Clinical and Biological Features of Chronic Lymphocytic Leukemia A Single Tertiary Centre Experience from India.

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Abstract:
Chronic lymphocytic leukemia (CLL) is the commonest leukemia in the western population. There is limited data on CLL from the Indian subcontinent. We undertook a descriptive retrospective study of all cases of CLL presenting at our centre over the last 5 years. 125 cases of CLL were diagnosed in this period. The median age was 60 years (range 34-85). 42 (33.6) patients were 55 years (young CLL). The male to female ratio was 3.1. At presentation, 52 were incidentally detected, 29 had lymphadenopathy, 5 had transfusion dependent anaemia and 1.6 had fever. Hepatomegaly, splenomegaly, anaemia and thrombocytopenia were seen in 47.2, 40.8, 46.4 and 20.8 respectively. The median WBC and absolute lymphocyte count at diagnosis was 40 x 10^9/L (range 6.8 to 528) and 33 x 10^9/L (range 4.2 to 512), respectively. Majority of patients presented in Rai stage stage III (25.6) and IV (27.2). CD 38 positivity on flowcytometry was seen in 36.8 of cases, with no difference in the clinical and laboratory parameters between CD 38 positive and negative patients at presentation. 69 patients received treatment. Of these, 17 achieved a partial remission and 7 achieved complete remission. While the overall clinical presentation was similar to data reported internationally in our series we found a more advanced stage of disease at presentation, a lower median age at diagnosis, a larger young CLL population and a higher incidence of splenomegaly in the young CLL. Chlorambucil and cyclophosphamide continues to be used widely as a therapeutic option.

Keyword: CLL, Demographics, India.

Introduction:
Chronic lymphocytic leukemia (CLL) is a clonal lympho-proliferative disorder characterized by the gradual accumulation of the malignant B-lymphocytes in the hematopoietic tissues, specifically blood, bone marrow, spleen and the lymph nodes(1). According to the world health organization 2008, chronic lymphocytic leukemia (CLL) is considered to be the most common leukemia in western population(2).
In a recent survey conducted by the American cancer society, based on the incidence data accumulated from the National Cancer Institute, the Centers for Disease Control and Prevention, the North American Association of Central Cancer Registries and mortality data from the National Center for Health Statistics, the incidence of CLL was found to be approximately 34% among all leukemia(3). Of these, the incidence of the CLL in the younger age group i.e. less than 55 years of age reported worldwide, has been found to be less than 15%(4–9). In comparison, the available limited information about the disease from the Indian subcontinent shows a clear preponderance of the disease in the younger patients (< 55 years)(7). We undertook this descriptive retrospective study of 125 patients with CLL to evaluate this further and also to review their baseline clinico hematological profile.

Patients and methods:
All patients with a diagnosis of CLL presenting to the Department of Haematology of our institute between the years 2007 to 2012 were included in this retrospective analysis. The case records of all these patients were retrieved and analyzed retrospectively. The diagnosis of CLL was based on the revised National cancer institute (NCI) guidelines (10), which specifically included demonstrating a peripheral blood lymphocytosis of more than 5 x 10^9/Lt as well as documenting a clonal B cell population based on B-cell surface antigens CD19, CD20, and CD23 positivity along with a co expression of the T-cell antigen CD5 on flow cytometry(10). The presence of CD38 positivity was also recorded. The case records were reviewed for their presenting complaints and their co morbidities at the diagnosis along with the past treatment received, if any. Their physical examination details were reviewed for the presence of any lymphadenopathy and/or any organomegaly.

Their baseline laboratory workup was studied for the presence of any lymphocytosis, anemia or any thrombocytopenia. The baseline diagnosis was established using peripheral blood immunophenotyping using flow cytometry. Their records were also studied to look for any evidence of autoimmune hemolytic anaemia or thrombocytopenia. Rai staging was used to establish the severity of the disease at the diagnosis (11). Patients who received therapy were classified into three groups depending on type of the treatment received. These groups were (i) Chrombucil based (ii) Cyclophosphamide based and (iii) Fludarabine based. The duration of treatment and its response were recorded and the status of the disease at the last follow up was analyzed based on the NCI working group guidelines(10).

Statistical Methods:
Differences in means were tested using a t-test or Mann-Whitney-U test as appropriate. Differences in proportions were assessed using the chi-square statistic or Fisher exact test. For all tests, a 2-sided P-value of 0.05 or less was considered statistically significant. Statistical analysis was performed using SPSS 16.0 software (SPSS, Chicago, IL).

Results:
One hundred and twenty five cases were diagnosed to have CLL in this period. The overall median age was 60 years (range; 34-85). Forty-two (33.6%) patients were < 55 years (young CLL), while 4 (3.2%) patients were < 40 years. The overall male to female ratio was 3:1. Sixty-four (51.2%) cases were incidentally detected. The presenting symptom in the remaining was
either lymph node enlargements or hepatosplenomegaly in 37 (29.6%), followed by symptoms of anemia requiring transfusions in 7 (5.6%) and complains of fever in 2 (1.6%) cases. At the time of diagnosis, the examination revealed lymphadenopathy in 87 (69.6%) patients. Out of these, 4 (3.2%) patients had bulk disease. Hepatomegaly was seen in 60 (48%) patients while splenomegaly was seen in 51 (40.8%) patients. Fifty-nine (47.2%) patients had anaemia with autoimmune haemolytic anaemia being seen in 4 (3.2%) patients. Thrombocytopenia (< 1 x 10^9 / Lt) was seen in 26 (20.8%) patients. The median white cell count and the absolute lymphocyte count were 40 x 10^9 / Lt and 31 x 10^9 / Lt, respectively.

Majority of patients presented in Rai stage IV [34 cases (27.2%) followed by stage III [32 cases (25.6%)], stage II [26 cases (20.8%)], stage I [22 cases (17.6%)], and lastly stage 0 [11 cases, (8.8%)]. Among the younger patients (<55 years), the median age at presentation was 48.5 years, while the sex ratio was similar to the overall population. The comparison of clinical and the biological parameters between the young and elderly are summarized in table 1. In our series, we also found CD 38 positivity in 46 cases (36.8%) of CLL, using 20 % as a positive value on flow cytometry. This was almost similar to the data reported previously(12,13). The distribution of the clinical and laboratory parameters according to the CD38 status is as shown in the table 2. Sixty-nine (55.2%) patients received treatment. These cases were classified into 3 groups depending on the type of the treatment received. Out of these 69 cases, follow up was available in 38 patients (Range 3 - 45 months). 17 patients (44.73 %) had partial remission, while 7 patients (18.42%) achieved complete remission. The response achieved according to the treatment arm is summarized in table 3.

Discussion:
This is a single centre, descriptive retrospective epidemiological study, done with the prime objective of characterizing the clinical and the biological features of the young as well as elderly patients with chronic lymphocytic leukemia. Chronic lymphocytic leukemia (CLL) has traditionally been found to occur in the later decades of life (1,14,15). Compared to the older adults, the incidence of the disease in the young has been found to be less than 15 % in the literature reported worldwide (5,6,8,14,15). There are very few studies describing this disease from an Indian perspective (7,16). In our study, we found a much higher incidence (33.6%) of the disease in the young (<55 years) as compared to the western literature. A similar higher incidence of CLL in the young has been previously reported from this region(7). The lower incidence of the disease in the elderly in our study could be explained by their lower life expectancy and under diagnosis compared to the western world, but the higher incidence in the young needs further evaluation of potential genetic predisposition to this disease. In our study, we also found a striking male preponderance of disease in the young and the elderly, as reported internationally(5,6,8). Most patients with CLL have been incidentally detected in an asymptomatic stage, due to the blood counts done for other medical or surgical conditions(2,9,17). In our series we found a significantly large cohort of patients presenting with symptoms related to the disease. Three patients presented while on treatment for second opinion. The presenting features were similar to that reported
The spectrum of the immune complications in chronic lymphocytic leukemia varies from the most commonly seen autoimmune hemolytic anemia followed by immune thrombocytopenia, pure red blood cell aplasia and even rarely autoimmune granulocytopenia (18–20). In our series, the only immune complication was of autoimmune hemolytic anemia, with an incidence similar to the reported literature. We found lymphadenopathy as the most common sign at presentation in our population. There was a significantly higher incidence of splenomegaly in our younger patients as compared to the elderly. The incidences of anemia, thrombocytopenia, the total median count and the absolute lymphocyte count at presentation, between the young and elderly patients with CLL were similar to the data reported in literature (5,6). CD38 has been identified as an adverse prognostic marker, with patients showing aggressive disease and poor overall survival (12,13,21–24). The incidence of CD38 positivity in our study was similar to that reported internationally(12,13). However, we did not find any statistically significant difference between the incidences of the CD38 positivity in the young versus the elderly. Both groups (CD38 positive and negative patients) were found to have a similar clinical and laboratory profile at presentation. Among the treatment groups, chlorambucil continues to be a wildly used therapeutic option for CLL worldwide(25–27). Cyclophosphamide too has been extensively used for the management of CLL, mainly in combination with either fludarabine alone or in combination with rituximab. But these combinations have significant toxicities in the form of neutropenia. We noted that chlorambucil or cyclophosphamide alone or in combination with steroids continued to be used widely and was most probably related to financial constraints which restricted the use of purine analogues or rituximab. We did not find any significant difference in the overall response rates between the patients who received chlorambucil versus cyclophosphamide-based chemotherapy. Impact of fludarabine-based therapy could not be interpreted due to low numbers.

REFERENCES:


Table 1: Comparison of baseline clinical and laboratory parameters between the young (<55 years) and the elderly CLL.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young (&lt; 55 years) n = 42</th>
<th>Elderly (&gt; 55 years) n = 83</th>
<th>Total n = 125</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) / Median(range)</td>
<td>N (%) / Median(range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>21 (50%) / 38 (48%)</td>
<td>38 (49%) / 53 (64%)</td>
<td>59</td>
<td>0.700</td>
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<td>Lymphadenopathy</td>
<td>34 (81%) / 53 (64%)</td>
<td>53 (64%) / 87 (108)</td>
<td>87</td>
<td>0.084</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>22 (52%) / 36 (49%)</td>
<td>36 (48%) / 60 (94)</td>
<td>60</td>
<td>0.571</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>26 (62%) / 25 (30%)</td>
<td>25 (30%) / 51 (68)</td>
<td>51</td>
<td>0.001</td>
</tr>
<tr>
<td>RAI stage III/IV</td>
<td>23 (54.6%) / 43 (51.0%)</td>
<td>43 (51.0%) / 66 (53)</td>
<td>66</td>
<td>0.850</td>
</tr>
<tr>
<td>CD 38 Positivity</td>
<td>18 (42.8%) / 30 (36%)</td>
<td>30 (36%) / 48 (62)</td>
<td>48</td>
<td>0.550</td>
</tr>
<tr>
<td>Median total count at presentation (x 10^9/Lt)</td>
<td>49.8 (6-8-305) / 33.88 (7-528)</td>
<td>40.1 (6-8-528) / 31.4 (4-4-512.6)</td>
<td>0.260</td>
<td></td>
</tr>
<tr>
<td>Median absolute lymphocyte count</td>
<td>42.6 (4-4-296.6) / 27.2(4.5-512.6)</td>
<td>31.4 (4-4-512.6) / 27.2(4.5-512.6)</td>
<td>0.270</td>
<td></td>
</tr>
<tr>
<td>Median Platelet count (x 10^9/Lt)</td>
<td>1.5 (0.03-6) / 1.38(0.06-9)</td>
<td>1.42 (0.03-9) / 1.38(0.06-9)</td>
<td>0.910</td>
<td></td>
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</table>

Table 2: Comparison of clinical and laboratory parameters between CD38 positive and negative patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CD38 (+) n = 48</th>
<th>CD38 (-) n = 77</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age in Years</td>
<td>58.4</td>
<td>60.3</td>
<td>0.336</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>37 (77.08%)</td>
<td>50 (64.93%)</td>
<td>0.304</td>
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<tr>
<td>Bulky Nodes</td>
<td>2 (4.2%)</td>
<td>2 (2.6%)</td>
<td>0.877</td>
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<tr>
<td>Hepatomegaly</td>
<td>25 (52.1%)</td>
<td>35 (45.5%)</td>
<td>0.581</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>22 (45.8%)</td>
<td>29 (37.7%)</td>
<td>0.465</td>
</tr>
<tr>
<td>Anaemia &lt; 11 mg/dl</td>
<td>22 (45.8%)</td>
<td>59 (48.1%)</td>
<td>0.278</td>
</tr>
<tr>
<td>Rai Stage III &amp; IV</td>
<td>24 (50%)</td>
<td>42 (54.5%)</td>
<td>0.713</td>
</tr>
<tr>
<td>Median total count at presentation (x 10^9/Lt)</td>
<td>33.6 (6-8-276.5) / 44.6(59.7-528)</td>
<td>44.6(59.7-528) / 33.6 (6-8-276.5)</td>
<td>0.081</td>
</tr>
<tr>
<td>Median absolute lymphocyte count</td>
<td>80.5 (4-4-251.6) / 84 (36.4-512.6)</td>
<td>84 (36.4-512.6) / 80.5 (4-4-251.6)</td>
<td>0.139</td>
</tr>
<tr>
<td>Median Platelet count (x 10^9/Lt)</td>
<td>1.35 (0.26-4.37) / 1.47 (0.03-9)</td>
<td>1.47 (0.03-9) / 1.35 (0.26-4.37)</td>
<td>0.448</td>
</tr>
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</table>

Cyclophosphamide based 17 11 2 6
Fludarabine based 6 2 2
Total 23 13 7 17

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