ORIGINAL ARTICLE

TREATMENT OUTCOMES OF PATIENTS WITH HAIRY CELL LEUKAEMIA; A 16-YEAR EXPERIENCE AT A TERTIARY CARE CENTER IN PAKISTAN

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Background: Hairy cell leukaemia (HCL) is an uncommon neoplasm of mature B-lymphoid cells which is characterized by cytopenias, commonly of all three cell lines, with typical hairy cells on peripheral smear and/or bone marrow along with organomegaly. Objective was to document the outcomes of HCL patients treated at a tertiary care hospital in Pakistan. **Methods:** Medical records of patients from 2004 to 2020 were reviewed and data was collected to assess patient's demographics, symptomatology, remission rate and overall survival. The record flies of all patients presenting to AFBMTC with HCL were included in the study. The record file with insufficient data were excluded **Results:** 26 patients with a mean age of 48.12±11.43 years were diagnosed with HCL and treated at AFBMTC. Out of these, 23 (88.4%) were male and 03 (11.5%) females. The main presenting complaints were generalized body aches (34.6%), fever (15.4%), incidental finding of cytopenias (11.5%) and abdominal discomfort (26.9%). Splenomegaly was found in 76.92% while hepatomegaly was found in 46.15% of patients. A total of 12 (46.15%) patients received Cladribine (either intravenous or subcutaneous) and splenectomy was done in 7 (26.92%) as 1st line treatment. Eleven patients out of 12 (83.33%) who received Cladribine and 05 (71.42%) patients out of seven who underwent splenectomy; achieved complete remission (CR) after 1st line of treatment. One patient received Cladribine as 1st line of treatment but did not respond and CHOP regimen was given as second line. Out of the 26 patients, 5 patients (19.23%) relapsed at a median interval of 5.83±6.6 years. Two patients received Cladribine + Rituximab while 03 patients received cladribine as their salvage therapy. Disease free survival (DFS) of 71.4% among the patients underwent splenectomy while 75.0% among the patients received Cladribine. DFS for combination therapy (included CHOP and CVP) was 66.7% while OS was calculated among patients who received cladribine, splenectomy and combination chemotherapy as 100%, 85.7%, 66.7% respectively. **Conclusion:** Cladribine has a significant efficacy and encouraging acute and long-term benefits when administered to patients with HCL. A single course of cladribine was able to induce CR in a vast majority of patients. At a median follow up of 4.6 years the OS was 100% with cladribine and 85% with splenectomy. Those who relapsed were successfully retreated with cladribine + Rituximab.

Keywords: Hairy cell leukaemia; Outcome; Cladribine

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INTRODUCTION

In 1958, Hairy cell leukaemia (HCL) was first described by Bournocle *et al*, characterized by a mature B-lymphoid neoplasm characterized by cytopenias of all three cellular lines (i.e., anaemia, leukopenia and thrombocytopenia). The name originated because of the appearance of cells having hairy projections in peripheral smear or Bone Marrow Aspirate (BMA).[1] These cells are composed of abundant cytoplasm with fine hairy projections and a characteristic nucleus without a nucleolus, in combination with splenomegaly/hepatomegaly and recurrent infections.[2] In the Bone Marrow Aspirate and Trephine Biopsy, presence of cells with distinct boarders giving rise to a fried egg appearance, with increased reticulin fibres, resulting in dry taps.[3] Immuno-phenotypically HCL express CD11c, CD25, CD103, pan B-cell antigens (CD19, CD20 and/or CD22) and tartrate-resistant acid phosphatase (TRAP).[4] The HCL has a male predominance, with male to female incidence reported as 4:1 and median age of presentation 55 years.[5] Recently whole genome sequencing identified the presence of mutant BRAF V600E gene.[6]

Significant advancements have been made in treatment options for HCL over the last few years. Traditionally, not everyone with a diagnosis of HCL requires treatment.[7] The indication for the initiation of treatment is patients presenting with or without symptomatic splenomegaly and cytopenias in two cellular lines.[8] Initially Splenectomy was thought to be

the only treatment until 1984.[8] The role of Interferon α in HCL patient was firstly described by Quesada et al. Studies with long term follow up of patients treated with interferon showed both, the low complete response (CR) and short-term partial response (PR).[9] Nucleoside analogues such as Pentostatin and cladribine, have been introduced recently and have emerged as effective therapeutic options with promising results.[10] Cladribine has demonstrated quite striking results in HCL, the documented response of pentostatin and Cladribine in attaining a CR is approximately 80–90% and overall survival (OS) of 90%.[11] Rituximab alone has only modest activity in patients with a relapsed HCL, albeit an increased response and long-lasting remissions has been recorded with the combination of Rituximab and a purine nucleoside analogue.[12] A key diagnostic and therapeutic marker, BRAF V600E mutation, has emerged recently and has been identified in >85% of the patients.[13] Objective of the study was to document the clinical outcomes of HCL patients treated at Armed Forces Bone Marrow Transplant Centre (AFBMTC), Rawalpindi, Pakistan.

MATERIAL AND METHODS

It was a retrospective, descriptive cross sectional, conducted on 26 patients with HCL presenting to AFBMTC from 2004 to 2020, after the approval of Ethical Board. The diagnosis of HCL was established by vigorous laboratory tests comprising bone marrow examination and flow-cytometry. The record files of the patients with insufficient data were excluded. The response to the treatment was divided into two categories, i.e., overall response and relapse. The overall response included patient achieving complete or partial remission. The complete remission (CR) was defined as resolution of organomegaly with cytopenias and absence of hairy cells in both the peripheral circulation and bone marrow.[14] Partial remission (PR) was defined as at least 50% reduction in palpable hepato/splenomegaly, ≥50% improvement in the peripheral blood counts and ≥50% reduction in number of circulating HCL cells.[7] The relapse was determined by either new or progressive cytopenias or recurrence of organomegaly.[15] Data was collected to assess patient's demographics, symptomatology, remission rate, disease free survival (DFS) and overall survival (OS). Data were analyzed using the Statistical Package for Social Sciences 23. The analysis yielded different variables amongst them for the categorical variables frequencies and percentages were calculated, while for continuous variables mean median and standard deviation was calculated.

RESULTS

From January 2004 to December 2020, a total of 26 patients with HCL were treated, with a mean age of 48.12±11.43 years. Out of these, 23 were male and 03 females. Majority of the patients presented with verity of cytopenias and Organomegaly, comprising Splenomegaly in 76.92% and hepatomegaly in 46.15% of patients. The demographics and the presenting symptoms of the patients are as shown in table-1.

Table-1: Demographics of the patients

	Frequency (n)	Percentage (%)
Gender		
Male	23	88.4
Female	03	11.5
Presenting Total Leukocyte Count		
< 4 x 109	13	50
4-10 x 109	9	34.6
> 10 x 109	3	11.5
Missing	1	3.8
Presenting Absolute Neutrophil Count		
<0.5	6	23.1
0.5-1.5	9	34.6
≥ 1.5	5	19.2
Missing	6	23.1
Presenting Haemoglobin		
< 8	4	15.4
8-12	15	57.7
> 12	6	23.1
Missing	1	3.8
Presenting Platelet count		
>50	10	38.5
50-100	9	34.6
>100	6	23.1
Missing	1	3.8
Organomegaly		
Measurement in cm	**Spleen (%)**	**Liver (%)**
0	46.2	23.1
<5	11.4	0.0
5-15	23.0	42.3
15-20	19.2	30.7
≥20	0	3.8

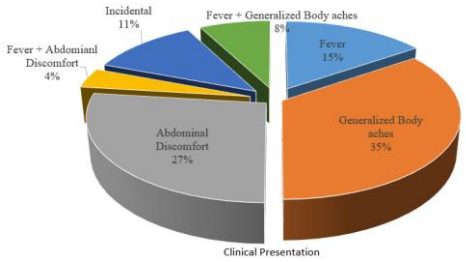

Figure-1: Presenting symptoms

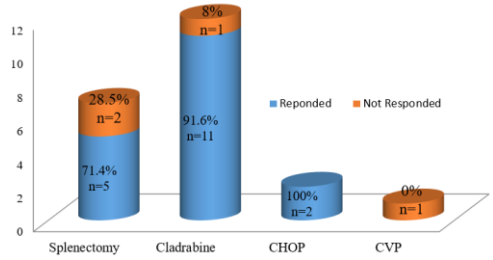

Figure-2: Response to the therapy

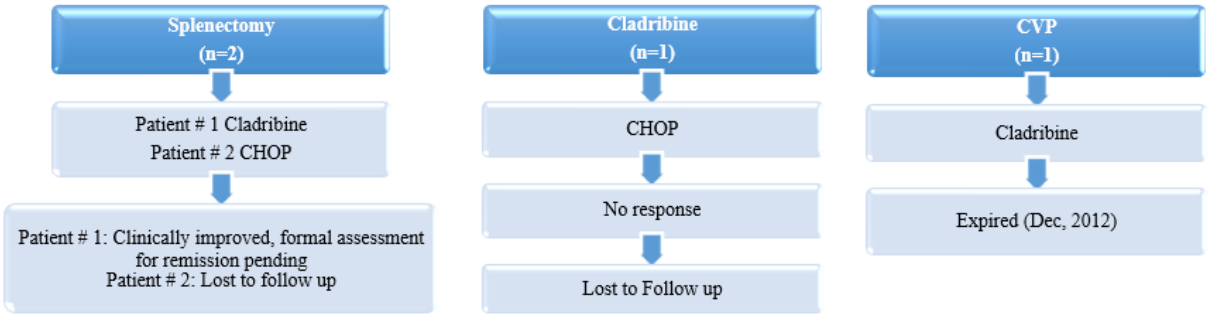

Figure-3: Response to salvage therapy

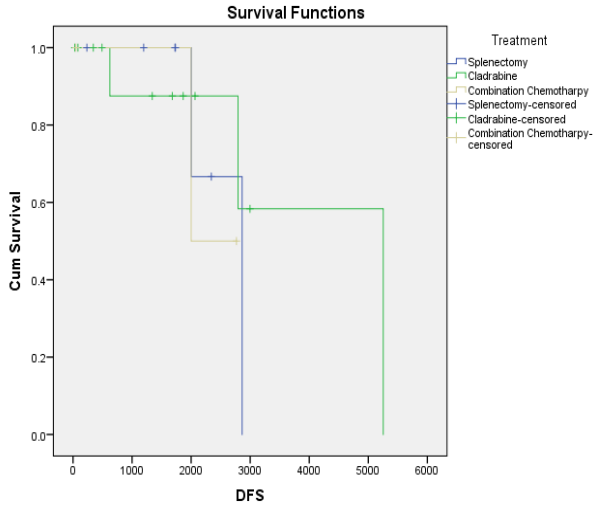

Figure-4: Disease Free Survival (Kaplan Meier Graph)
***p*-0.602**

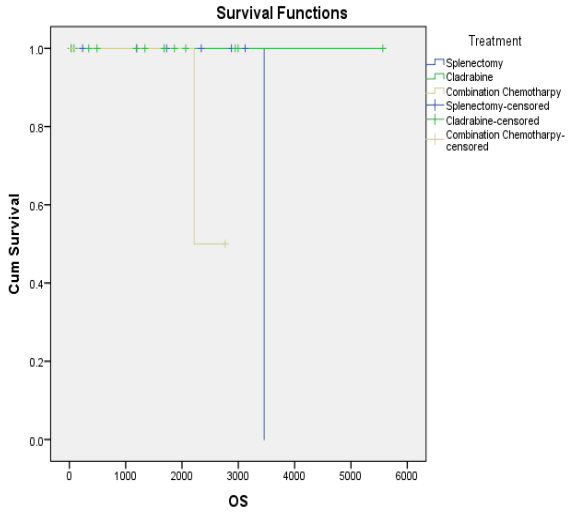

Figure-5: Overall Survival (Kaplan Meier Graph)
***p*-0.131**

The main presenting complaints were generalized body aches (34.6%), fever (15.4%), incidental finding of cytopenias (11.5%) and abdominal discomfort (26.9%) which was secondary to organomegaly. The fig 1 given below shows the common presenting complaints.

A total of 04 patients were excluded from the analysis due to insufficient data. Out of 22 patients, 12 patients received Cladribine (either intravenous or subcutaneous). Both daily dose and weekly dosage of cladribine protocols were used. Splenectomy was done in 07 patients, 02 patients received Cyclophosphamide, Doxorubicin hydrochloride, Vincristine sulphate, and prednisone (CHOP) while only one patient received Cyclophosphamide, Vincristine and Prednisolone (CVP) as their 1st line treatment. The figure 2 given below shows the response to the therapy given.

Out of 12, receiving Cladribine as first line therapy eleven patients achieved and CR, out of which 03 patients relapsed at a median time of 7.89 years. Only one patient did not respond to the initial therapy. Patient who was not responsive to the cladribine, received CHOP as a salvage therapy. He didn't respond to the CHOP therapy after which he was lost to follow up.

Five patients who underwent splenectomy; as 1st line therapy, two patients did not show any improvement in their peripheral blood count and cytopenias persisted. One patient received cladribine while 2nd patient received CHOP, as salvage therapy. The former patient showed improvement in cytopenia but his formal response assessment is still not done, while the later was lost to follow up after the completion of 1st cycle. Two patients out of three who initially responded to the splenectomy relapsed at a median time of 7.2 years.

Two patients received CHOP as first line therapy and both of them achieved CR. There was only 01 patient who received CVP as his 1st line therapy, who did not respond to the therapy and his death was reported in Dec, 2012. A scheme of the lines of treatment is shown below in the figure 3.

Out of the 18 patients who responded to 1st line therapy, 05 patients (27.77%) relapsed, at a median interval of 7.76±6.43 years (cladribine as first line

therapy) and 6.75±1.69 years (splenectomy as first line therapy) respectively. Response to second line therapy is shown below in table 2. The relapse rate among the patients who received Cladribine as 1st line therapy was 27.27% while it was 66.66% in patients undergoing splenectomy.

Table-2: Response to 2nd line therapy

	1st line Therapy	Disease Free Survival (No. of days)	2nd Line therapy	Response
Patient #1	Cladribine	2794	Cladribine	PR
Patient #2	Cladribine	624	Cladribine + Rituximab	CR
Patient #3	Cladribine	5253	Cladribine + Rituximab	CR
Patient #4	Splenectomy	2002	Cladribine	Lost to Follow up
Patient #5	Splenectomy	2863	Cladribine + Rituximab	CR

DFS was calculated for the patients at a median follow up of 4.6 years, when divided into groups based on the 1st line therapy they received, showed a DFS of 71.4% among the patients belong to splenectomy group while 75.0% among the patient in Cladribine group. DFS for combination therapy (included CHOP and CVP) as calculated as 66.7%. OS was calculated among patients who received cladribine, splenectomy and combination chemotherapy as first line treatment as 100%, 85.7%, 66.7%. The DFS and OS shown in the figure 4 & 5.

DISCUSSION

In the study, the patients had a comparable demographic profile with the previously published studies; i.e., a median age of 48 years and higher male to female ratio.[16] A recent cohort, conducted in Pakistan, included 21 patients of HCL; all male.[1] Our study encompasses the demographic characteristics of patients and the outcomes of 26 HCL patients being treated at AFBMTC.

Out of 26, 12 patients were treated with cladribine. 11 (92%) patients achieved CR while 03 (27.27%) patients who responded to the treatment initially, relapsed at a median follow-up of 4.6 years. Rosenberg et al stated a CR of 88%, where 88 patients were treated with cladribine.[17] A number of other studies have reported very promising response rate with cladribine, reporting an overall response (OR) and CR rates ranging from 75 to 100% and 72 to 98%, respectively.[12,18] Our study showed a CR rate of 92%, which is in concordance with reported international studies. Another study conducted in Pakistan reported, 29% of the patients relapsed after initial response. Some other studies have reported approximately similar relapse rates, i.e., 26–38%[19] while others have reported a higher percentage of 58%. Another study conducted in Peshawar, Pakistan reported a CR of 100% with no relapse in 2 patients, out of seven, who were treated with cladribine.[20]

Worth mentioning here that the studies reporting low relapse rates have shorter median follow up. Low relapse could be due to the indolent nature of HCL, the mutant clone might take time to produce an evident relapse. Studies have reported that in case of relapsed disease, an effective option is chemo-immuno-therapy with rituximab and cladribine. The rituximab and cladribine combination achieve a longer lasting CR and improved OS when compared to cladribine monotherapy.[21] Rituximab + Cladribine was given to two patients in out cohort, both of them responded to the therapy and achieved normalization peripheral blood cell count though their formal assessment of remission is awaited.

An OS of 91% was documented by a study conducted in Brazil where 68% of patients were treated with 2-CdA, cladribine.[22] Our study documents a comparable outcome where 46.15% of the patient were treated with standard of care, i.e., cladribine. In our study, OS is reported as 100% in cladribine treated patients, 85.7% with splenectomy and 33.3% with combination chemotherapy.

Limitations: Main limitation of the study was small number of patients.

CONCLUSION

In developing countries with limited resources and high infection risk, single agent cladribine is safe and effective first line therapy of HCL patients.

AUTHORS' CONTRIBUTION

YM: Conception and designing of the work; or the acquisition, analysis, or interpretation of data for the work. Drafting the work or revising it critically for important intellectual content. KMA: Conception of the work; revising the draft critically. IR: Conception of the work, revising it critically for important intellectual content. CQUN: Final approval of the version to be published. SN, AU, JH: Revising it critically for important intellectual content.

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