Disease characteristics and clinical outcomes in patients aged less than 40 with chronic lymphocytic leukemia

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1. Introduction

Chronic lymphocytic leukemia (CLL) is a disease of older people, with a median age at diagnosis of 71 years [1]. The definition of what constitutes “young” patients with CLL has not been well defined. Two prominent publications [2,3] within the last decade arbitrarily used age 55 as the cut-off between “young” and the remainder of the patients. Both Mauro [2] and Parikh [3] used age 55 as the cut-off, but the median age was 49 in the former and 50 in the latter. Little information was provided regarding patients who were less than age 40, a group we arbitrarily define as “very young” [4] as they represented outliers falling outside of 2.5 standard deviations of the mean age of CLL patients seen at our center. Importantly, while the study by Parikh utilized recognized prognostic features such as IGHV mutation status and FISH to more completely categorize the risk features of both age groups, chemotherapy regimens given during that time period (1995–2012) did not uniformly include rituximab in combination with a purine analog which was, until the recent advent of specific pathway targeted therapy, considered the standard therapeutic approach in all fit young patients.

In order to better understand the disease features and outcomes of very young patients, we retrospectively reviewed all patients seen at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2005 and December 31, 2015 with CLL diagnosed before age ≤ 40. We examined disease characteristics, incidence of Richter’s transformation, outcomes following rituximab-containing therapy, and survival. We compared the results to matched patients aged over 40 seen at MSKCC. SEER was used to additionally compare survival for very young patients at MSKCC to matched older patient controls. SEER used was to additionally compare survival for very young patients using a population-based registry.

2. Patients and methods

2.1. Patients

This was a single center retrospective analysis of CLL patients’ age ≤ 40 at diagnosis evaluated and treated at MSKCC between January 1, 2005 and December 31, 2015. The Memorial Hospital Investigational Review Board approved this study. We compared the outcomes of all very young patients at MSKCC to matched older patient controls. Patients were matched by date of diagnosis (± 2 years) and the time from diagnosis (± 2 years) to the first MSKCC visit. Two controls were identified for every very young patient. We also used the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database to compare survival based on the predefined age categories. Detection of monoclonal IGHV rearrangement was performed by PCR and sequence analysis with a cutoff of > 2% in the variable region used to determine mutated status (Cancer Genetics Lab, Rutherford New Jersey). Expression of CD38 > 30% and ZAP70 > 20% (when
available) by flow cytometry defined positive expression. Cytogenetics
were analyzed by G-band karyotyping or FISH and institutional lab-

oratory normal ranges were applied to Beta-2-microglobulin (B2M)
(< 2.7 mg/L) and LDH (< 200 IU/L) measurement. B2M was not cor-

drected for glomerular filtration rate. Complex karyotype was defined
as three of more structural abnormalities [5]. All prognostic variables
were assessed at the time of diagnosis. Secondary malignancies
were defined as any neoplasm diagnosed following CLL diagnosis and
excluded non-melanoma skin cancer. Response criteria were defined
clinically within the realms of retrospective analysis. Definitions in-
cluded: Hematologic complete response (CR): normalization of ANC
and clinical resolution of adenopathy or organomegaly; partial response
(PR): > 50% reduction in ALC without increase in adenopathy; stable
disease (SD): < 50% reduction in ALC and PD: increase in ALC or in-
crease in adenopathy. Patients with small lymphocytic lymphoma (SLL)
were included while those with monoclonal B-cell lymphocytosis were
excluded.

2.2. Statistical analysis

CLL related deaths included mortality due to infection, Richter’s
transformation or progressive disease, while death due to other ma-
signancies was classed as CLL unrelated. All cases of Richter’s trans-
formation had histology reviewed by MSKCC pathologists.

Descriptive and summarize statistics were used to compare patient
and disease characteristics across the young and old cohorts.
Conditional logistic regression assessed for differences across the two
groups. In a cohort of patients seen at MSKCC within three months of
diagnosis, Kaplan-Meier methods were used to estimate overall sur-
vival, and cumulative incidence functions were used to estimate the
time-to-first and the time-to-second treatment. Cox proportional
hazards regression with a frailty term assessed the association between
selected risk factors and overall survival. A cause-specific Cox model
evaluated the association between prognostic risk factors and the time-
to-first treatment. The SEER database was used to compare the ob-
served all-cause survival and relative survival of patients < 40 years
with those > 40 diagnosed between 2005 and 2013. Statistical analysis
was performed using the R statistical package and SEER data was
analyzed using SEER*Stat software.

3. Results

3.1. Patient characteristics

A total of 3455 patients with CLL were seen at our center during the
time period of this study. The median age of the group was 56 years
(range 21–94). Seventy-one patients aged ≤ 40 years at diagnosis were
identified (2%). A total of 142 patients aged > 40 (median 61, range
41–86) who were diagnosed with CLL within ≥ 2 years of each case in
the very young age group were identified as controls. The percentage of
females in each group was 45% and 42%, respectively. Table 1 com-

tares the patient characteristics between the two groups. Very young
patients had more B-symptoms at presentation, lower B2M and a trend
to lower incidence of del(17p)/complex karyotype.

A family history of hematologic malignancy was noted in 20% of the
71 very young patients and in 18% of the older patients (p = 0.340).
Both groups had a 9% incidence of having family members with non-
Hodgkin lymphoma (other than CLL) while the incidence of CLL in
family members was also similar in both groups (4% v 3%).

3.2. Treatment programs according to age groups

Forty eight percent of the very young patients required treatment
during the time period of the study (Table 2), as did 48% of the older
patients (34 of 71 vs 68 of 142, respectively). The median follow-up
from date of diagnosis was similar in each group, 54 and 48 months,

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>≤ 40 years</th>
<th>&gt; 40 years</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>CBC</td>
<td></td>
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<tr>
<td>ALC (x10^9/L)</td>
<td>61</td>
<td>113</td>
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<tr>
<td>ANC (x10^9/L)</td>
<td>51</td>
<td>98</td>
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<td>Platelets (x10^9/L)</td>
<td>224</td>
<td>200</td>
<td>0.087</td>
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<tr>
<td>Hemoglobin (g/ dl)</td>
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<td>13.5</td>
<td>0.135</td>
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<td>Kappa expressing, N (%)</td>
<td>65</td>
<td>114</td>
<td>0.238</td>
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<tr>
<td>IgM, medium (g/dL)</td>
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<td>69</td>
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<td>Narrow histology at diagnosis</td>
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<td>55</td>
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<tr>
<td>Diffuse</td>
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<td>106</td>
<td>0.326</td>
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<tr>
<td>Nodular</td>
<td>12</td>
<td>10(18%)</td>
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<tr>
<td>Intestinal</td>
<td>5</td>
<td>10</td>
<td></td>
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<td>Clinical prognostic markers at diagnosis</td>
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<td>B2M, median (mg/L)</td>
<td>32</td>
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<td>LDH, median (U/L)</td>
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<td>LDT, median (months)</td>
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<td>45</td>
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<td>CD38+</td>
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<td>104</td>
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<td>del(13q)</td>
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<td>25</td>
<td>NS</td>
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<td>del(11q)</td>
<td>18</td>
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<td>Other</td>
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<td>Number of patients with autoimmune cytopenia</td>
<td>71</td>
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<td>Pure red cell aplasia</td>
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<td>Richter’s transformation</td>
<td>6</td>
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<td>0.211</td>
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</table>

SLL: Small lymphocytic lymphoma, CBC: Complete blood count, ALC: absolute lympho-
cyte count, ANC: absolute neutrophil count, B2M: beta-2-microglobulin, LDH: Lactate
dehydrogenase, LDT: lymphocyte doubling time.

This calculation excludes patients who were diagnosed with Richter’s transformation
within 3 months of CLL diagnosis.

Incidence of autoimmune manifestations and Richter’s transformation were cata-
louged during the entire patient follow-up period.
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