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Retrospective Evaluation of Patients with Hairy Cell Leukemia: A Decade Experience at a Single Center

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ABSTRACT

In this study, we aimed to investigate the demographic characteristics, treatment modalities and response rates in patients with Hairy Cell Leukemia (HCL) which have been diagnosed and followed up in our center.

Data of the 27 patients diagnosed with HCL at our center between 2007 and 2018 were retrospectively evaluated. Patients diagnosed with HCL according to WHO 2016 classification of lymphoid neoplasms by bone marrow biopsy. Flow cytometry, clinical and demographic data of the patients were evaluated. BRAFV600E mutational status evaluated in selected cases. All patients were given cladribine as first line treatment.

Eight of our patients (29.6%) were female and 19 (70.3%) were male. In 20 patients (74%), complete remission was detected with first-line cladribine treatment, while in 3 patients (11.1%) partial remission was achieved, and 4 patients (14.8%) were unresponsive. Rituximab was administered to 3 refractory patients while one patient received pentostatine. Two patients who could not achieve remission died due to severe and critical infection, while one patient died due to cerebrovascular disease. 24 of our patients are still alive.

Cladribine confers a safe and effective treatment modality. Although purine analogs have improved response rates and progression-free survival, progress has yet to be made for resistant and relapsing patients.

Key Words: Hairy Cell Leukemia, Cladribine, Real World Data

Introduction

Hairy Cell Leukemia (HCL) is a B cell lymphoproliferative disease; characterized by lymphocytic cells with cytoplasmic extensions in the peripheral blood and splenomegaly. It accounts for approximately 2% of all adult leukemia and approximately 1000 new cases seen in the USA each year. The median age is 50-55 years and is reported as four times more common in men (1). As a low grade lymphoproliferative disease with a B lymphocyte phenotype HCL may be surveyed without treatment in asymptomatic patients. In symptomatic patients which are defined as symptoms related to enlarged spleen or patients with blood count abnormalities including hemoglobin <10 gr/dl, platelet count <100x10^9/L, neutrophil count <1000x10^9/L. Cladribine or pentostatine have been used as first line treatment with an average survival of approximately 10-15 years (2, 3). Although life expectancy is high, the rare nature of the disease requires experience based information with retrospective studies.

In this study, we aimed to investigate the demographic characteristics, treatment modalities and response rates in patients with HCL which have been diagnosed and followed up in our center.

Materials and Methods

In this study, data of 27 patients who were revised diagnosed as Hairy Cell Leukemia according to WHO 2016 classification of lymphoid neoplasms between 2007 and 2018 in Trakya University Faculty of Medicine Department of Hematology were evaluated in a retrospective manner. Clinical features, laboratory values, spleen size, presence of lymphadenopathy, treatment modalities and response to treatment were evaluated. Patients were diagnosed with hairy cell leukemia according to bone marrow trephine biopsy findings. Besides, flow cytometry analysis with CD19, CD20, CD11c, CD22, CD25, CD103, FMC7, CD79b performed. And lastly BRAFV600E mutations performed in selected cases. All patients were given 5 day cladribine, 0,5 mg/kg/day

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intravenously as first line treatment. Patients were evaluated for treatment response 6 months after treatment and also bone marrow biopsies performed at least 6 months after cladribine treatment to show eradication of leukemia. Complete remission was defined as normalization of cytopenias, improvement of complaints as well as splenomegaly and complete disappearance of hairy cell lymphocytes in peripheral smear. A partial response is defined by near normalization of the peripheral blood counts with a minimum of 50% improvement in both splenomegaly and bone marrow biopsy infiltration with HCL

Results

Eight of our patients (29.6%) were female and nineteen (70.3%) were male. The mean age at diagnosis was 55.70 ± 12.8 years. Twenty-one of our 27 patients had splenomegaly at the time of diagnosis. Five patients had localized lymphadenopathy. The mean hemoglobin value at the time of diagnosis was 8,70 gr / dl, leukocyte count was 6520 $x10^9$/L and platelet count was 61,000 $x10^9$/L In 13 patients, grade 3 (48.1%), in 7 patients grade 2 (25.9%), in 7 patients grade 1 (25.9%) increase in reticular fiber found on bone marrow trephine biopsy. Demographic data of the patients were summarized in Table 1. In 20 patients (74%), complete remission was detected with first-line cladribine treatment, while in 3 patients (11.1%) partial remission was achieved, and 4 patients (14.8%) were unresponsive to cladribine. Response evaluation of the patients were demonstrated in Table 2. Rituximab was administered to 3 of 4 refractory patients while one patient received pentostatine. BRAFV600E mutation was found in two refractory patients. One patient who was in remission with cladribine administration, relapsed approximately 6 years later and achieved complete response with a second course of cladribine. Two patients who could not achieve remission during their follow-up died due to severe and critical infection, while one patient died due to cerebrovascular disease. 24 of our patients are still alive and on follow up. Median follow-up time was 71 months (min:1 max: 142). Ten year overall survival of the patients were % 88.8.

Discussion

Ewald first used the term leukemic reticuloendotheliosis in 1923 to define pancytopenia, splenomegaly and monocytic cells in peripheral blood (4). Later Leukemic reticuloendotheliosis was described clearly by 26 cases with Bouroncle and collegues in 1958. They reported 26 cases with male predominance (21 were male) and almost all of them with splenomegaly (25 of them). The prominent findings were leukopenia and reticulum cells in the peripheral blood. The survival was very poor at the time barely exceeding beyond five years (5). Later in 1974 Catovsky et. al. (6) used the term hairy cell leukemia for leukemic reticuloendotheliosis. Splenectomy and interferon-α treatments were used in the seventeens and eighties (7-11). With these agents' survival was raised slightly. But there were still unmet needs and treatment requirements especially for those who progress after interferon-α.

In Hariy cell leukemia Cladribine treatment was first used in 1990 (12). Piro et. al reported eleven CR in tweleve patients with cladribine. Since then cladribine has been used as the first choice of HCL treatment. Long term follows up in a retrospective analysis which included 86 patients showed % 87 overall survival rate after 12 years which is thought to be excellent. In their analysis 31 of the 86 patients have relapsed and 23 of them re-treated with cladribine. This study shows long-term data of cladribine in hairy cell leukemia patients which shows a safe, effective treatment modality (14). Cladribine revolutionized the treatment of hairy cell leukemia and improved the survival percentages. Remission rates have been reported as >90% with cladribine(13-15) though in our cohort, we observed a complete plus partial response rate as 85%. Cladribine fulfilled the unmet needs but rarity of this disease makes it difficult to perform randomize controlled trials. Therefore, it is important to note that accumulation of knowledge is mandatory; so there is a particular need for retrospective case series.

As a purine analogue, cladribine is related with post treatment complications including prolonged neutropenia, lymphopenia and immune deficiency and life threatening infections. This concern has led to the pursuit of more non-cytotoxic treatments. After the development of anti-CD 20 chimeric monoclonal antibody, rituximab, treatment decisions of HCL have been advancing towards the use of this particular monoclonal antibody but still, with cladribine or as second line treatment. Other treatment options included interferon alpha and splenectomy though they are accepted as outdated.

Serious and life threating infections are one of the challenging difficulties in HCL patients. These

Table 1. Demographic, Characteristic, Clinical and Therapeutic Features of Patients

Characteristics	Number (%)
Gender Male / Female (%)	19/8 (%70.3/29.6)
Age (mean at diagnosis)	55.70 ± 12.8 years
Splenomegaly at diagnosis (Yes/None)	21/6 (%77.7/22.2)
Lymphadenomegaly (Yes/None)	5/22 (%18.5/ 81.5)
Mean Hemoglobin level at the time of diagnosis gr/dl	8.70 gr/dl ± 1.97
Mean Leukocyte count at the time of diagnosis x109/L	6.520x109 ± 8.882
Mean Platelet count at the time of diagnosis x109/L	61x109 ± 20.31
Bone marrow fibrosis degree 1	7(%25.9)
Bone marrow fibrosis degree 2	7(%25.9)
Bone marrow fibrosis degree 3	13(48.1)

Table 2. Evaluation of the patients according to cladribine treatment

Parameter	No (%)
Mean Hemoglobin level one year after treatment gr/dl	13.23 gr/dl ± 2.00
Mean Leukocyte count one year after treatment x109/L	7.392 x109 ± 5.280
Mean Platelet count one year after treatment x109/L	158 x109 ± 50.47
Complete remission No/(%)	20 (%74)
Partial remission No/(%)	3 (%11.1)
Unresponsive No/(%)	4 (%14.8)
Median Follow Up Time (months)	71 months (min:1 max:142)

infections may occur following cladribine administration or more frequently occurs in treatment refractory patients (16). Granulocyte colony stimulant factors and interferon-α treatment has been suggested for controlling infectious complications but none of them resulted clear benefits (17). In our data we lost two patients who did not respond to serial systemic treatment options. In these patients, life-threatening and fatal infections occur due to prolonged neutropenia and impaired immune system. Prophylaxis with local protocols and, if necessary, broad-spectrum antibiotics should be started immediately.

Recent developments in the pathophysiology of the disease revealed mutational pathways in hairy cell leukemia. In 2011, a BRAFV600E mutation was identified in patients with HCL. This mutation was a significant advance in understanding the pathophysiology as well as a new target for the treatment HCL (18). The B-raf proto-oncogene (7q34) consists of 18 exons and the mutation occurs in the exon 15 position (19). BRAFV600E mutation is reported in 80-90% of patients with HCL and BRAF inhibitors may be used as first line in HCL patients with mutation as tailored therapy or second or third line treatment in refractory patients. In our cohort we performed BRAF mutational analysis in two relapsed patients and found positive for BRAFV600E. BRAF inhibitor Vemurafenib treatment showed a complete response in six of fifteen patients with relapse refractory settings and median event free survival was 17 months (20). In addition to the development BRAF inhibitors CD22 immuntoxin; Moxetumomab pasudotox shows promising results and is approved by FDA in relapsed/ refractory disease after failure of two systemic therapies (21). In near future mutational status can direct treatment of disease and these new drugs could play a much higher role in treatment of HCL

To conclude, cladribine confers a safe and effective treatment modality. Although cladribine and other purine analogs have improved response rates and progression-free survival, progress has yet to be made for resistant and relapsing patients.

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard. Informed consent was obtained from all individual participants included in the study. Trakya University Ethical Committee Approval: 2019/99 Date: 25.02.2019

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