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Single Agent Cladribine Therapy for Hairy Cell Leukaemia: A 10-Year Retrospective Analysis with Focus on Drug Access Challenges and Need for Policy Change in Pakistan

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Abstract

Objective: Hairy cell leukemia is an indolent B cell lymphoma presenting with constitutional symptoms, splenomegaly and cytopenia. Cladribine remains the standard first line therapy, used with or without rituximab with a remission rate of 85%-90%. We aim to analyze the results of using single agent cladribine in hairy cell leukemia, keeping in mind drug availability issues in our resource limited setting.

Methodology: A retrospective, descriptive cross-sectional study was conducted at a tertiary care hospital in Lahore. Medical records from 2015 to 2024 of patients who received single agent cladribine were reviewed and data collected. The complete remission rate and overall survival was documented. Moreover, source of drug procurement, cost borne by the patient and difficulty in drug access was documented.

Results: A total of 11 patients were included in the study. Common presenting symptoms were infection (81%) and fatigue (72%). On clinical examination splenomegaly was present in all patients. All patients received cladribine at dose of 0.1mg/kg/day IV continuous infusion for 7 days. 82% of patients achieved complete remission. In patients who achieved complete remission, no relapse was reported till date. All patients bought drug through unofficial channels with no support from government health insurance programs.

Conclusion: Cladribine demonstrates excellent efficacy in this cohort with a remission rate of 90.9% comparable to international data. However, it is not registered with drug regulatory authority of Pakistan and not available through official drug sources. Its lack of availability in Pakistan causes inequity in access and treatment delay for patients of hairy cell leukemia.

Keywords: Hairy cell leukemia, Cladribine.

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Introduction

Hairy cell leukaemia is an indolent splenic B cell malignancy comprising about 2% of all leukaemias.1 It involves the peripheral blood, bone marrow and the spleen.[2] The median age of diagnosis is around 55 years. Patients usually present with signs and symptoms of fatigue, recurrent infection, abdominal discomfort, and splenomegaly. Complete blood count shows cytopenia(s).[3] The diagnoses of hairy cell leukaemia is based on bone marrow biopsy and flowcytometry. Bone marrow biopsy shows atypical lymphoid cells with cytoplasmic projections and fried egg appearance on trephine.[4] The typical immunophenotype for classical hairy cell leukaemia is positive for CD11c, CD103. CD25, CD123 and Annexin A1 and negative for CD5 and CD10.[5] The diagnosis is further augmented by molecular analysis to detect BRAF V6OOE mutation.[6]

Different treatments have been suggested over the years. Hairy cell was being treated with splenectomy and interferons in late 1990s and early 2000.[7] Cladribine was tested in early 2010 and it emerged as an effective single agent treatment with remission rate of 83%.[8] Later rituximab was added in combination in relapsed/refractory cases or as single agent treatment for the elderly frail patient.[9] After discovery of BRAFV600E as defining molecular feature in classic hairy cell leukaemia the therapeutic landscape further expanded and introduced BRAF inhibitors (vemurafenib, dabrafenib) alone or in combination, has demonstrated high efficiency in relapsed or refractory cases.[10] Despite the efficacy of drug, the management of Hairy cell leukaemia is difficult in low- and middle-income counties because of different challenges like delayed presentation, drug availability only through unofficial channels and cost constraints. Cladribine is unavailable in Pakistan through official channels. The drug is not registered with the drug

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regularity authority of Pakistan (DRAP). This increases the financial burden because of improper invoicing and also leads to treatment delay due to procurement difficulties.

The objective of my study is to document the clinical presentation, treatment response and follow-up outcome of patients diagnosed with Hairy cell leukaemia at a tertiary care hospital in Lahore over a decade. This study aims to highlight the gap in accessing cladribine through unofficial sources in Pakistan which causes serious concerns about drug quality, treatment delay, and financial toxicity. As cladribine has an 83.5%.[11] remission rate it should be available through proper channels approved by Pakistan drug regulatory.

Methodology

This is a retrospective, descriptive single center observational study conducted at department of clinical hematology at INMOL hospital Lahore. Ethical approval was obtained from Institutional review board prior to data collection (IRB reference number: INMOL -53-(213)).As this was a retrospective study data was collected from hospital records there was no direct patient contact, so formal informed consent was not required. Patient confidentiality was strictly maintained and all data was anonymized prior to analyses. This study aims to evaluate clinical outcomes of hairy cell leukemia in patients treated with single agent cladribine and challenges faced in accessing cladribine in a resource limited setting.

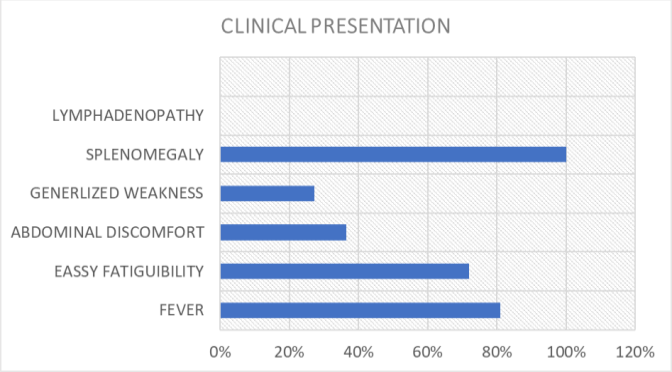
Inclusion criteria

- Adult patients >18 years with confirmed diagnosis of hairy cell leukemia on bone marrow immunohistochemistry and/or immunophenotyping. BRAF mutation was tested in patients who could afford testing.
- Patient who received cladribine as single agent treatment
- Patient with complete follow up records available till a minimum of 1.5-year post treatment.

Exclusion criteria

- Patient with hairy cell leukemia variant
- Patients who received treatment other than cladribine (interferon, splenectomy, rituximab or combination therapy)
- Patients who had lost to follow up

Data taken from the hospital files included demographic profile (age, sex, gender, occupation, address), presenting features, baseline hematological parameters, treatment details i.e., dose and schedule of cladribine. Response to therapy was assessed by bone marrow biopsy results 4 months after treatment completion and relapsed status and current survival status was recorded. Information regarding the source and cost of cladribine was obtained directly from the patients or their caregivers during the follow-up visit. This information was self-reported and cross verified with two to three patients who provided details of acquisition process [including appropriate cost and vendor type]. Data was entered and analyzed using IBM SPSS statistics 30. Given the small sample size only descriptive statistics were applied. Continuous variables (e.g., age duration of symptoms) were presented as median and range. Categorical variables (gender, clinical features, outcomes) were summarized as frequencies and percentages.



COMPLETE REMISSION: Near normalization of peripheral blood counts: hemoglobin >11g/dl: platelets >100,000/mcL: ANC>1500/mcL. Regression of splenomegaly on physical examination. Absence of morphological evidence on peripheral blood and bone marrow.[12]

PARTIAL REMISSION: Near normalization of peripheral blood count as in complete remission with minimum of 50% improvement in organomegaly and bone marrow biopsy infiltration with HCL.

RELAPSE: Morphological relapse is defined as reappearance of HCL in peripheral blood, the bone

marrow biopsy, or both by morphological stains in the absence of hematological relapse. Hematological relapse is defined as reappearance of cytopenia(s) below the threshold defined above in CR.

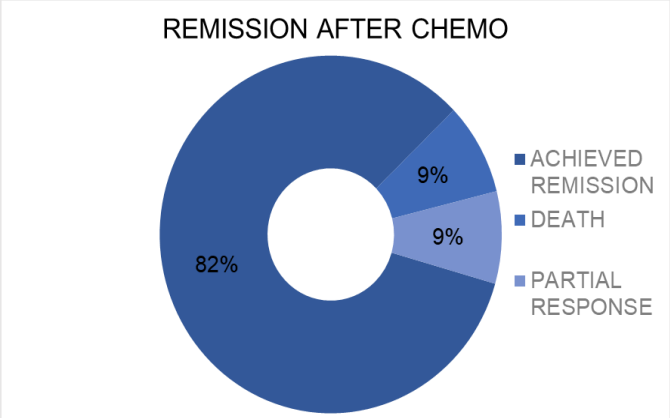
Results

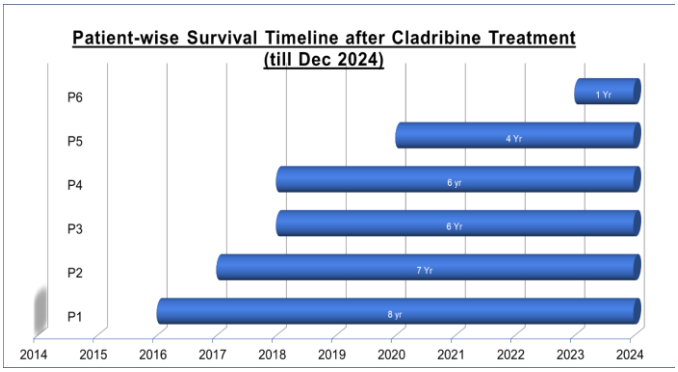
From January 2015 to December 2024, a total of 11 patients received single agent Cladribine for hairy cell leukemia treatment. Out of them 9 patients were male, and 2 patients were females. The age range was 35 to 63 years with median age at diagnosis 49 years. Majority of patients (81%) presented with history of fever followed by history of easy fatigability (72%), abdominal discomfort (36.4%) and generalized weakness (27.3%). No history of bleeding was present in any of the patients. On clinical examination 100% of patients presented with palpable splenomegaly. Spleen size ranged from 16 to 25 cm.

At presentation, the mean ANC (Absolute neutrophil count) was around 0.76 x10^9/L (range 0.2-2 x10^9/L). of the patients had severe neutropenia and 5 had moderate neutropenia. The mean ALC (absolute lymphocyte count) among the available data was1.79 x10^9/L with range of 0.23-2.8 x10^9/L. Bone marrow aspirate and trephine in all patients showed classical findings of lymphoid infiltrate with some egg fried appearance on trephine. Flowcytometry was consistent with B cell phenotype with uniform expression of CD19, CD20, and CD22, and co-expression of CD11c, CD103, Annexin A1. BRAFV600E mutation testing was performed in only three patients. it was unavailable in majority of patients due to unavailability of testing in Lahore, the city where research was being conducted. Patient had to travel to other cities for testing which was not financially feasible for many.

All the patients received singe agent treatment Cladribine according to the standard dose of 0.1mg/kg/day for 7 days. Supportive care was given during and after treatment. At 4-month post treatment bone marrow assessment showed 9 patients (82%) achieved hematological and bone marrow remission. One patient (9%) died during hospitalization post treatment, due to infection. One patient (9%) demonstrated partial response with partial regression of spleen but persistence of 50% of atypical lymphoid cells in bone marrow. In this patient BRAVFV600E mutation was not performed.

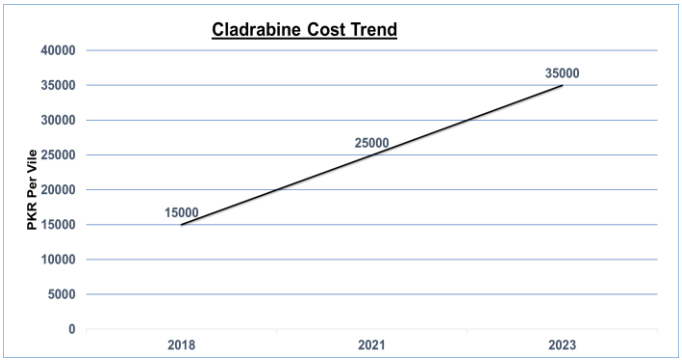
PARAMETER	MEAN	MEDIAN	RANGE
ANC(*10^9/L)	0.76	0.7	0.2-2.0
ALC(*10^9/L)	1.79	2.3	0.23-2.8





Among the 9 patients who received remission after single agent cladribine therapy, 6 patients (54.5%) are fit and fine and have not relapsed till date. 3 patients (27.3%) were lost to follow up after 1.5 years of treatment and could not be contacted for their status. The fit patient received their treatment in year 2016, 2018, 2018, 2018, 2018, 2020 and 2024; so, their life expectancy was around 8 years, 7 years, 6 years for 2 patients, 4 and 1 years respectively.

As cladribine is not officially available in Pakistan informal cost data were obtained from three patients who independently purchased cladribine at different time point. Due to lack of proper invoicing and unofficial source, the cost of 10mg vial, as stated by patients or their care givers was PKR 15000 in year 2018, PKR 25000 in 2021 and PKR35000 in 2024. Arranging medicine was tedious and time consuming, with frequent delays at the source end. One of the patients had to wait around 1 month to arrange resources to get this medicine.



Discussion

Hairy cell leukemia is a rare B cell lymphoproliferative disorder. It has a high remission rate when treated with Purine analogs (Cladribine).(13). International data reports an overall response rate of about 85% or greater. A multicentric Italian study was done in 2022 showing experience of 30 years with cladribine treatment, result showed median OS of 95.3%, 92.4%, and 81.8% of patients were estimated to be alive at 5, 10, and 15 years, respectively. 9.5% deceased, causes of death was infection in 2.7% cases and progression of HCL in 2 cases.(14).

Similarly, a study was conducted in Pakistan in 2019 at Agha Khan University Hospital. It included 21 patients treated with cladribine, reported 100% complete remission rate initially, with relapses manged successfully during follow up. Reported a overall survival of 90% at a median of 35 month follow up.[15] This study shows higher remission rate but with a shorter over all follow up period. Similarly, another study published in 2022 demonstrated a 16-year experience in treating Hairy cell leukaemia with different modalities out of which 83.3% complete remission rate reported among those receiving Cladribine as first line therapy.[16] These studies vary in design and duration they reflect almost the same remission rate as in our cohort. This consistency of our data with the global benchmark reveals the efficacy of cladribine in treating HCL in a resource limited setting.

Clinical presentation and disease features in our study are similar to international data with frequent infections, splenomegaly and cytopenias being dominant features.[17] Immunophenotyping was consistent with the expected B cell markers CD19, CD20, CD22 with hairy cell associated antigens CD11C, CD103 and annexin A1.[18] The limited molecular testing of BRAFV600E was done in 3 patients and they all achieved remission and till date hadn't relapsed.

Although Cladribine is highly effective, it has serious post induction cytopenias and according to the international data myelosuppression remains one of the major causes of death in HCL patients. In our study 1 patient died due to infection in induction therapy.[19] This emphasizes the critical need for intensive supportive care measures with infection control and prophylaxis.

Our study emphasizes that a substantial barrier in management of HCL in resource limited countries like Pakistan are lack of legal registration and regulated supply of cladribine by the Drug Regulatory Authority of Pakistan. Patients had to source it through unofficial channels incurring excessive cost (15000-35000 per vial) and delay of many days to purchase the drug. The average per capita annual income is PKR 450,000 to 500,000. This income is barely able to manage patient's living expenses and can't support added cost of cladribine treatment. This cost was not covered by any insurance company or government sponsorship programs. delays and financial burden increase the risk of complications, limits the equity of access and delays treatment initiation. Patients have to arrange the finances on their own, at times by selling out their valuables. The dependence on small scale importers raises concern regarding batch quality, storage conditions, and cold chain maintenance particularly in temperature sensitive cytotoxic agents like cladribine.

Cladribine officially recognized at the end of 2025 in Pakistan. this study was conducted before this. There are many hematological drugs which are not officially recognized in Pakistan similar challenges are faced while using those drugs one example is arsenic trioxide which is a cornerstone agent in management of Acute Promyelocytic Leukemia.

Conclusion

HCL had a high remission rate in the first line setting with single agent cladribine in our institutional cohort, consistent with the international benchmarks. Ensuring affordable and timely access to cladribine is important for the management of these patients. The health department and concerned governing bodies should focus on legal registration of all such essential oncologic medications, ensuring protected supply chains,

transparent pricing and subsidized cost to facilitate patients of our lower middle-income country.

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