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Retrospective Evaluation of Hairy Cell Leukemia Patients: Single Center Experience

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ABSTRACT

Hairy cell leukemia (HCL) is a rare B-cell leukemia. This study aimed to investigate the clinical and demographic features and treatment responses of HCL patients diagnosed and treated at our center.

Thirteen patients were diagnosed between March 2019 and February 2024. Morphology, immunohistochemistry, and flow cytometry were used for diagnosis. All patients received cladribine as first-line treatment. Patients with partial response or less and those who relapsed received salvage therapy.

The median age of the patients was 53. Seven patients (53.8%) had pancytopenia. BRAF V600E mutation was positive in 9 patients (69%). Splenomegaly was present in 10 patients (76.9%) at diagnosis. Cladribine treatment achieved complete response in 11 patients (84%), partial response in 1 patient (7%). One patient did not respond to treatment. Two patients relapsed and achieved complete remission with pentostatin or rituximab treatment. The 5-year overall survival (OS) rate was 92.3% and progression-free survival (PFS) rate was 84.6%.

The demographic and laboratory features and treatment outcomes of HCL patients followed at our center are consistent with the literature. Cladribine is highly effective as a first-line treatment in HCL and provides high response rates. Pentostatin and rituximab monotherapy were found to be effective in relapsed patients.

Keywords: Hairy Cell Leukemia, Cladribine, Pentostatin, Rituximab, PFS, OS

Introduction

Hairy Cell Leukemia (HCL) is a rare, slow progression lymphoid malignancy characterized by the accumulation of neoplastic B cells with cytoplasmic extensions. HCL accounts for 2% of all leukemias and less than 1% of lymphoid neoplasms. The median age at diagnosis is 50-55 years (1).

Most patients with HCL present with malaise, fatigue, infections of variable severity and hemorrhagic symptoms associated with splenomegaly or cytopenias. Approximately 25% are asymptomatic and are diagnosed incidentally with splenomegaly or cytopenia (2). Splenomegaly is a classic feature of HCL and is reported in 80-90% of patients. Hepatomegaly and lymphadenopathy are found in approximately 20% and 10% of patients, respectively (1).

Laboratory findings include pancytopenia, monocytopenia and neutropenia. Mononuclear cells with cytoplasmic extensions involved in the pathogenesis of the disease are oval or round cells with eccentric nuclei. These cells are found in the bone marrow, peripheral blood and red pulp of the spleen(3).

Definitive diagnosis is based on immunophenotyping and flow cytometry of a bone marrow biopsy sample(4). The bone marrow sample is hypercellular. Interstitial or diffuse infiltration of hairy cells and increased reticulin fibers are observed(5). Hairy cells stain immunophenotypically positive for Pan-B cell antigens (CD19, CD20, CD22), CD103, CD11c, CD25 and annexin A1, but negative for CD5, CD10, CD21, CD23 and CD27.(6) These cells typically express one or more immunoglobulin heavy chains and monotypic light chains.

Asymptomatic patients can be followed without treatment as early treatment has no clear advantage in these patients. Treatment is indicated in patients with severe cytopenias, symptomatic splenomegaly and lymphadenopathy or constitutional manifestations of the disease(2). Purine analogs (cladribine or pentostatin) are preferred for initial treatment(7). Cladribine and pentostatin had similar overall response rates (100% and 96%, respectively) and CR rates (76% and 82%) (8).

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Up to 5% of patients treated with purine analogs do not respond to treatment, while up to 20% achieve only partial remission. In these patients, it is recommended to switch to an alternative purine analog or vemurafenib + rituximab. In patients refractory to two or more treatments, vemurafenib, bendamustine + rituximab, single agent rituximab or splenectomy is recommended. In relapsed disease, the treatment of choice depends on the response to initial treatment. If previous remission is ≥24 months, purine analog + rituximab, if initial remission is <24 months, re-evaluate the diagnosis and if appropriate, vemurafenib + rituximab or alternative purine analog can be administered (9).

We aimed to examine the clinical and demographic characteristics, treatments and treatment responses of our patients diagnosed and treated in our center in this leukemia, which affects the middle age group and has a high response rate to treatment.

Materials and Methods

In this study, 13 patients diagnosed and treated with HCL in our center between March 2019 and February 2024 were retrospectively analyzed. Ten of the patients were male and three were female and their ages ranged between 39 and 70 years.

The diagnosis of HCL was made on the basis of morphologic and immunohistochemical staining of peripheral blood and bone marrow biopsies and the results of flow cytometry in those who could obtain bone marrow aspirate. All hematologic and biochemical investigations were performed before treatment. Spleen size was measured by ultrasonography and those larger than 200 mm were considered as massive splenomegaly. BRAF V600E mutation test was performed by polymerase chain reaction method.

All patients received cladribine 0.15 mg/kg/day intravenously (IV) for 7 days in the first-line setting. Pentostatin was administered as iv infusion at a dose of 4 mg/m2/week and rituximab was administered as IV infusion at a dose of 375 mg/m2/week for 4 weeks.

After initial treatment, patients were evaluated monthly by hemogram and physical examination. In the fourth month of treatment, a comprehensive evaluation including ultrasonographic measurement of spleen size, whole blood measurement and bone marrow biopsy was performed to determine patients' response to treatment.

Patients with normal peripheral blood findings, normal bone marrow biopsy and no splenomegaly were considered in complete remission. Peripheral blood remission criteria were hemoglobin ≥11 g/dL without transfusion, platelets ≥100.000/mm³ and absolute neutrophil count ≥1500/mm³ (10).

Patients with partial response and less response and patients with relapse were treated. Progression-free survival was defined as the time from complete response to relapse. Overall survival was defined as the time from the diagnosis of the disease until death from any cause or the last follow-up date.

In accordance with the Declaration of Helsinki, our study was approved by the ethics committee dated 17.11.2023 and numbered 569.

Statistical Analysis: Data were analyzed using SPSS 25.0 statistical program. The sample size was calculated to ensure adequate statistical power, and the Shapiro-Wilk test was performed to assess the normality of the data. Descriptive statistics of the evaluation results were presented as number and percentage for categorical variables and mean and standard deviation for numerical variables. Comparisons between normally distributed variables were conducted using the paired t-test, while the Mann-Whitney U test was used for non-normally distributed variables. Survival rates were calculated by Kaplan-Meier survival analysis. Statistical significance was accepted as $p<0.05$. Statistical significance was accepted as p=0,05**.**

Results

The study included 13 HCL patients. Ten (77%) of the patients were male and 3 (23%) were female. The mean age was 53 years (age range: 39-70). Seven patients (53.8%) presented with pancytopenia. The mean WBC value at the time of diagnosis was 2500 ± 2340/μL, ANC 1500 ± 1100/μL, Hgb 11 ± 2.7 g/dL, PLT 75.000 ± 38.425/μL and monocytes 110 ± 92/μL. Eleven patients (84%) had monocytopenia. BRAF V600E mutation was positive in nine patients (69%) and negative in 4 patients (31%). Splenomegaly was present in 10 patients (76.9%) at the time of diagnosis. Of these, 4 were massive splenomegaly. The mean splenic size at diagnosis was 173.5 mm.

All patients were treated with intravenous cladribine at a dose of 0.15 mg/kg/day for 7 days. Complete response was observed in 11 patients (84%) and partial response in 1 patient (7%). One patient did not respond to treatment.

Table 1: WBC, ANC, Hgb, PLT and Monocyte Values at Pre-Treatment and Post-Treatment (4th month)

Patient no	WBC (μL)		ANC (μL)		Hgb (g/dl)		PLT (μL)		Monosit (μL)	
	Pre*	Post¶	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	2730	7600	660	3900	5,7	14	79000	216000	200	500
2	2400	5700	1840	2800	11,4	16	120000	143000	120	380
3	1740	2500	730	1800	11,7	13,1	61000	210000	50	680
4	1600	5000	900	3000	10	15	90000	204000	210	450
5	2500	7450	650	4810	13,5	14,5	77000	184000	180	310
6	1500	4200	850	1650	10,5	13,5	56000	277000	50	500
7	2700	3500	540	2100	9,7	12,5	26000	280000	118	600
8	1700	890	590	330	9,9	11	33000	122000	130	320
9	980	6600	150	4300	7,7	16	51000	177000	10	250
10	1400	1800	540	900	7,7	9,8	50000	87000	90	490
11	3700	3900	730	2800	11,9	11,8	75000	201000	170	120
12	26000	12000	7000	3000	10	13	80000	167000	130	500
13	3900	5600	1300	4600	13	13	93000	228000	252	490

*pre-treatment values, ¶ post treatment values

The mean WBC value was 4000 ± 3260/μL (p=0,001), ANC value was 2500 ± 1920/μL (p=0,011), Hgb value was 13 ± 4.2 g/dL (p=0,002), PLT value was 150.000 ± 89.512 /μL (p=0,001) and monocyte value was 450 ± 254 /μL (p=0,035) in the blood count at the fourth month after treatment. Table 1 shows the laboratory values of the patients at diagnosis and after treatment.

Recurrence was observed in two patients. Relapses occurred after a mean of 28.3 months. One of the relapsed patients achieved a complete response with 7 cycles of pentostatin 4 mg/m2/week and the other with 4 cycles of rituximab 375 mg/m2/week. In the patient who did not respond to initial treatment, complete remission was achieved with a 4-week course of rituximab.

In terms of side effects, myelosuppression, infection, nausea, and vomiting were observed with cladribine. Skin rash and fatigue were observed with pentostatin. Side effects were mild and transient. One patient who went into partial remission after cladribine died in the 6th month after pancreatic adenocarcinoma was detected during the treatment phase.

The mean follow-up period of our patients was 24.4 months (95% CI: 18.2 - 30.6 months). 12 patients are still being followed up in our clinic. The five-year overall survival (OS) rate was 92.3%, and the progression-free survival rate was 84.6**%.** Figure 1 shows Kaplan Meier graph.

Discussion

HCL is a rare B-cell lymphoproliferative disorder characterized by the presence of atypical lymphocytes with prominent peripheral cytoplasmic extensions in the bone marrow and spleen. The average age of onset is 50 - 55 years. It is 4 times more common in men than in women (11,12). In our patient group, 77% of our patients were male and the mean age was 53 years. The mean age of the group and male gender predominance were similar to the literature (3,13).

60-80% of HCL patients present with pancytopenia due to bone marrow infiltration and splenomegaly. Anemia is detected in approximately 85% of these patients. Platelet counts are in the range of 20,000 - 100,000/microL in 80% of patients (12,14,15). The rate of pancytopenic patients in our study group was 53%, which was lower than the literature data. Anemia was seen in 85% of our patients, consistent with the literature. Platelet count was below 100,000/microL in 92% of our patients. Monocytopenia and neutropenia are common in hairy cell leukemia and studies indicate that both conditions are seen in 80%.(1) In our study, we detected these cytopenias in 84% of our patients in accordance with the data of previous studies.

Leukocytosis is seen in 10-20% of patients with hair cell leukemia. While HCL cells constitute 20% or less of leukocytes in the peripheral blood of patients with HCL, hairy cells may be the predominant circulating cell in patients presenting

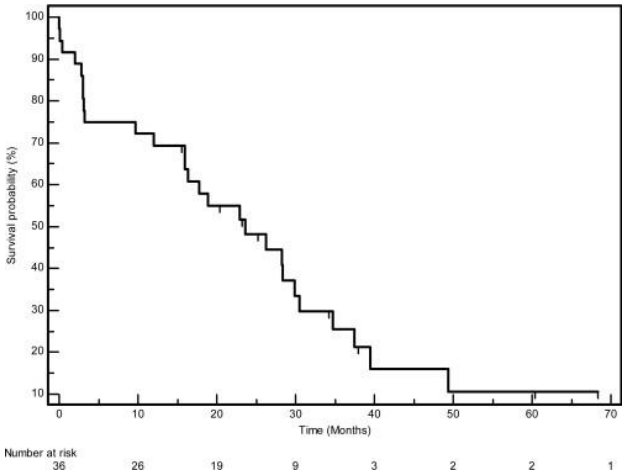

Fig. 1. Progression-free Survival Curve

with leukocytosis. In the peripheral blood smear of one of our patients who presented with leukocytosis, hairy cells constituted 80% of the leukocytes (4).

BRAF V600E mutation was studied in all of our patients. Mutation positivity was 61.5%. This rate has been reported as >97% in the literature (16). The fact that BRAF V600E positivity was found to be lower in our patients compared to the literature was associated with the fact that our number of patients may not reflect the general average in terms of this parameter.

At the time of diagnosis, 76.9% of our patients had splenomegaly. In 19% of these patients, splenomegaly was massive. Similarly, splenomegaly was reported in 80% and massive splenomegaly in 20% of HCL cases in the literature(1).

Indication for treatment in HCL is a blood count with absolute neutrophil count <1000/microL, hemoglobin <11 g/dL or platelet count <100,000/microL or symptomatic splenomegaly/lymphadenopathy or constitutional symptoms (17). Since all of our patients had one or more cytopenia or massive splenomegaly requiring treatment, treatment was initiated in all of our patients.

Currently, the purine analogs cladribine and pentostatin are considered the first choice agents compared to splenectomy and interferon. Due to the ease of administration, a single course of cladribine treatment is more preferred (10). In a study by Saven et al., 349 patients received a single course of 0.1 mg/kg 7-day intravenous cladribine infusion. Complete response (CR) and partial response (PR) rates were 91% and 7%, respectively. The four-year overall survival (OS) rate was 96%. Relapse rates in patients with CR and PR were 16% and 54%, respectively. In the same study, 53 patients who experienced first relapse after remission with cladribine achieved CR and PR rates of 62% and 26%, respectively, after re-treatment with cladribine (18). The complete response rate in cladribine treatment has been found to be between 80-100% in other studies in the literature (9,10).

We administered one course of cladribine treatment to all of our patients. As a result of the treatment, 84% of our patients had a complete response and 7% had a partial response. One of our patients had no response. In our patient with partial response, pancreatic carcinoma was diagnosed in the 4th month and the patient died without any additional treatment for HCL. Our patient who did not respond to initial treatment was treated with rituximab for 4 weeks and complete remission was achieved. Two of the patients who had a complete response later experienced relapse.

In the study by Falini et al. the mean time to relapse was 19 months after complete response and 6 months after partial response (19). In our study, the mean time to relapse was 28.3 months. One of our patients who experienced relapse was treated with pentostatin and the other with rituximab monotherapy and complete remission was achieved in both patients. Currently, 12 patients are being followed up in our clinic. In our five-year follow-up period, the overall survival rate was 92.3% and the progression-free survival rate was 84.6%.

In conclusion, the demographic and laboratory characteristics and treatment outcomes of HCL patients in our center are consistent with the literature. Our study showed that cladribine is highly effective as first-line treatment in HCL and provides high response rates (complete response 84%). In relapsed patients, pentostatin and rituximab monotherapy was also effective and complete remission was achieved again in both patients.

Ethical approval: Ethics Committee approval was obtained from Gazi Yasargil Training and Research Hospital Clinical Research Ethics Committee with decision number 569 dated 17.11.2023.

Conflict of interest: The authors have no conflict of interest related to this study.

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