Original Article

Hairy cell leukemia - clinical profile and treatment outcome from a Tertiary Regional Cancer Institute in South India

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ABSTRACT

Background: Hairy cell leukemia (HCL) is an indolent neoplasm of small mature B lymphoid cells. It is characterized by pancytopenia, splenomegaly, bone marrow fibrosis, and presence of atypical lymphoid cells with hairy projections in peripheral blood, bone marrow and spleen. HCL is potentially curable and treatment with purine analog cladribine induces complete remission (CR). **Materials and Methods:** This is a retrospective analysis of 10 HCL cases diagnosed in the Department of Medical Oncology at a Tertiary Regional Cancer Institute, South India, over 7 years. The clinical features, laboratory parameters, bone marrow findings, cytochemistry, immunophenotyping, and outcome with treatment were studied. **Results:** Among 8 cases of HCL who were treated with cladribine, 7 achieved remission and 1 succumbed to infection during course of treatment. Median overall survival in these 7 cases was 61 months. **Conclusion:** HCL is a chronic lymphoproliferative neoplasm with potentially curative treatment. Cladribine is treatment of choice and majority of patients achieve long-lasting CR. Upon relapse, these patients can be successfully salvaged with cladribine retreatment.

Key words: Cladribine, hairy cell leukemia, India, relapse, remission

INTRODUCTION

Hairy cell leukemia (HCL) is an indolent neoplasm of small mature B lymphoid cells. It comprises 2% of all leukemias[1] and it occurs more frequently in men (male:female - 4:1).[2] The mean age at diagnosis is approximately 52 years.[2] It was initially described in 1958 by Bouroncle *et al.* and is also called as leukemic reticuloendotheliosis. HCL is characterized by the presence of atypical lymphoid cells with oval nuclei and abundant cytoplasm with "hairy" projections involving the peripheral blood and infiltrating the bone marrow and splenic red pulp.[3]

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In this article, we describe 10 cases of HCL, with respect to their clinical profile, morphology, cytochemistry, immunophenotypic (IPT) features and outcome with treatment.

MATERIALS AND METHODS

This study included 10 patients diagnosed and treated as HCL at the Department of Medical Oncology at a Tertiary Care Centre in South India, during the period 2007–2014. The study was approved by the Institutional Ethics Committee and done in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki and its later amendments.

A written informed consent was obtained from the patients prior to procedures and treatment. The presenting symptoms

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at diagnosis, clinical signs and laboratory parameters were analyzed. Among clinical signs, splenomegaly, hepatomegaly, lymphadenopathy, and any evidence of infections were looked for. Investigations included complete blood cell count, differential count, peripheral blood smear examination, a bone marrow aspiration (BMA) and biopsy with immunohistochemistry for Annexin A1 in selected cases and flow cytometric IPT of peripheral blood or BMA. The types of chemotherapy, complications, and the relapse rate were analyzed.

The definition of achieving a complete remission (CR) included recovery of hemoglobin (Hb) to more than 12 g/dL, absolute granulocyte count more than 1500/mcL, and a platelet count more than 100,000/mcL for at least 1 month. In addition, there should be no evidence of HCL cells by morphologic examination of the bone marrow biopsy or the peripheral blood. Patients should have had resolution of organomegaly by physical examination and be asymptomatic from their disease.[4]

RESULTS

Demography

The patient age ranged from 32 to 66 years, with median age at presentation being 48 years. Majority of the patients were males (8/10); male:female ratio was 4:1. The median duration of symptoms was 3 months (range, 1–24 months). The most common symptom was fever and was noted in 80% of cases, followed by weakness/fatigability (70%), weight loss (40%), infection (30%), awareness of mass (20%), and bleeding (10%) are shown in Table 1.

Clinical examination [Table 2] revealed that 4 (40%) patients had hepatomegaly and 9 (90%) patients had massive splenomegaly. Lymphadenopathy was seen in 2 (20%) patients. Cervical, axillary and intraabdominal lymphadenopathy was seen, as detected on computed tomography (CT) scan imaging. A history of infection prior to diagnosis was reported by 3 (30%) patients – of these, 1 had cellulitis and 2 had pneumonia.

Laboratory features

Anemia (Hb <12 g/dL) was present in 8 (80%) with a median Hb of 9.0 g/dL (range, 6.2–13.8). The requirement for transfusion was observed in 2 (20%) of the patients. Leucopenia was noted in 5 (50%) cases with median total leucocyte count of 6.2 (range, 1.4–14.4) $\times 10^9$/L and the mean platelet count was 57 (range, 26–189) $\times 10^9$/L with 60% of patients presenting with thrombocytopenia. Only 2 (20%) patients had leukocytosis at presentation. Pancytopenia was present in 3 (30%) cases. Classical hairy cells were seen among 5 (50%) cases in peripheral blood, while all cases showed similar cells in bone marrow [Figure 1]. Tartrate resistant acid phosphatase positivity was seen in 5 (50%) of cases. In two cases where flow cytometric IPT could not be done, immunohistochemistry for Annexin A1/DBA.44 helped in arriving at a final diagnosis [Table 3].

Flow cytometric immunophenotyping

Flow cytometric data was available in only six cases. All the six cases expressed characteristic HCL phenotype, that is, positivity for CD19, CD20, CD11c, CD25, CD103, and CD123 [Figure 2]. Of the 6 cases evaluated for light chain

Table 1: Presenting symptoms among subjects

Reported symptom	Present study (%)	Galani *et al.* (%)	Somasundaram *et al.* (%)
Weakness/fatigue	70	80	74
Fever	80	56	40
Abdominal mass	20	20	34
Weight loss	40	12	14
Bleeding	10	12	8.5
Infection	30	-	-

Table 2: Clinical features of subjects

Clinical feature	Present study (%)	Galani *et al.* (%)	Somasundaram *et al.* (%)
Pallor	50	68	-
Lympadenopathy	20	24	8.5
Splenomegaly	90	92	74
Hepatomegaly	40	28	51

Table 3: Laboratory finding of the subjects

Parameter	Present study (%)	Galani *et al.* (%)	Somasundaram *et al.* (%)
Anemia	80	88	74
Leukopenia	50	77	48
Leukocytosis	20	31	23
Thrombocytopenia	60	8	60
Pancytopenia	30	54	28
Monocytosis	0	4	-

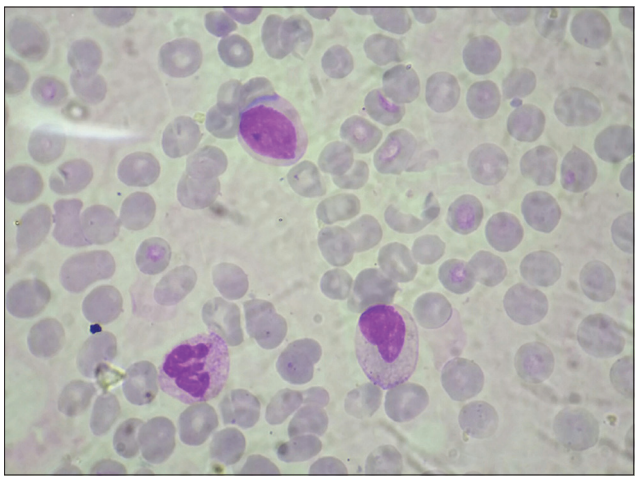

Figure 1: Hairy cells in bone marrow

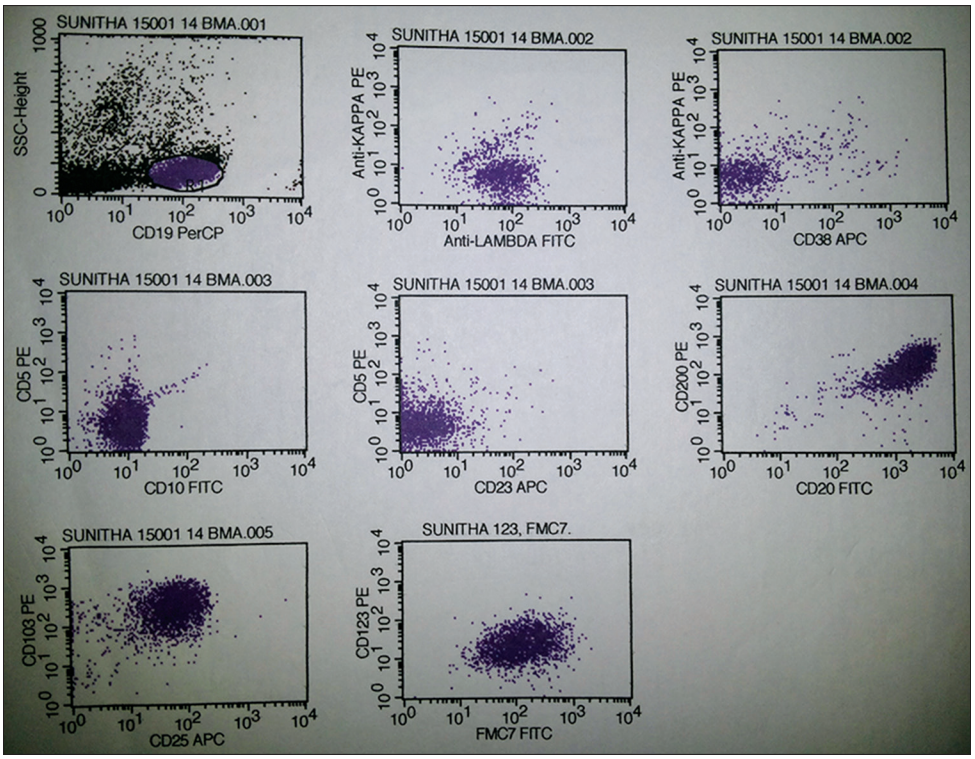

Figure 2: Flow cytometric findings in hairy cell leukemia

restriction, 2 showed kappa chain restriction, while 4 of the cases showed lambda chain restriction; 2 cases expressed CD10, whereas 4 cases demonstrated FMC7 expression. CD79a expression was present in two of the cases. All cases were negative for T cell markers such as CD2 and CD5.

Treatment and follow-up

Of the 10 patients, 8 received treatment with the purine analogues, mainly cladribine. Due to financial constraints, 2 out of 10 did not opt for any chemotherapy and were managed with best available supportive care and eventually lost to follow-up.

Among the 8 patients who were treated with purine analogues, 2 were initially treated with interferon alpha at a dose of 3 million IU on alternate days for duration of 2–3 months. Both cases achieved remission, however had an early relapse at 4 and 12 months, respectively. Among the rest, 1 patient received chlorambucil with prednisolone initially; however since he did not achieve any remission, he later received treatment with fludarabine and subsequently achieved remission.

The other seven patients received cladribine at a dose of 0.09 mg/kg/day for 7 days, given as a continuous 24 h infusion. During the course of treatment, one patient died due to septicemia. All the remaining six patients who received cladribine achieved CR. BMA was done 4 weeks subsequent to cladribine infusion or when there was hematological remission and showed Mo status- marrow in remission. The treatment outcomes are shown in Table 4.

All 8 patients developed neutropenia during treatment with cladribine and fludarabine and 1 was supported with recombinant growth factors. Median time to response in these 7 patients was 3 months (range, 2–7). Median duration of follow-up was 61 months (range, 2–96). Median duration of remission after cladribine treatment was 54 months (range, 24–64). One out of 10 cases (10%) died due to sepsis during the course of treatment. Two out of 10 patients (20%) relapsed at 4 months and 12 months respectively after treatment with interferon alpha. Both achieved a second CR with cladribine. The median overall survival in these 7 patients was 61 months (range 24–96 months). Among these 7 patients on follow-up, none developed second malignancy.

DISCUSSION

HCL is a rare B cell chronic lymphoproliferative disorder representing 2% of all leukemias.[1,5] In this study, we included 10 cases of HCL diagnosed over 7 years, which co relates with the French study of around 30 cases over 25 years.[2] In our study, the median age was 47.7 years, similar to a recent Indian study of 35 patients by Somasundaram *et al*. (50 years)[6] and the Romanian study with 39 patients.[7] The median age in a study by Saven *et al*.

Table 4: Treatment outcome of the subjects

Parameter	Present study	Somasundaram *et al.*
Complete response (%)	88	93
Relapse (%)	20	18
Median DFS (months)	54	23
Median OS (months)	61	26

DFS: Disease-free survival, OS: Overall survival

was 53 years.[8] However, in the present series, the median age was significantly lower compared to the French study with a reported median age of 67.8 years.[2] This indicates that HCL probably occurs at a younger age in patients in the Indian setting, as compared to the Western World. The presenting symptoms were similar to those reported earlier in Western and Indian literature,[6-10] with fever being the most common symptom in this series. Splenomegaly was the most common examination finding (90%). Hepatomegaly was noted in 40%. This was almost similar to the study by Somasundaram *et al*. (51%), but a little higher than that reported by Galani *et al*. (28%) and the other Western literature.[6,10-12] In this series, almost 30% of patients had history of infection, similar to the 30% incidence reported by Allsup and Cawley.[13]

Anemia was the most common laboratory finding (80%), which is similar to the other studies, followed by thrombocytopenia (60%) and leukopenia (50%). Pancytopenia was seen in 30% patients, a little lower compared to the study by Bhargava *et al*.[14] Lymphadenopathy was unusual and noted by CT scan imaging in 20% of patients, similar to the earlier Indian study by Galani *et al*.[10]

There is a need to diagnose HCL accurately because chemotherapy with purine analogues is associated with high CR rates and long relapse-free survival in HCL, but it is less effective in patients with other chronic B-cell leukemias or lymphomas.[15,16] Also IPT helps in distinguishing classic HCL from the HCL variant which is an aggressive form of disease and may not respond to standard therapies. Classic HCL shows CD5–, CD10–, CD11c+ (bright), CD20+ (bright), CD22+ (bright), CD25+ (bright), CD103+, CD123+ (bright), cyclin D1+, and Annexin A1+. In contrast, HCL variant is uniformly CD25– and Annexin A1 negative.[4] In the majority of cases in this study (6/10), diagnosis was based on IPT. All 6 cases showed expression of the characteristic markers of HCL namely CD11c, CD25 and CD103. CD10, a marker for lymphoid cells with germinal center origin, has been reported positive in HCL in a relatively higher percentage compared with other B cell neoplasms.[17,18]

The National Comprehensive Cancer Network (NCCN) guidelines says the indications for treatment in a case of HCL are systemic symptoms, splenic discomfort, recurrent infection, cytopenias (Hb <12 g/dL, absolute neutrophil count < 1000/mcL, and platelet count <100,000/mcL). Asymptomatic patients may be managed by close observation ("watch and wait" approach) until indication develops. When indicated, treatment should be with either of purine analogues. In general, cladribine should be avoided in patients with active life-threatening infections or recurrent (chronic) infections.[4] Patients in this study were managed as per the NCCN guidelines.

The overall response rate in this study was 88%, which is similar to those reported previously.[9,15,16,19] Some other studies have reported no responses in 11–13% of patients.[20-22]

Long-term studies in the literature reported at 5–10 years of follow-up with both pentostatin and cladribine show that the remissions are usually long-lived for most of the cases. Both drugs have contributed to the improved overall survival in HCL. In spite of this good achievement with monotherapy, the disease-free survival curves for either agent have not plateaued, and both agents have a similar relapse rate of approximately 30–40% in longitudinal studies. Long-term follow-up studies from the Royal Marsden Hospital on 233 patients, found that pentostatin and cladribine are essentially the same with respect to outcome. With a median of 16 years of follow-up from diagnosis in that study, pentostatin and cladribine are considered interchangeable and equal in efficacy.[23] The 20% rate of relapse reported in our study is similar to the Indian study by Somasundaram *et al*. but lower than those reported in other series (27–39%),[6,15,24,25] reasons for which are unknown. In this study, one patient died due to septicemia soon after treatment with cladribine, probably due to the associated immunosuppression from treatment.

Earlier studies have shown that severely anemic patients and those with severe thrombocytopenia have a worse outcome which was also seen in the current study.[10]

None of the patients on follow-up developed second malignancy, however, the incidence of second malignancies reported in literature is as high as 22% as noted by Goodman *et al*.[19] and 8% by Saven *et al*.[8] These studies reported a median time from diagnosis of the second cancer to cladribine therapy of 77 months (range, 1–440 months). The median follow-up in the present study was 61 months (range 2–96), and these patients need to be further followed up to know the exact incidence of second malignancy.

CONCLUSION

HCL is a rare lymphoproliferative disorder with potential curative treatment with excellent CR. Hence, there is a need for early and accurate diagnosis of HCL with the necessary laboratory and IPT bone marrow examination. Even though the disease is associated with second relapses, they usually

respond well to retreatment with purine analogs like cladribine and also have a favorable outcome.

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Conflicts of interest
There are no conflicts of interest.

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