Chronic lymphocytic leukemia in young (≤ 55 years) patients: a comprehensive analysis of prognostic factors and outcomes

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SUPPLEMENTARY MATERIAL

METHODS

Patients

Baseline clinical factors abstracted from the clinical records on all patients include age, sex, Rai stage, Eastern Co-operative Oncology Group (ECOG) performance status, complete blood count (CBC), absolute lymphocyte count (ALC), beta-2 microglobulin (β2M), *IGHV* status, cytogenetic abnormalities detected by interphase *FISH*, and expression of ZAP-70, CD49d and CD38. Since the novel prognostic markers (including *IGHV* gene mutation status, *FISH* analysis, ZAP-70 and CD38 expression) were not routinely obtained during the entire study period, results from these assays were not available for all patients.

Statistical Analysis

Patients receiving early treatment (i.e., not meeting the 1996 CLL working group consensus criteria for treatment) as part of experimental protocols were censored as untreated on the date experimental therapy was initiated. The Kaplan-Meier method was used to estimate the probability of TFT and OS; Cox proportional hazards models were used to evaluate associations between TFT or OS and patient prognostic factors. Since not all patients had all novel prognostic markers available, the independent value of each prognostic factor (e.g. CD38, CD49d, ZAP-70, IGHV mutation status, and FISH risk category) was assessed individually in separate models after adjusting for age, sex and Rai stage. Hazard ratios and 95% confidence interval were calculated from the Cox models.

Table 2: Comparison of characteristics of young CLL patients according to age groups ≤45, 46-50 and 51-55 years

Characteristic		≤ 45 yrs n (%)	46-50 yrs n (%)	51-55 yrs n (%)	p-value
N		204	272	368	
Median Age, years (range)		42 (17-45)	48 (46-50)	54 (51-55)	
Sex (male)		141 (69)	179 (66)	239 (65)	0.59
Median white cell count (x10^9/L) (range)		17.4 (1.3-431.1)	20.5 (2.2-443.0)	17.1 (0.7-413.8)	0.26
Median absolute lymphocyte count[¶] (x10^9/L) (range)		6.0 (0.0-248.3)	10.2 (0.1-272.0)	8.7 (0.0-380.6)	**0.03**
Median absolute B-cell count[¶] (x10^9/L) (range)		14.8 (0.4-114.8)	12.3 (0.6-134.8)	9.6 (0.1-294.3)	0.24
Median hemoglobin (gm/L) (range)		14 (56-177)	139 (68-179)	138 (49-171)	0.57
Median platelets (x10^9/L) (range)		183 (10-469)	191 (20-713)	195 (2-585)	0.31
Median beta-2 microglobulin (mg/dL) (range)		2.2 (1.0-6.9)	2.2 (0.9-22.3)	2.4 (1.0-26.0)	**0.02**
Beta-2 microglobulin >2 x ULN	Yes	15 (13)	28 (15)	43 (19)	0.31
	No	102 (87)	154 (85)	184 (91)	
	Missing	87	90	141	
Rai Stage	Low (0)	66 (34)	114 (44)	169 (49)	**0.009**
	Intermediate (I, II)*	121 (62)	136 (53)	168 (49)	
	High (III, IV)	9 (5)	9 (3)	7 (2)	
	Missing	8	13	24	
Presentation subcategories	SLL presentation	21 (10)	282 (12)	44 (12)	0.84
	MBL[¶¶]	7 (4)	25 (12)	21 (8)	**0.04**
ECOG Performance Status	0	182 (92)	245 (93)	328 (92)	0.80
	1-2	16 (8)	19 (7)	26 (7)	
	3-4	0 (0)	0 (0)	1 (0.3)	
	Missing	6	8	13	
IGHV Mutation Status	Mutated, *IGHV* homology <98%	43 (39)	91 (54)	94 (44)	**0.03**
	Unmutated, *IGHV* homology ≥98%	67 (61)	77 (46)	118 (56)	
	Missing	94	104	156	
ZAP-70	Negative (<20%)	56 (47)	108 (60)	132 (56)	0.10
	Positive (≥20%)	63 (53)	73 (40)	104 (44)	
	Missing	85	91	132	
CD49d	Negative (<30%)	60 (65)	109 (77)	125 (69)	0.10
	Positive (≥30%)	32 (35)	32 (23)	57 (31)	
	Missing	112	131	186	
CD38	Negative (<30%)	95 (64)	151 (69)	194 (66)	0.54
	Positive (≥30%)	54 (36)	67 (31)	98 (34)	
	Missing	55	54	76	
FISH category	Normal	36 (36)	41 (25)	48 (25)	0.48
	13q-	41 (41)	69 (43)	86 (44)	
	Trisomy 12	12 (12)	23 (14)	33 (17)	
	11q-	6 (6)	19 (12)	20 (10)	

	17p-	4 (4)	7 (4)	7 (4)	
	Other	2 (2)	3 (2)	1 (0.5)	
	Missing	103	110	173	
Positive Family history of CLL		20 (10)	32 (12)	40 (11)	0.79
Underwent SCT		28 (14)	14 (5)	13 (4)	**<0.0001**
Referral status	Local	48 (24)	80 (29)	98 (27)	0.36
	Referred	156 (76)	192 (71)	270 (73)	

¶: Although all patients had an ALC at diagnosis, only a subset of patients had an absolute B-cell count available. For the 54 patients in the ≤45 years age group in whom both ALC and B-cell counts were available, the median ALC was 16.6 x109/L (range, 2.0-134.2). For the 105 patients in the 46-50 years age group in whom B-cell counts were available, the ALC was 16.6 x10^9/L (range, 4.7-183.3). For the 110 patients in the 51-55 years age group in whom B-cell counts were available, the median ALC was 13.6 x10^9/L (range, 0-297.3)

*: Patients with an SLL presentation are grouped with Rai intermediate stage patients

¶¶: All patients in this series met the 1996 consensus criteria for a diagnosis of CLL which were in effect for the majority of the study interval. The 2008 consensus criteria revised the criteria for diagnosis of CLL from an ALC>5 x109/L to an absolute B-cell count>5 x109/L. This row indicates the number of patients in each group who would be reclassified to MBL when classified by the 2008 criteria.

Abbreviations Used: ULN: upper limit of normal; ECOG: Eastern Oncology Co-operative Group; SLL; small lymphocytic leukemia; MBL: monoclonal B-lymphocytosis; *IGHV*: immunoglobulin heavy chain gene; *FISH*: fluorescence *in-situ* hybridization; SCT: stem cell transplantation

Table 3: Cox Regression analysis of factors predicting time to first treatment and overall survival of all patients ≤55 years (n=844). Since not all patients had all prognostic markers available, the prognostic value of each factor was evaluated in a separate regression adjusting for age, sex, and Rai stage. See statistical methods.

Variable	p-value	Hazard ratio	95% CI	N available for analysis
Time to First Treatment				
ECOG performance status >0	0.60	1.1	0.7-1.7	794
CD38 ≥30%	**<0.0001**	2.3	1.8-3.0	623
CD49d ≥30%	**<0.0001**	2.6	1.9-3.6	394
ZAP-70 ≥20%	**<0.0001**	1.9	1.4-2.5	510
Unmutated *IGHV*	**<0.0001**	2.8	2.1-3.8	472
Intermediate-risk *FISH* (+12)	**<0.0001**	2.5	1.6-3.9	440
High-risk *FISH* (11q- or 17p-)	**<0.0001**	2.9	1.9-4.5	440
Overall Survival				
ECOG performance status >0	0.44	0.8	0.4-1.5	794
CD38 ≥30%	**0.002**	1.9	1.3-2.7	623
CD49d ≥30%	0.15	1.6	0.8-3.2	394
ZAP-70 ≥20%	**0.01**	1.9	1.2-3.0	510
Unmutated *IGHV*	**<0.0001**	6.4	3.2-13.2	472
Intermediate-risk *FISH* (+12)	**0.006**	3.1	1.4-7.0	440
High-risk *FISH* (11q- or 17p-)	**0.005**	3.3	1.4-7.7	440

Abbreviations Used: ECOG: Eastern Oncology Co-operative Group; *IGHV*: immunoglobulin heavy chain gene; *FISH*: fluorescence in-situ hybridization