia, bone marrow fibrosis, and splenomegaly.[5-7]

HCL is commonly diagnosed by infections, splenomegaly, or the presence of cytopenia but can be discovered in asymptomatic patients due to the increased frequency of regular peripheral blood screenings. It is usually diagnosed by the highly distinct morphological identification of hairy cells in a peripheral blood smear and the expression of specific markers on their surface, including CD11c, CD25, CD103, pan B-cell antigens such as CD19, CD20, and CD22, and tartrate-resistant acid phosphatase. Recently, whole-exome

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gene sequencing revealed that the majority of HCL patients have the BRAF V600E mutation, demonstrating disease-specific oncogene dependence. These indicators can aid in the diagnosis of HCL, along with other tests such as blood counts and bone marrow biopsy. HCL is a chronic disease, and the symptoms are variable. Some patients may be asymptomatic and only require monitoring, while others may require treatment due to severe cytopenia or if the disease is causing significant organ dysfunction.[8,9]

The therapies used to treat HCL are often extremely effective; however, they are immunosuppressive, the standard treatment for HCL typically involves purine analog chemotherapy drugs such as cladribine or pentostatin.[10] Immunotherapy and targeted therapy are also used in some cases. Although these treatments can induce long-lasting remissions in many patients, HCL remains an incurable disease, and some patients may require ongoing treatment or experience relapses after initial treatment. It is essential to monitor HCL patients closely and provide appropriate supportive care.[11]

Initially, the traditional therapeutic strategy was to undergo splenectomy, particularly in symptomatic patients.[12] Interferon was first investigated as a potential treatment for HCL in 1984 by Ahmed S, *et al*. However, the use of interferon was found to have unsatisfactory outcomes, with only rare and brief periods of complete remission.[13] Later, nucleoside analogs such as pentostatin and cladribine were introduced and have become commonly used treatments for HCL. Nucleoside analog monotherapy is now the primary treatment for patients with HCL who require intervention.[14,15] Despite not being curative, cladribine has shown remarkable efficacy in treating HCL, with most treatment-naïve patients achieving long-lasting complete remission. In addition, cladribine has demonstrated impressive activity in cases of relapsed disease.[16] Rituximab has moderate single-agent activity in patients with relapsed HCL, but when coupled with purine nucleoside analogs, response rates and duration of remissions are boosted. Most recently, the BRAF inhibitor vemurafenib achieved effectiveness in a single, severely resistant HCL patient.

As a result of the paucity of studies on outcomes of HCL in the Kurdistan Region, this study was dedicated to evaluate the outcome of HCL patients who were treated with a variety of therapeutic modalities according to the type of treatment and age group along with overall survivor rate.

Patients and Methods

Study design and setting

This study was a retrospective case report study that was conducted in the period between 2004 and 2022 at Nanakali Hospital for blood diseases and cancer, which is a tertiary center for benign and malignant hematology and oncology disorders in Erbil City, Kurdistan Region.

Patients and data collection

All the patients diagnosed with HCL during this period were recruited (50 patients) for this study. Data from hospital records were collected. This included details like age, gender, symptoms at diagnosis (fever, weakness, abdominal pain, weight loss, bleeding, and infection), clinical signs (enlarged spleen, liver, and lymph nodes), ECOG performance level, findings from blood smear and bone marrow examination, flow cytometry results, treatment types, complications, and relapse rates. The recommendations for treatment included the disease-associated symptoms such as fatigue, complaining splenomegaly or hepatomegaly, a weight reduction of >10% in the prior 6 months, cytopenia (anemia, platelets $<100 \times 10^9$/L, and/or absolute neutrophil count ($<1 \times 10^9$), progressive lymphocytosis, or lymphadenopathy. Treatment options were (cladribine, rituximab, splenectomy, cladribine/rituximab, and interferon-alpha). Prophylactic antibacterial, antiviral, and antifungal drugs were continued for at least 2 months after recovery of blood counts. All patients had been hospitalized until their neutrophil counts improved. Patients with febrile neutropenia were given growth factors and intravenous antibiotics. The response was evaluated using consensus guidelines regarding the diagnosis and treatment for patients with classical HCL. Complete response is within establishing normality of peripheral blood counts: hemoglobin >11 g/dL (without transfusion), platelets $>100 \times 10^9$/L, absolute neutrophil count $>1.5 \times 10^9$/L, regression of splenomegaly on physical examination, and absence of morphological evidence of HCL on both the peripheral blood smear and the bone marrow examination.[16]

Data management and statistical analysis

The data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 28 (SPSS Inc., Chicago, IL, USA). The categorical variables were expressed as frequencies and percentages. Chi-square test was used to compare the variables, with a statistical significance level of ≤ 0.05.

Ethical consideration

This study was submitted to the Research Protocol Ethics and Scientific Committees of Medicine program at Kurdistan Higher Council of Medical Specialties for scientific and ethical approval which was granted.

Results

A total of 50 cases were enrolled in the study, with a mean age of 52.64 ± 12.37 years, and the median

age was 53 years. Most of the cases (84%) were male residing urban settings (92%). At presentation, the majority of patients (60%) had various symptoms, but only two percent had fever and persistent infections. whereas regarding their labrotary findings almost all of the patients (98%) had hairy cells in the blood film, 76% had platelets <100,52% had an ANC ratio <1000,Though 18% exhibited symptomatic splenomegaly, the grading of the spleen ranged from moderate (46%), severe (42%), hepatomegaly (20%), and lymphadenopathy (2%) [Table 1].

For all the 22 relapsed cases, the relapse happened in <24 months after receiving the treatment. The majority of the patients (92%) had an indication for treatment. most of them received cladribine, followed by 10.9% received rituximab. Only 4.3% of patients were given both cladribine and rituximab. 73.9% of cases responded to treatment, 67.4% with complete remission and 6.5% in partial remission. Post therapy More than half (58.7%) of the patients developed febrile neutropenia and 41.3% experienced hematological toxicity (Grade III-IV), including persistent neutropenia, thrombocytopenia and anemia; 47.8% had a recurrence of the disease, in whom 70% survived and 30% died [Table 2].

The Table 3 reveals a statistically significant statistical association between outcomes and ANC ratio. ANC ratios greater than 1000 were linked with death in 73.3% (*P* value of 0.019). The study found a substantial association between outcomes and comorbidities. Comorbidities were present in 86.7% of dead cases and There was a significant statistical association between outcomes and type of response(81.3%) of survived cases sustained complete remission. Chi-square test was done and *P* value was <0.05.

Table 4 shows that there was a significant statistical association between type of response and type of treatment, all (100%) of cladribine rituximab, (78.1%) of cladribine monotherapy had complete response. Chi-square test was done and *P* value was 0.001.

Figure 1 demonstrates that individuals aged 50 years or younger had a longer survival time with a mean of 54.696 months compared to those older than 50 years, who had a shorter survival time with a mean of 47.023 months. This suggests that age might play a role in response to treatment and survival time.

Figure 2 indicates that individuals in the complete remission group had the longest survival time with a mean of 56.38 months. Those in the partial remission group had a slightly shorter survival time with a mean of 56 months. The shortest survival time was observed in the no response group, with a mean of 35.41 months. This suggests that the type of response to treatment significantly impacts survival time.

Table 1: Initial symptoms and hematological measures

Variables	Categories	Frequency (%)
Initial symptoms	Symptomatic splenomegaly	9 (18)
	Recurrent infection	1 (2)
	Incidental	1 (2)
	Fever	2 (4)
	Fatigue	7 (14)
	More than one symptom	30 (60)
WBC count (mL)	>4000	24 (48)
	<4000	26 (52)
ANC ratio	<1000	26 (52)
	>1000	24 (48)
Platelet count	>100	12 (24)
	<100	38 (76)
Hairy cell in blood film	Yes	49 (98)
	No	1 (2)
Grade of splenomegaly	No splenomegaly	2 (4)
	Mild	4 (8)
	Moderate	23 (46)
	Severe	21 (42)
Hepatomegaly	Yes	10 (20)
	No	40 (80)
Lymphadenopathy	Yes	1 (2)
	No	49 (98)
Total		50 (100)

WBC=White blood cell, ANC=Absolute neutrophil count

Discussion

The predominant initial characteristics and hematological parameters of 50 patients with HCL were symptomatic splenomegaly (18%), followed by fatigue (14%), fever (4%), and recurrent infections (2%). This is consistent with the studies of Else *et al*. and Ravandi, which show that splenomegaly and fatigue are the most common early symptoms.[17,18] More than half had low white blood cell counts (<4000) and ANC counts (<1000) indicative of bone marrow suppression, consistent with previous results.[19] Most had severe

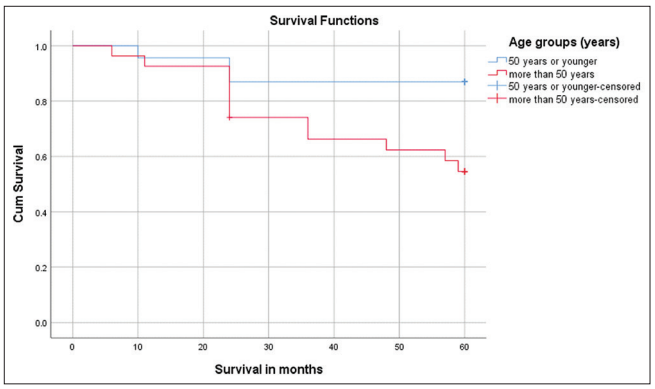

Figure 1: Survival months according to age group of participants

thrombocytopenia <100, which was expected for this disease.[20] In the majority (92%) of cases there was an indication to start treatment, mostly treated with cladribine with a complete responce (78.1%), which is comparable with cladribine response rates (75-80%) in other studies.[17,20] and 67.4% of cases treated with any other therapy options achieved remission absolutely, higher than the full response in Zinzani PL *et al.* trial which was (47%).[21] However, relapse remained an issue, with 47.8% recurring at two years, which is consistent with other cladribine studies.[17,19]

Table 2: Treatment of the cases and treatment outcomes

Variables	Categories	Frequency (%)
Indication for treatment	No	4 (8)
	Yes	46 (92)
Type of treatment	Cladribine	32 (69.6)
	Rituximab	5 (10.9)
	Cladribine and rituximab	2 (4.3)
	Interferon	4 (8.7)
	Combination therapy	3 (6.5)
Response to treatment	Yes	34 (73.9)
	No	12 (26.1)
Type of response	Complete remission	31 (67.4)
	Partial remission	3 (6.5)
	No response	12 (26.1)
Adverse events after treatment	Hematological toxicity Grade III–IV	19 (41.3)
	Febrile neutropenia	27 (58.7)
Relapse	Yes	22 (47.8)
	No	24 (52.2)
Outcome of therapy	Alive	35 (70)
	Dead	15 (30)

Table 3: Association between disease outcome and absolute neutrophil count ratio, comorbidities, and type of response

Variable	Categories	Outcome of therapy		*P*
		Alive (%)	Dead (%)	
ANC ratio	<1000	22 (62.9)	4 (26.7)	0.019
	>1000	13 (37.1)	11 (73.3)	
Comorbidities	Yes	9 (25.7)	13 (86.7)	0.001
	No	26 (74.3)	2 (13.3)	
Type of response	Complete remission	26 (81.3)	5 (35.7)	0.004
	Partial remission	2 (6.3)	1 (7.1)	
	No response	4 (12.5)	8 (57.1)	

ANC=Absolute neutrophil count

Survival was 70%, compared with a reported 5-year survival of almost 85% in Ravandi F *et al*.,[22] possibly reflecting this group's lack of maintenance therapy.[21,22] However, relapse remained an issue, with 47.8% recurring at 2 years, which is consistent with other cladribine studies.[17,19] Survival was 70%, compared with a reported 5-year survival of almost 85%,[22] possibly reflecting this group's lack of maintenance therapy.[21]

The correlation of comorbidities and type of response in our study with the disease outcome indicates that the patients with comorbidities were associated with a higher mortality rate (86.7%, $P = 0.001$) in comparison to 13.3% only in those of no comorbidities. While regarding type of response, strong prediction of survival was seen in those with complete response than the nonresponders (81.3% vs. 12.5%, $P = 0.004$).[23] The relationship between treatment type and response type highlights the effectiveness of cladribine in achieving complete responses. That cladribine has a notably high rate of achieving a complete response (78.1%, $P = 0.001$),[17] The lack of response to rituximab monotherapy is observed in 100% of cases, in contrast to 100% complete response when combined with cladribine.[24] This highlights the superiority of cladribine over rituximab alone.[25]

The median survival time in months varied based on age groups. Patients aged 50 years or younger had a median survival of 54.7 months, whereas those older than 50 years

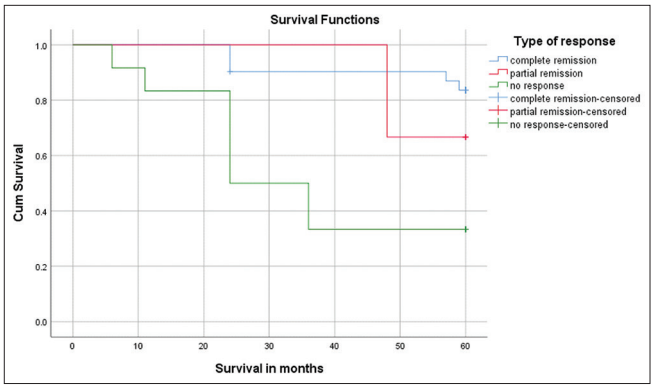

Figure 2: Survival time according to type of response to treatment among patients

Table 4: Association between type of response and type of treatment

Type of treatment	Type of response			*P*
	Complete remission (%)	Partial remission (%)	No response (%)	
Cladribine	25 (78.1)	1 (3.1)	6 (18.8)	0.001
Rituximab	0	0	5 (100)	
Cladribine rituximab	2 (100)	0	0	
Interferon	2 (50)	2 (50)	0	
More than one	2 (66.7)	0	1 (33.3)	
Total	31 (67.4)	3 (6.5)	12 (26.1)	

had a median survival of 47 months. This showed a trend of decreasing survival with increasing age at diagnosis which is consistent with the findings of the study of Else *et al*. showing elderly patients associated with decreased cell survival.[17] The difference in 5-year survival between age groups younger than 60 years was reported to be as high as 97% compared to 76% in older than 60 years, which is consistent with Ravandi's study.[18] Figure 2 illustrates the survival time categorized by treatment response. Patients achieving complete responses had a median survival of 56.4 months; in contrast, nonresponders exhibited the shortest median survival of 35.4 months. This observed decrease in survival among individuals with inadequate treatment responses is consistent with research documenting the correlation between complete hematologic response and favorable overall survival free. This trend of decreased survival with poor treatment response is associated with studies by Chihara *et al*. and Goodman *et al*. reporting complete hematologic response and excellent failure-free overall survival.[19,20] The 12-year survival rate was 92% of patients with a complete response in one study, accounting for 57% treatment failure.[20] In summary, these data demonstrate that there is a significant association between older age at diagnosis, inadequate treatment response and reduced survival and significantly influence the prognosis in patients with HCL.[17-20] Early diagnosis and greater response will remain key to long-term survival.

Conclusions

The findings indicate that cladribine with or without rituximab is effective and safe as initial treatment, in line with existing literature. However, around half of the patients experienced relapse within 2 years, and by the 10-year mark, 30% had passed away, exceeding the anticipated survival rate of over 90%. Additional studies are required to identify factors predicting poor prognosis in order to enhance risk management for HCL. As novel targeted therapies emerge, it is crucial to investigate the most effective combination of long-lasting treatments. Overall, a collective effort is necessary to maximize both prognostic and therapeutic outcomes.

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Conflicts of interest
There are no conflicts of interest.

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