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Original Article-1

Hairy Cell Leukemia : Experience at a Tertiary Cancer Centre in Northern India

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ABSTRACT

Background : The prognosis of Hairy cell leukemia (HCL) has improved markedly following treatment with cladribine (2-CdA), a nucleoside analogue. We reviewed data on patients with HCL treated in our department.

Methods – Between 1995 and 2004, 23 patients with hairy cell leukemia (HCL) were diagnosed Patients median age was 48.5 years (range, 32 to 66 years), there were 18 males and 5 females. The common presenting symptoms were: fatigue (82.6%), fever (34.7%), abdominal discomfort (21.7%), arthralgia/bone pains (13%) and bleeding (17.3%). 22 of 23 (95.6%) patients had enlarged spleen, and hepatomegaly (65%). Lymph node enlargement was present in 17% of patients. Investigations revealed-median Hb of 7.8g% (5.7 to 12.9 g%), thrombocytopenia (median 55000/cmm) and median WBC count of 3500/cmm (range, 600 to 20,200/cmm). Bicytopenia or pancytopenia was present in 87% and bone marrow fibrosis in 75% of cases. Immuno-phenotyping studies revealed expression of CD11C (60%), CD25 (60%), FMC7(47.8%), CD23(34.8%), CD103 in 39% of cases.

20 of 23 patients received treatment; two received treatment else where and one patient died of liver failure prior to treatment. 17 of 20 patients were treated with 2-CdA, 2 with interferon alfa (IFN-a) and one patient underwent splenectomy alone. Three patients received 2-CdA as second line therapy for treatment of relapse: this includes – one patient each, treated with IFN- a and splenectomy both and one patient received 2-cdA twice in view of relapse.

Results – Following treatment with 2CdA – 95% of patients responded; complete-84.2% and partial response in 10.5%. one (5.2%) patient died of toxicity. Two patients relapsed at a mean follow up of 25 months. The common side effects were febrile episodes (n=10) and grade I-II myelosuppression. One patient died of toxicity to 2-CdA. This patient was a known case of multidrug resistant disseminated tuberculosis. He had severe myelosuppression with fungal sepsis with multiorgan failure and BM Aspirate was positive for AFB. Other infections documented were Pulmonary tuberculosis in 2 and herpes zoster in one patient. The patient who underwent Splenectomy achieved remission but relapsed after 3 years and was salvaged with 2-CdA again. Median time for normalization of blood counts after 2-CdA was 28 days and median time to regress spleen was 41.5 days .

Conclusion – Present study confirms good outcome with 2-CdA (cladribine) therapy for patients of hairy cell leukemia.

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INTRODUCTION

Hairy cell leukemia (HCL), first described by Bouroncle et al [1] in 1958 is an indolent chronic B-cell lymphoproliferative disorder (CLPD) involving the bone marrow and spleen. It is an uncommon disease of middle aged adults and patients commonly present with pancytopenia, splenomegaly and history of repeated infections. Its defining features are mononeuclear cells with prominent cytoplasmic projections, which contain tartarate resistant acid phosphatase (TRAP) and show typical pattern of cellular infiltration in bone marrow and spleen. The morphologic findings on the bone marrow biopsy consists of a diffuse infiltration by lymphocytes that are spaced wider than expected – the 'fried-egg' appearance. Reticulin staining is increased reflecting the fibrosis, which accounts for the difficulty usually encountered when attempting to aspirate the bone marrow. Immunophenotypic analysis of the abnormal cells in HCL reveals CD11C, CD19, CD20, CD22 CD25, CD103 and kappa or lambda light chain positivity and the absence of CD5 and CD21 antigen expression [2-3].

Until 1984, splenectomy was the only treatment for HCL ; this was associated with normalization of blood counts in 50-70% of patients, with a median response duration of 5-20 months and five year overall survival of 70%.[3-4] Interferon alfa (IFN-a) was the first systemic agent to induce complete remission in this disease. IFN-a-2b demonstrated an overall response rate of 75% in untreated HCL patients with complete responses (CR) in 5% of patients.[5] In the past fifteen years, newer purine analogues i.e. 2-deoxycoformycin (DCF) and 2-CdA (Cladribine) have revolutionized the treatment of HCL, both agents have potent lymphocytotoxic activity and are capable of producing faster and superior CR rates (80-90%) than those observed with IFN-a.[6-7] These results have been confirmed in smaller studies reported from India. Abhayankar et al reported CR rate of 100% in 18 HCL patients treated with 2-CdA.[8] Jaynanth et al reported CR rate of 93.7% in 15 patients of HCL treated with cladribine.[9] We have recently analysed our experience with hairy cell leukemia . This report describes the results.

PATIENTS AND METHODS

Between Jan 1995 and Oct 2004, 23 consecutive patients with symptomatic HCL were seen at our institute. Patients characteristics are shown in table-I. All patients underwent detailed clinical examination. The diagnosis was based on clinical and hematological parameters mainly bone marrow aspiration, trephine biopsy and TRAP positivity. The immunophenotype of peripheral blood and bone marrow aspirate using monoclonal antibodies (mAbs) and flowcytometry was performed. The immunological diagnosis of hairy cells required high reactivity with monoclonal antibodies CD 103 and the co-expression of Pan B cell antigens CD19, CD20, CD22, CD11C, CD25 and FMC7 was examined in 20 cases.

TREATMENT

The cladribine (2-CdA) was given in 0.09mg/kg/day dose for seven days as continuous 24-hour intravenous infusion in normal saline through central line on an in-patient basis. All patients had normal hepatic and renal functions. Blood counts, differential counts and biochemistry profile was done daily or alternate day for first three weeks and later on once weekly till normalization of counts. Two patients received Interferon in the dose of 3-mU subcutaneous thrice a week for 18-24 months. One patient had underwent splenectomy Packed RBC and platelets concentrates were given for hemoglobin less than 8.5gm% or symptomatic anemia and platelets less than 20,000/cumm respectively. All patients receiving 2-CdA, were given prophylactic fluconazole and acyclovir for atleast 12 weeks. Patients also received PCP (penumocystitis carinii) prophylaxis using trimethoprim 15mg/kg twice a week for one year.

RESPONSE ASSESSMENT

Patients were evaluated for response after hematological recovery usually within 3-4 weeks

after therapy. Evaluation included - assessment of clinical symptoms and signs, complete blood counts and differential counts, bone marrow examination for morphology and TRAP staining. Patients were followed up every 2 months during first year, 3 monthly in second year then at 4 - 6 months interval in 3rd year and thereafter. Response criteria were defined according to NCI guidelines. Briefly, complete remission (CR) was defined as the regression of physical symptoms/ signs, ANC (absolute neutrophil count) $^{3}1.5\times109/L$, Hb =12.0 gm/L, Platelets $=100\times 10^{9}$ /L and the absence of hairy cells on peripheral blood smear. Morphologic absence of disease on bone marrow aspiration and biopsy specimen was required. Partial remission was defined as decrease by more than 50% of hairy cells on bone marrow biopsy and reduction by more than 50% of hepato-splenomegaly. No response if no change or increase in the number of hairy cells in the blood and bone marrow was observed. Toxicity was graded according to NCI's common toxicity criteria (NCI CTC Toxicity scale version 2.0).

RESULTS

Patients median age was 48.5 years (range 32-66 years). Eighteen patients were male and five were females (M: F ratio=78.2:21.8). The most common presenting symptoms were - fatigue and fever followed by abdominal discomfort, joint pain and bleeding. The detailed clinical and laboratory characteristics are summarized in Table I & II

The median hemoglobin was 7.8gm/dl (range 5.7-12.9/G %), median platelet count was 55,500/mm^3 (range 32,000-1, 15,000/mm^3). While the median TLC was 3500/mm^3 (range 600-20,200). All the patients had hairy cells in bone marrow and 75% had hairy cells in peripheral smear. Bone marrow was hypercellular in 66%, normocellular in 25% and hypocellular in 9% of patients. Bone marrow fibrosis was documented in 75% cases. The TRAP positivity was found in 82.6% (Total 19) and CD11C (60%) CD25 (60.0%), CDFMC-7 (47.8%), CD23 (34.7%) CD103 (39.1%) positivity were detected.

20 patients received treatment; one patient died prior to treatment due to hepatic encephalopathy possibly of viral origin, however autopsy was not done, and two patients received treatment elsewhere. Among 20 patients, 17 received 2-CDA as primary therapy, 2 received IFN- a and one underwent splenectomy. Of the 2 patients treated with IFN- a , one attained CR but relapsed after 3.5 years and received 2-CdA at the time of relapse while the other patient attained partial remission and continues to have stable disease. One patient who underwent splenectomy relapsed later and received 2-CdA for salvage. Thus, a total of 19 patients received 2-CdA (17 as primary therapy and 2 as salvage). Of these 16 (84.2%) achieved CR and two patients had PR (10.5%), giving an overall response rate of 94.7%. Two patients treated with 2-CdA relapsed within 3 years who on re-treatment with 2-CdA achieved CR. The treatment response is summarized in table III.

Toxicity : The drug was well tolerated. The immediate side effects were mild, most commonly seen were - acute febrile episodes (culture negative) seen in 10 patients (52.6%). In six patients (6/10) fever lasted 24-48 hours and probably was not infection related. Remaining four patients (4/10) with fever and neutropenia received empirical IV antibiotics and improved. One patient died due to severe prolonged neutropenia with fungal pneumonia and multi-organ failure. He was a case of pre-existing disseminated multi drug resistant (MDR) tuberculosis with bone marrow positive for AFB. Other common side effects were neutropenia alone 5(26.3%), neutropenia and thrombocytopenia - 6(31.5%) and fatigue in 4 (23%). During the long term follow up, late opportunistic infections were seen in 3 patients two developed pulmonary TB and another patient had herpes zoster. None of the patient died of drug related toxicity.

DISCUSSION

Hairy cell leukemia is a rare chronic lymphoproliferative disorder, which accounts for 2% of all adult leukemias in the United

States.[10] The incidence of HCL in India is unknown. At our institute we could find only 23 cases over 10 years, constituting 0.27% of all cases of haematological malignancies seen during this period. Similarly, in another major cancer centre, only 35 cases of HCL were diagnosed over 10 years period suggesting a low incidence.[8] Jayanth et al from South India have recently reported another case series of 15 patients over a period of 6 years.[9] Clinical and laboratory characteristics of our patients were similar to those reported from other centers in India[8-9] and in a large multicentric study from USA.[10]

Table I: Patients Characteristics

Characteristics	Present study	Abhayankar et al (8)	Jayanth et al (9)	Cheson et al (10)
Total no. of patients	23	18	15	928
Age (years)				
Range	32-66	37-61	34-68	25-94
Median	48.5	44	56.5	56
Sex				
Male	18 (78.2%)	12(66.6%)	13(86.6%)	80%
Female	5 (21.8%)	6(33.4%)	2(13.4%)	20%
Clinical Feature				
Fatigue	19(82.6%)	11(61.1%)	11(73.3%)	----
Fever	8(34.7%)	5(27.7%)	7(46.%)	----
Abdominal discomfort	5(21.7%)	11(61.1%)	94%	47%
Arthralgia/bone pain	3(13%)	-----	-----	----
Bleeding	4(17.3%)	-----	-----	----
Splenomegaly	22(95.6%)	11(61.1%)	94%	47%
Hepatomegaly	15(65.2%)	7(38.8%)	6(37.5%)	10%
Lymphadenopathy	4(17.3%)	2(11.1%)	4(25%)	9%
Previous treatment				
Splenectomy	1(4.3%)	1(5.5%)	-----	27%
Interferon a	2(8.6%)	4(22.2%)	-----	----
DCF	-----	-----	-----	8%
Radiothrapy	-----	-----	-----	1%

DCF - doxycorformycin

Table II : Laboratory Characteristics

Characteristics	Present study	Abhayankar et al (8)	Jaynath et al (9)	Cheson et al (10)
Hemoglobin (gm%)			<10gm%=87.5%	
Median	7.8	8.2		11.5
Range	5.7-12.9	5-11.2		3.9-17.4
Platelet (cmm)			<100,000/cmm=93.75%	
Median	55,500	1,54,000		87,000
Range	32,000-1,15,000	44,000-3,50,000		6000-7,07,000
TLC (cmm)			ANC<500/cmm=62.5%	
Median	3500	9300		3300
Range	600-20,200	2000-20,000		300-31,200
Cytopenias				
Pancytopenia	12(52.17%)	NA	NA	NA
Bicytopenia	8 (35%)			
Monocytopenia	4 (17%)			
Hairy cells in bone marrow	23(100%)	32%	NA	NA
TRAP (positive)	19(82.6%)	100%	NA	NA
Flow cytometry				
CD11c	14(60%)	100%		
CD25	14(60%)	100%	NA	NA
FMC7	11(47.8%)	100%		
CD23	8(34.8%)	44.4%		
CD103	9(39.1%)			
Bone Marrow cellularity				
Normal	25%	NA	NA	NA
Increased	66%			
Fibrosis	75%			

NA-not available

Table III : Treatment Results

Response	Present study	Abhayankar et al (8)	Jaynath et al (9)	Cheson et al (10)
No	19*	18	15	861
CR	16(84.2%)	18(100%)	14(93.7%)	50%
PR	2(10.5%)	---	1(16.66%)	37%
CR+PR	18(94.7%)	18(100%)	15(100%)	87%
Relapse	2(10.5%) at 25 months	3(16.6%) at 16 months	1(6.66%) at 9.5 months	134(18%) at 52 months
Mortality	1(5.2%)		1(6.66%)	62(7%)

*17 patients received 2-CdA as primary treatment (CR-14, PR-2 and Died-1) and 2 patients were treated with 2-CdA following relapse (CR-2)}

During the past few years the treatment of HCL has changed remarkably . Earlier in 1970's splenectomy and in 1980's interferon-a were the main treatments available. Deoxy corformycin (pentostatin) in early 1990s and more recently cladribine (2-CdA) has dramatically improved the clinical course and outcome for patients with hairy cell Leukemia. Both these drugs result in high complete remission (CR) rates. Remission rates (complete & partial) of 94% including CR rate of 84% in our study is similar to those reported from two other centres in India (100% and 93%)[8-9] and abroad.[10-13] In a larger group of 144 patients reported by Piro et al, CR was obtained in 123 (85%) and PR in 17(12%) giving an overall response rate of 97%.[7] Cheson et al from NCI in a large series of 979 patients reported an overall remission rate of 87% (CR 50%, PR 37%) at a median follow up of 52 month.[10] In this NCI study CR rate (50%) was lower; possibly due to inclusion of large no of patients receiving 2-CdA as salvage therapy.

Although responses with 2-CdA in HCL are durable in most patients,[11-13] relapses can occur in up to 20% after achievement of CR. In our study, 2 patients (10.5%) relapsed at a median follow up of 25 months. Both these patients were asymptomatic and relapse was diagnosed on routine peripheral smear and bone marrow examination. In a similar study from Mumbai, India, 3 of 18 patients (16%) relapsed at a median follow up of 16 months.[8] While in another study from South India, one patient (1/14) relapsed at a median follow up of 9.5 months.[9] Relapse in most asymptomatic cases is diagnosed mainly by morphological reappearance of the hairy cells. Relapse rates are higher if more sensitive molecular means of minimal residual disease assessment are used . Asymptomatic relapse is not an indication for treatment. However, salvage treatment must be considered for patients who are symptomatic or having progressive cytopenia. In the present study, both patients at relapse were treated with 2-CdA and achieved CR. Fludarabine or rituximab has been used successfully for the treatment of patients refractory or resistant to 2CdA.[14-15]

The toxicity to 2-CdA in present study was acceptable. Culture negative febrile episodes were the most common side effect noted in 10 (52.6%) patients . Fever following 2-CdA therapy has been observed by others and is presumably due to release of cytokines and opportunistic infections.[7,10] In our study, among 6 patients

(6/10) patients fever subsided in 24-48 hours while remaining four patients received empirical antibiotics in view of persistent fever. The other toxicity was grade III-IV myelosuppression with neutropenia in 5 (26.3%) and both neutropenia and thrombocytopenia in another 6 (31.5%) cases. Myelosuppression mainly, neutropenia and/or thrombocytopenia has been reported in up to 70% of patients with febrile episodes in 30-40% patients.[8-9,16] G-CSF can reduce the period of neutropenia in such patients who are severely neutropenic and have evidence of sepsis.[16] It is important to note here that the patients of hairy cell leukemia are prone for opportunistic infections and the risk is further increased with administration of cladribine as this drug is associated with severe and prolonged lymphocytopenia with marked reduction of CD4+cells. Reduction in cell mediated immunity makes these patients prone for opportunistic infections (tubercular,viral and fungal).[17] In our study two patients developed pulmonary tuberculosis and one had herpes infection. One patient in our study died due to severe prolonged neutropenia with fungal pneumonia and multiorgan failure that had preexisting disseminated MDR tuberculosis and bone marrow was also positive for AFB. Therefore, it is important that all patients on cladribine therapy are monitored closely for these complications and broad spectrum antibiotics must be started on the earliest suspicion of infection. Other side effects noted in our study were fatigue, bodyache and nausea.

One patient during the follow up developed idiopathic thrombocytopenic purpura (ITP) which is a known complication of 2-CdA therapy. Another potential complication of prolonged immunosuppression is risk of secondary malignancy after many years in patients who are already prone because of the disease- induced immunosuppression [10-13]. In our study none showed malignancy although longer follow up may be needed to assess the oncogenic role of 2-CdA.

In conclusion, our study confirms the efficacy and relative safety of 2-CdA in inducing complete and long lasting remission in HCL patients.

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