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Research paper

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

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ABSTRACT

Outcomes in very young CLL patients (age ≤40) are not well characterized. We compared 71 consecutive patients aged ≤40 with 142 "older" matched patients > 40 from our institution and used SEER database as an independent comparison group. Patients in the two age groups were diagnosed at similar Rai stage. At diagnosis, very young patients had a similar rate of adverse cytogenetics, IGHV mutation and ZAP70 expression and had lower beta-2-microglobulin and a lower incidence of second malignancies. There was no difference between the groups with respect to incidence of autoimmune manifestations, family history of lymphoma, time to initiation of CLL therapy, response to therapy, or Richter's transformation. Variables including un-mutated IGHV and elevated LDH were associated with shorter times to treatment initiation in both groups. A trend to longer 5-year survival for very young patients in our institution (93% v 82%, p = 0.082) was validated by SEER data.

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 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

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available) by flow cytometry defined positive expression. Cytogenetics were analyzed by G-band karyotyping or FISH and institutional laboratory normal ranges were applied to Beta-2-microglobulin (B2M) (< 2.7 mg/L) and LDH (< 200 IU/L) measurement. B2M was not corrected 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 included: Hematologic complete response (hCR): normalization of ALC 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 increase 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 malignancies was classed as CLL unrelated. All cases of Richter's transformation 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 survival, 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 observed 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 compares 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 1
Patient Characteristics at CLL diagnosis: Very Young Patients versus Older Patients.

	≤40 years		> 40 years		P-value
	N		N		
Total		71		142	
Median age (range)		38 (21–40)		61 (41–86)	
Female N (%)		32 (45.1%)		60 (42.3%)	0.706
SLL (% of all cases)		12 (16.9%)		26 (18.4%)	0.803
RAI Stage (N)	68		131		0.635
0		30 (44.1%)		67 (51.2%)	
1		29 (42.6%)		51 (38.9%)	
2		3 (4.4%)		4 (3.1%)	
≥3		6 (8.5%)		9 (6.3%)	
B-symptoms	69	6 (8.7%)	133	2 (1.5%)	0.036
Mass > 2 cm at presentation	70	39 (55.7%)	133	64 (48.1%)	0.304
Laboratory features at diagnosis					
CBC					
ALC ($x10^9$/L)[a]	60	11 (1.7–138.2)	113	8.6 (0.2–117.0)	0.650
ANC ($x10^9$/L)	51	4.6 (1.0–23.6)	98	3.9 (1.1–13.6)	0.073
Platelets ($x10^9$/L)	59	224 (97–470)	115	200 (50–428)	0.087
Hemoglobin (g/dL)	59	13.8 (4.9–16.9)	114	13.5 (6.9–17.5)	0.135
Kappa expressing, N (%)	65	43 (66%)	106	60 (57%)	0.238
IgG, median (g/dL)	39	863 (217–1348)	69	875 (295–2597)	0.801
Marrow histology at diagnosis	38		55		0.409
Diffuse		20 (53%)		34 (62%)	
Nodular		12 (32%)		10(18%)	
Interstitial		5 (13%)		10 (18%)	
Clinical prognostic markers at diagnosis					
B2 M, median (mg/L)[b]	32	1.7 (1.1–5.5)	56	2.4 (1.4–9.3)	0.034
LDH, median (U/L) [c]	48	169 (125–1327)	85	184 (104–734)	0.194
LDT, median (months)	29	20 (1–216)	45	20 (1–96)	0.389
CD38 +	64	39%	104	41%	0.871
IGHV mutated	34	52.9%	59	45.8%	0.158
Diagnostic cytogenetics	60		91		
Normal		27 (45%)		32 (35%)	NS
del(13q)		14 (23.3%)		25 (27.5%)	NS
del(11q)		8 (13.3%)		12 (13.3%)	NS
del(17p)		1 (1.7%)		5 (5.5%)	NS
del(17p) or Complex karyotype		1 (1.7%)		10 (10.9%)	0.070
Other		10 (16.7%)		12 (13.2%)	NS
Number of patients with autoimmune cytopenia[d]	71	7 (9.9%)	142	17 (12.0%)	0.819
Hemolytic anemia		5 (7%)		12 (8.5%)	0.660
Immune Autoimmune thrombocytopenia		4 (5.6%)		6 (4.3%)	0.656
Pure red cell aplasia		2 (2.9%)		2 (1.4%)	0.488
Richter's transformation[d]		6 (8%)		6 (4%)	0.211

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

[a] This includes patients presenting with SLL and CLL hence the ALC range includes patients with normal ALC that were diagnosed with SLL. After excluding patients with SLL the ALC for ≤40 (median = 13.7 range 5.4–138) and > 40 (median = 10.7 range 5.3–117) were similar (p = 0.186).

[b] B2M was elevated (> 2.7 mg/L) in 6/32 (18.8%) patients age ≤40 and in 23/56 (41.1%) patients > 40 (p = 0.032).

[c] This calculation excludes patients who were diagnosed with Richter's transformation within 3 months of CLL diagnosis.

[d] Incidence of autoimmune manifestations and Richter's transformation were cataloged during the entire patient follow-up period.