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

Sameer A. Parikh,[1] Kari G. Rabe,[2] Neil E. Kay,[1] Timothy G. Call,[1] Wei Ding,[1] Susan M. Schwager,[1] Deborah A. Bowen,[1] Michael Conte,[1] Diane F. Jelinek,[3] Susan L. Slager,[2] and Tait D. Shanafelt[1]

[1]Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN; [2]Division of Biomedical Statistics & Informatics, Mayo Clinic, Rochester, MN; and [3]Department of Immunology, Mayo Clinic, Rochester, MN, USA

## ABSTRACT

The clinical characteristics and outcomes of younger (≤55 years) patients with chronic lymphocytic leukemia in the era of modern prognostic biomarkers and chemoimmunotherapy are not well understood. Baseline characteristics and outcomes of patients with chronic lymphocytic leukemia ≤55 years who were seen at the Mayo Clinic between January 1995 and April 2012 were compared with those of patients >55 years. The overall survival of patients ≤55 years was compared to that of the age- and sex-matched normal population. The characteristics of 844 newly diagnosed chronic lymphocytic leukemia patients ≤55 years old (median, 50 years) were compared to those of 2324 patients >55 years old (median, 67 years). Younger patients were more likely to have Rai stage I or II disease ($P$<0.0001), be *IGHV* unmutated ($P$=0.002) and express ZAP-70 ($P$=0.009). These differences became more pronounced when the ≤55 age group was sub-stratified into age ≤45, 46-50 and 51-55 years. After a median follow-up of 5.5 years, 426 (51%) patients ≤55 years old had received treatment, and 192 (23%) had died. The time to treatment was shorter in patients ≤55 years than in those older than 55 years (4.0 years *versus* 5.2 years; $P$=0.001) and those ≤55 years had longer survival (12.5 years *versus* 9.5 years; $P$<0.0001). However, patients ≤55 years had significantly shorter survival than the age- and sex-matched normal population (12.5 years *versus* not reached; $P$<0.0001). Our study is the first comprehensive analysis of younger patients with chronic lymphocytic leukemia in the modern era. Adverse prognostic markers appear more common among young patients. Although the survival of young chronic lymphocytic leukemia patients is longer than that of those >55 years old, their survival relative to the age- and sex-matched normal population is profoundly shortened.

## Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the Western world. According to the American Cancer Society, an estimated 15,680 individuals in the United States will have been diagnosed with CLL in 2013.[1] The median age at diagnosis ranges from 65-70 years.[2-4] Based on the National Cancer Institute's Surveillance and Epidemiology End Results (SEER) database, 11% of all patients diagnosed with CLL in 2009 were less than 55 years of age.[5] Population-based studies from Europe also indicate that between 7% and 20% of patients with CLL are <55 years of age at diagnosis.[2,6-9] These retrospective studies have described the clinical characteristics of younger patients with CLL, and have compared these to the characteristics of older CLL patients. These historical series were small (e.g. <200 patients) and are more than two decades old.[6,8-11] The most recent and largest series was reported in 1999 and included 204 patients.[7]

The past decade has been a time of tremendous change in the clinical care of patients with CLL. The most widely used prognostic biomarkers, such as immunoglobulin heavy chain variable region gene somatic mutation status (*IGHV*), genetic abnormalities detected by fluorescence *in-situ* hybridization (FISH), expression of zeta-associated protein-70 (ZAP-70), and expression of CD38, were all developed after 1999. Extensive treatment advances have also occurred with the introduction of new therapeutic agents,[12-14] the development of combination chemotherapy,[15-17] the introduction of chemo-immunotherapy,[18,19] better definition of the role of allogeneic stem cell transplant,[20,21] and the use of common recurring genetic characteristics to inform therapy selection.[22-25]

Due to these profound changes, data from historical reports on clinical outcomes of younger patients with CLL are of uncertain relevance in the modern era.[6,8-11] In the present study, we aim to describe the clinical characteristics, time to first treatment and overall survival of CLL patients ≤55 years old in the current era.

## Methods

### Patients

The Mayo Clinic CLL database includes information on all patients with a diagnosis of CLL seen in the Division of Hematology at the Mayo Clinic since 1995, and who permit their records to be used for research purposes.[26-28] Baseline demographics, clinical factors, treatment history, disease-related complications, time to first treatment and survival are abstracted from clinical and research records on all patients and maintained on a prospective basis. We used this database

 doi:10.3324/haematol.2013.086066
The online version of this article has a Supplementary Appendix.
Manuscript received on February 18, 2013. Manuscript accepted on August 1, 2013.
Correspondence: shanafelt.tait@mayo.edu

to evaluate the experience of CLL patients who were ≤55 years of age at the time of diagnosis. The threshold of ≤55 years was selected to classify age based on a similar cutoff used to define young CLL patients in historical studies.[5,7,29,30] Patients diagnosed with CLL between January 1995 and April 2012 and who fulfilled the 1996 criteria for CLL[31] and/or the World Health Organization (WHO) criteria for small lymphocytic lymphoma[32] were included in this analysis. Rai stage was ascertained within 12 months of the initial diagnosis. Since FISH results can change during the course of disease or after treatment,[33] only pre-treatment FISH results were used in this study. To adjust for potential referral bias, we compared the characteristics of patients who resided within 120 miles of the Mayo Clinic (excluding the twin cities of Minneapolis and St. Paul) to those who resided >120 milesaway.[34,35] The clinical characteristics and outcomes of CLL patients ≤55 years old were compared to those of CLL patients >55 years old. To further explore associations with patients with young onset CLL, those ≤aged 55 years were also divided into three groups based on their age at diagnosis: (i) ≤45 years, (ii) 46-50 years, and (iii) 51-55 years. The overall survival of patients ≤55 years old was also compared to that of the age- and sex-matched normal population of the state of Minnesota. The Mayo Clinic Institutional Review Board approved this study.

### Statistical analysis

Patients' characteristics are summarized using medians and ranges for continuous variables and frequencies (percentages) for categorical variables. Overall survival was defined as time from diagnosis to date of death due to any cause or last follow-up time, whichever occurred first. Time to first treatment was defined as the time between the date of diagnosis and the date of initiation of treatment or date of last follow-up at which the patient was known to be untreated. Since the indications for treatment under both the 1996[31] and 2008[36] consensus criteria are identical, the indications to initiate treatment were consistent throughout the entire study interval. Expected survival was calculated using the cohort (Hakulinen) method[37] with estimates based on the age- and sex-matched Minnesota population.[38] *P* values <0.05 were considered statistically significant. All statistical analyses were conducted using the SAS 9.2 software package (SAS Institute, Cary, NC, USA). More details on the methods and statistical analysis can be found in the *Online Supplementary Appendix*.

## Results

### Baseline characteristics of patients ≤ 55 years of age relative to those >55 years old

Between January 1, 1995 and April 9, 2012, 844 patients ≤55 years old (median age, 50 years) with CLL were seen at the Mayo Clinic. A comparison of the baseline characteristics and prognostic profile of these patients relative to the 2324 CLL patients >55 years old (median age, 67 years) seen at the Mayo Clinic during the same time period is shown in Table 1. When compared to patients >55 years old, patients ≤55 years old were more likely to present with intermediate Rai stage (I and II) disease (*P*<0.0001), have unmutated *IGHV* (*P*=0.002), and express ZAP-70 (*P*=0.009). Similar trends for Rai stage (*P*<0.0001) and *IGHV* mutation status (*P*=0.047) were observed when the analysis was restricted to non-referred patients. Serum β2-microglobulin levels were lower in patients ≤55 years old (*P*<0.0001) and these patients were also less likely to be CD49d-positive (*P*=0.01). Younger patients were slightly more likely to report having one or more first-degree relatives with CLL (familial CLL) than were older patients (11% *versus* 9%; *P*=0.04). No significant differences were seen in gender distribution, CD38 status, or FISH risk category among those ≤55 years old relative to those >55 years old. The median time from CLL diagnosis to evaluation at the Mayo Clinic was ≤3 months for patients in both the age groups: ≤55 years and >55 years. Although statistical differences were observed between the two age groups in white cell count, absolute B-cell count and hemoglobin concentration at the time of initial diagnosis (Table 1), the absolute differences were small and thus unlikely to be of clinical significance. As would be expected in an older population, a significantly higher proportion of patients in the >55 year age group had an ECOG performance status of >0.

We next divided patients ≤aged 55 into three groups based on their age at diagnosis: (i) age ≤45 years (n=204, 24%), (ii) age 46-50 years (n=272, 32%) and (iii) age 51-55 years (n= 368, 44%). Patients ≤45 years were more likely to present with intermediate (I or II) and high (III and IV) Rai risk (*P*=0.009) and be *IGHV* unmutated (*P*=0.03) compared to those in the groups 46-50 or 51-55 years old (*Online Supplementary Table S2*). These findings again persisted after limiting the analysis to non-referred patients. No other differences in baseline characteristics, prognostic parameters or prevalence of familial CLL were noted between the groups aged ≤45, 46-50 and 51-55 years.

After a median follow-up of 5.5 years (range, 0-17 years), 426/844 (51%) patients ≤ 55 years old had been treated. Substantial changes in the treatment of CLL occurred during the study period (1995-2012), with the introduction of monoclonal antibodies and the development of chemoimmunotherapy. As initial therapy, 153 (36%) patients received chemoimmunotherapy, 67 (16%) received a single-agent purine nucleoside analog, 60 (14%) received monoclonal antibody therapy with or without corticosteroids, 59 (14%) received single-agent alkylator therapy with or without corticosteroids, 42 (10%) received combination chemotherapy consisting of an alkylator with (n=24) or without (n=18) rituximab, 17 (4%) received a combination of purine nucleoside analog and alkylator, and 28 (7%) patients received other treatments. A higher proportion of patients in the group ≤55 years old received chemoimmunotherapy (36% *versus* 27%, *P*=0.005), single-agent purine nucleoside analog (16% *versus* 8%, *P*<0.001), or a combination of purine nucleoside analog and alkylator therapy (4% *versus* 2%, *P*=0.009) compared to patients >55 years.

Fifty-five patients (7%) underwent an allogeneic stem cell transplant in the ≤55 years age group compared to 23 (1%) patients in the >55 age group (*P*<0.0001). The association between age and allogeneic stem cell transplant persisted when patients ≤55 years were further stratified by age with those ≤ 45 years (14%; 28/204) of age at diagnosis more likely to undergo stem cell transplantation than those 46-50 years (5%; 14/272) or 51-55 (4%; 13/368) years of age (*P*<0.0001).

### Time to first treatment and overall survival

After a median follow-up of 5.5 years (range, 0-17 years), 1095/3168 (25%) patients have died; 192 (23%) in the ≤55 year old group and 903 (39%) in the >55 year old group. For the entire group, the median time to first treatment was 4.8 years, and the median overall survival was

**Table 1. Baseline characteristics of young (≤55 years) CLL patients compared to older CLL patients (>55 years).**

| Characteristic | ≤ 55 years n. (%) | > 55 years n. (%) | *P* value |
|---|---|---|---|
| Number | 844 | 2324 | |
| Median age, years (range) | 50 (17-55) | 67 (56-97) | |
| Sex (male) | 559 (66) | 1562 (67) | 0.60 |
| Median white cell count ($x10^9$/L) (range) | 17.9 (0.7-443.0) | 14.5 (0.3-997.3) | **0.0001** |
| Median absolute lymphocyte count¶ ($x10^9$/L) (range) | 8.4 (0.0-380.6) | 7.3 (0.0-341.3) | 0.11 |
| Median absolute B-cell count¶ ($x10^9$/L) (range) | 11.2 (0.1-294.3) | 8.2 (0.0-666.7) | **0.0006** |
| Median hemoglobin (g/L) (range) | 139 (49-179) | 135 (43-182) | **<0.0001** |
| Median platelets ($x10^9$/L) (range) | 192 (2-713) | 186 (4-1229) | 0.16 |
| Median beta-2 microglobulin (mg/dL) (range) | 2.3 (0.9-26.0) | 2.7 (0.9-31.9) | <0.0001 |
| Beta-2 microglobulin >2 x ULN | | | **<0.0001** |
| Yes | 86 (16) | 319 (28) | |
| No | 440 (84) | 814 (72) | |
| Missing | 318 | 1191 | |
| Rai Stage | | | <0.0001 |
| Low (0) | 349 (44) | 1223 (57) | |
| Intermediate (I, II)* | 425 (53) | 807 (37) | |
| High (III, IV) | 25 (3) | 134 (6) | |
| Missing | 45 | 160 | |
| Presentation subcategories | | | |
| SLL presentation | 95 (11) | 282 (12) | 0.5 |
| MBL¶¶ | 53 (9) | 205 (13) | **0.002** |
| ECOG Performance Status | | | **0.0007** |
| 0 | 755 (92) | 1966 (88) | |
| 1-2 | 61 (8) | 258 (11) | |
| 3-4 | 1 (0.1) | 15 (1) | |
| Missing | 27 | 85 | |
| *IGHV* mutation status | | | **0.002** |
| Mutated, *IGHV* homology <98% | 228 (46) | 555 (55) | |
| Unmutated, *IGHV* homology ≥98% | 262 (54) | 450 (45) | |
| Missing | 354 | 1319 | |
| ZAP-70 | | | **0.009** |
| Negative (<20%) | 296 (55) | 754 (62) | |
| Positive (≥20%) | 240 (45) | 465 (38) | |
| Missing | 308 | 1105 | |
| CD49d | | | **0.01** |
| Negative (<30%) | 294 (71) | 572 (64) | |
| Positive (≥30%) | 121 (29) | 326 (36) | |
| Missing | 429 | 1426 | |
| CD38 | | | 0.81 |
| Negative (<30%) | 440 (67) | 1177 (67) | |
| Positive (≥30%) | 219 (33) | 572 (33) | |
| Missing | 185 | 575 | |
| FISH category | | | 0.17 |
| Normal | 125 (27) | 291 (25) | |
| 13q- | 196 (43) | 476 (40) | |
| Trisomy 12 | 68 (15) | 233 (20) | |
| 11q- | 45 (10) | 105 (9) | |
| 17p- | 18 (4) | 61 (5) | |
| Other** | 6 (1) | 11 (1) | |
| Missing | 38 6 | 1147 | |
| Positive family history of CLL | 92 (11) | 197 (9) | 0.04 |
| Underwent SCT | 55 (7) | 23 (1) | <0.0001 |
| Referral status | | | 0.001 |
| Local | 226 (27) | 762 (33) | |
| Referred | 618 (73) | 1561 (67) | |

10.1 years. Patients ≤55 years old had a shorter time to first treatment (4.0 years *versus* 5.2 years; *P*=0.001, Figure 1A) compared to patients >55 years old. This difference disappeared after adjusting for Rai stage and *IGHV* mutation status, suggesting that differences in disease stage and biological characteristics (rather than age) were responsible for this difference. Despite the shorter time to first treatment, patients ≤55 years old had a longer overall survival (12.5 years *versus* 9.5 years; *P*<0.0001, Figure 1B) compared to patients >55 years old. Patients ≤55 years old also had a longer overall survival compared to 968 patients between 56-65 years of age (12.5 years *versus* 11.0 years, *P*=0.001). In contrast, no differences in time to first treatment or overall survival were observed when patients aged ≤55 years were sub-stratified into ≤45, 46-50, and 51-55 age groups (Figure 2A,B). The molecular biomarkers ZAP-70 and CD38, *IGHV* mutation status, and cytogenetic abnormalities on FISH analysis each independently predicted time to first treatment and overall survival in the group ≤55 years old after adjusting for age, sex and Rai stage (*Online Supplementary Table S3*).

### Comparison of overall survival with the general population

As a group, CLL patients ≤55 years old have significantly shorter overall survival than the age- and sex-matched population (median CLL=12.5 years; median population=not reached; *P*<0.0001, Figure 3A). However, the survival of patients ≤55 years old who had Rai stage 0 disease and were *IGHV* mutated was comparable to that of the age- and sex-matched general population (*P*=0.97, Figure 3B). Similarly, patients ≤55 years old who had Rai stage 0 disease and either 13q- or normal FISH also had a survival comparable to that of the age- and sex-matched general population (*P*=0.27, Figure 3C).

Among the 358 young patients with both FISH and *IGHV* results available, 171 were in Rai stage 0. Of these 171 patients, 97 (56.7%) had both mutated *IGHV* and a favorable FISH risk category, 54 (31.5%) had one unfavorable factor and 20 (11.7%) had two unfavorable factors. The median survivals in the groups with 0, 1, and 2 unfavorable factors were not reached, 13.0, and 7.7 years, respectively (*P*<0.001, Figure 3D).

## Discussion

In the past decade, considerable advances have been made in our ability to predict outcome and treat patients with CLL. This study is the first comprehensive report on

*Footnote to Table 1*

*¶Although all patients had an absolute lymphocyte count (ALC) at diagnosis, only a subset of patients had an absolute B-cell count available. In the 269 patients ≤55 years for whom B-cell counts were available the median ALC was 15.6x10⁹/L (range, 0.6-297.3). In the 717 patients >55 years for whom B-cell counts were available, the ALC was 11.8x10⁹/L (range, 0.5-280.7) *Patients with a small lymphocytic lymphoma 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 most of the study interval. The 2008 consensus criteria revised the criteria for the diagnosis of CLL from an ALC >5x10⁹/L to an absolute B-cell count >5x10⁹/L. This row indicates the number of patients in each group who would be reclassified to monoclonal B-cell lymphocytosis when classified by the 2008 criteria. **FISH analysis revealed the following: In the ≤ 55 year age group, four patients had 6q-, one patient had t(14;18) and one patient had* IGH*x3; In the >55 year age group, five patients had 6q-, three had t(14;18), two had 14q-, and one had t(8;14). ULN: upper limit of normal; ECOG: Eastern Oncology Co-operative Group; SLL: small lymphocytic lymphoma; MBL: monoclonal B-cell lymphocytosis;* IGHV*: immunoglobulin heavy chain gene; FISH: fluorescence* in-situ *hybridization; SCT: stem cell transplantation.*

the clinical characteristics and outcomes of a cohort of young CLL patients (≤55 years old) in the modern era and is approximately four times larger than any previous series of young CLL patients. Furthermore, information on *IGHV* gene mutation status and genetic abnormalities detected by FISH was available for slightly more than half (55%) of the patients, providing insight into the associations between age and molecular biomarkers. Significant differences in the presentation of young CLL patients relative to older patients were observed: young patients were more likely to present with intermediate Rai risk disease, have unmutated *IGHV* gene mutation status and express ZAP-70. Although the overall survival of young CLL patients as a group is longer than that of CLL patients >55 years old, the survival of all CLL patients is markedly shorter than that of their age- and sex-matched population.

To the best of our knowledge, our study is the first to report that young CLL patients have a higher prevalence of adverse clinical and biological characteristics. These differences persisted when we limited our analysis to non-referred patients and became even more pronounced when patients ≤55 years old underwent further age substratification. This observation suggests that young CLL patients are more likely than older patients to have biologically aggressive disease. CLL patients aged ≤55 years old were treated sooner than those >55 years old (median time to first treatment: 4 *versus* 5.2 years, respectively). It is possible that healthcare providers may have a bias towards treating young CLL patients sooner than older CLL patients who may have multiple other co-morbidities. However, the fact that the shorter time to first treatment among young patients was no longer significant after adjusting for Rai stage and *IGHV* mutation status

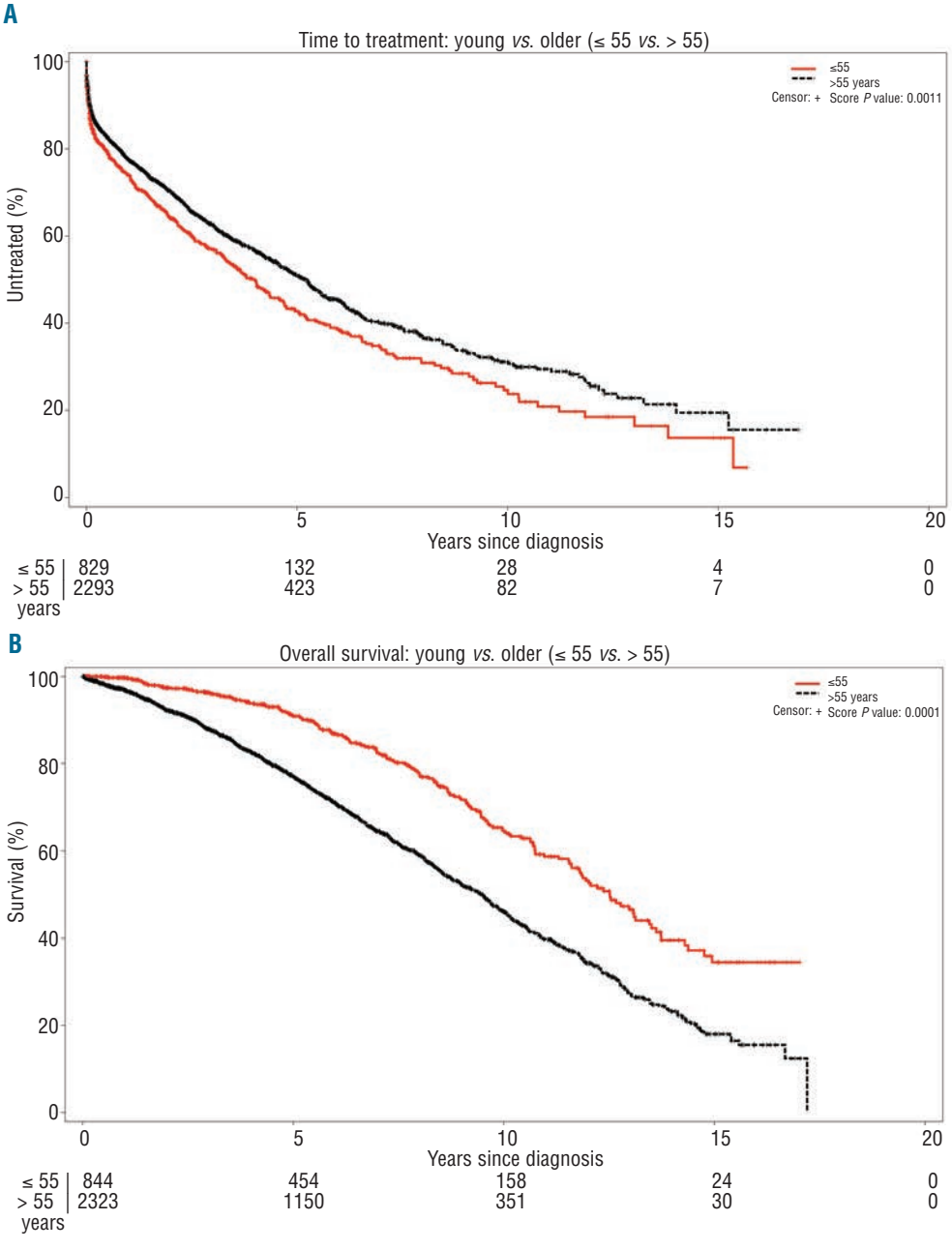


**Figure 1.** (A) **Time to first treatment in patients ≤ 55 years *vs.* >55 years.** (B) **Overall survival of patients ≤ 55 years *vs.* >55 years**

suggests that the shorter time to first treatment among young patients is driven by differences in disease biology rather than age or the impact of co-morbidities. There were no differences noted in time to first treatment among the subgroups aged ≤45, 46-50 and 51-55 years old.

In the 1990s, Montserrat *et al.* reported that the overall survival of young CLL patients is worse than that of the age- and sex-matched normal population.[9] More than 20 years later, our study confirms these findings. However, with the inclusion of several novel prognostic markers, we identified a subset of young patients whose survival is similar to that of the age-and sex-matched general population. Among the ~50% of the young patients in our series who had Rai stage 0 disease, slightly more than half (25% of all young patients) had both mutated *IGHV* and favorable FISH findings. The 15-year survival rate in these patients was >90%. Such individuals should be carefully followed to prevent disease-related complications - with attention to vaccinations, vitamin D levels, skin cancer surveillance, and monitoring for infectious and autoimmune complications of CLL. The rest of the patients are at high risk of disease progression and represent ideal candidates for enrollment into early intervention trials. This would allow us to study the impact of novel treatments in altering the natural history of this disease, and improve disease-free survival and overall survival.

As expected based on transplant age-related eligibility considerations, young CLL patients were more likely to undergo stem cell transplantation. One in 16 patients ≤55 years old received a stem cell transplant. Notably, while age alone would not be an exclusion criterion to stem cell transplantation in any patient ≤55 years old, the proportion of patients who underwent stem cell transplantation became even more pronounced when patients aged ≤55 years old were sub-stratified further by age. In the group ≤45 years old, 14% received a stem cell transplant compared to 5% in the group 46-50 years old and 4% in the group 51-55 years old. The highest proportion of stem cell transplantation was seen in patients <40 years of age among whom one out of every five patients was eventually transplanted.

How do these results compare to those of historical studies of young CLL patients? The influence of age on the outcome of patients with CLL was first described in the seminal publication by Rai *et al.* in 1975.[39] In this classic paper, 25 patients <50 years of age had a median overall

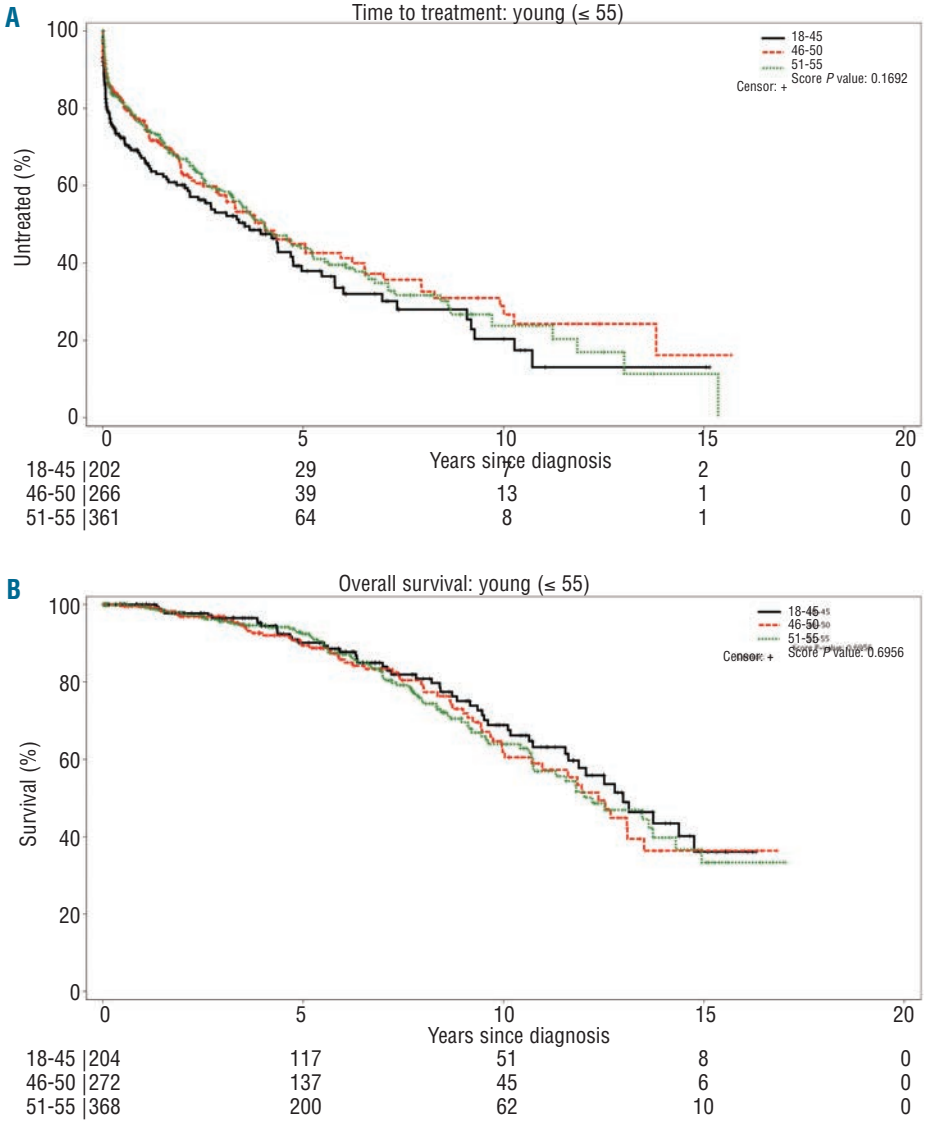


**Figure 2.** (A) **Time to first treatment in ≤ 45 *vs.* 46-50 *vs.* 51-55 years the age groups.** (B) **Overall survival in the age groups ≤ 45 *vs.* 46-50 *vs.* 51-55 years.**

survival of 12.3 years which was superior to that of patients in the older age groups. In a retrospective analysis of 62 CLL patients <50 years published by Dhodapkar *et al.* from our institution in 1993,[10] the median survival was 11.7 years, and was better among early Rai stage patients and those with a lymphocyte doubling time of >12 months. In a retrospective analysis of 117 CLL patients ≤55 years old reported in 1991, Montserrat *et al.*[9] could not identify any distinctive clinical or prognostic features (e.g., stage, absolute lymphocyte count, bone marrow histology) among young patients relative to older patients. The median overall survival of their cohort was 12 years. In 1994, Molica *et al.*[8] published their experience of 53 young CLL patients. There were no significant differences in traditional prognostic factors between these patients and older adults; the median overall survival was 7.1 years compared to 4.1 in the older age group. Two subsequent retrospective series (each with ~200 patients aged ≤55 years) confirmed these results.[7,30] Although the vast majority of the aforementioned studies did not report any differences in the traditional prognostic parameters between young and old CLL patients, we did find significant differences in these two populations of patients in the modern era. It is notable that cohorts of patients with CLL cared

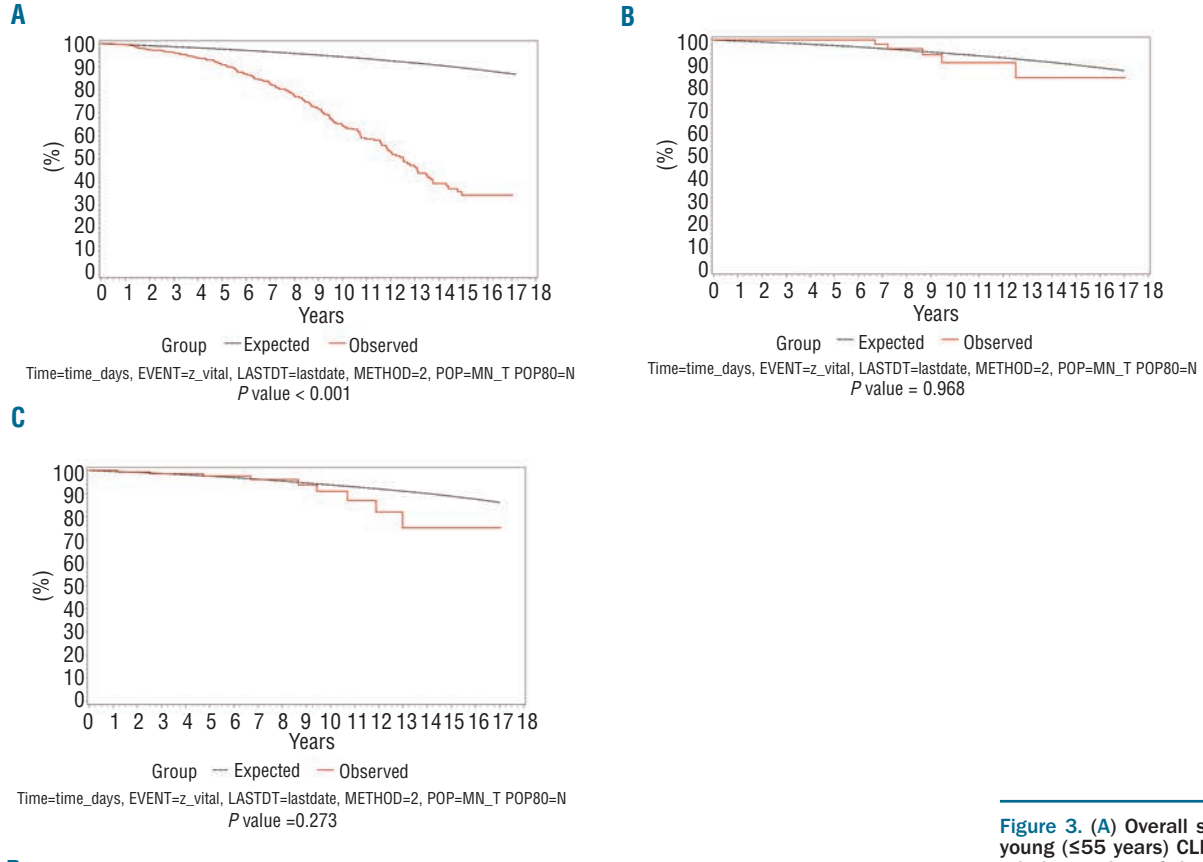


**Figure 3.** (A) Overall survival of young (≤55 years) CLL patients relative to that of the age- and sex-matched normal population. (B) Overall survival of young (≤55 years) CLL patients with Rai stage 0 and mutated *IGHV* gene (red solid line) compared to that of the age-and sex-matched normal population (black dashed line). (C) Overall survival of young (≤55 years) CLL patients with Rai stage 0 and favorable-risk FISH category (normal or 13q-, red solid line) compared to an age-and sex-matched normal population (black dashed line). (D) Overall survival of young (≤55 years) CLL patients with Rai stage 0 stratified by *IGHV* mutation status and FISH analysis. Black solid line represents 0 unfavorable factors (mutated *IGHV* and favorable FISH), the red dashed line represents one unfavorable factor and the green dashed line represents two unfavorable factors.

for in the 1970s and 1990s all had the same median overall survival of 12 years. This is exactly what we find in our study more than three decades later, which is a reminder that we need to be vigilant in developing and offering treatment options that improve not only disease-free survival but overall survival as well.

Our study has several limitations. Not all patients had novel molecular/biological parameters available for inclusion in multiple analyses, given that these have only been used routinely in the past 5-10 years. Also, the treatment options for patients with CLL have undergone considerable changes during the study period. In addition, this was a single-center, retrospective analysis which needs validation among other cohorts of patients. Although we found that young CLL patients in Rai 0 stage with favorable *IGHV* and FISH results have a comparable survival to that of the general population over a 10-year interval, prolonged follow-up will be necessary to determine if this holds true in the long term.

In summary, this study helps to formulate general concepts regarding the management and natural history of patients who are diagnosed with CLL well under the median age of presentation of this disease. Young CLL patients have an adverse clinical and molecular risk profile (i.e, Rai stage, *IGHV* mutation status) compared to older patients. As a collective group, the median overall survival of CLL patients aged ≤55 is 12 years - which is significantly shorter than that of the age- and sex-matched population. Despite this discouraging group average, we found that approximately 25% of young patients in our study who have Rai Stage 0 disease and either mutated *IGHV* genes or a favorable FISH risk category (such as normal cytogenetics or 13q-) have a survival comparable to that of the age- and sex-matched general population. Accordingly, information from prognostic testing of molecular biomarkers can be used to stratify outcome in younger patients and identify those most likely to benefit from participation in trials testing early intervention strategies.

***Acknowledgment***

*Dr. Shanafelt is a clinical scholar of the Leukemia and Lymphoma Society.*

***Funding***

*This work was supported in part by the Predolin Foundation.*

***Authorship and Disclosures***

*Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.*

## References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11-30.
2. Abrisqueta P, Pereira A, Rozman C, Aymerich M, Gine E, Moreno C, et al. Improving survival in patients with chronic lymphocytic leukemia (1980-2008): the Hospital Clinic of Barcelona experience. Blood. 2009; 114(10):2044-50.
3. Brenner H, Gondos A, Pulte D. Trends in long-term survival of patients with chronic lymphocytic leukemia from the 1980s to the early 21st century. Blood. 2008;111(10): 4916-21.
4. Call TG, Phyliky RL, Noel P, Habermann TM, Beard CM, O'Fallon WM, et al. Incidence of chronic lymphocytic leukemia in Olmsted County, Minnesota, 1935 through 1989, with emphasis on changes in initial stage at diagnosis. Mayo Clinic Proceedings Mayo Clinic. 1994;69(4):323-8.
5. Ferrajoli A. Treatment of younger patients with chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;82-9.
6. Bennett JM, Raphael B, Oken MM, Rubin P, Silber R. The prognosis and therapy of chronic lymphocytic leukemia under age 50 years. Nouv Rev Fr Hematol. 1988;30(5-6):411-2.
7. Mauro FR, Foa R, Giannarelli D, Cordone I, Crescenzi S, Pescarmona E, et al. Clinical characteristics and outcome of young chronic lymphocytic leukemia patients: a single institution study of 204 cases. Blood. 1999;94(2):448-54.
8. Molica S, Brugiatelli M, Callea V, Morabito F, Levato D, Nobile F, et al. Comparison of younger versus older B-cell chronic lymphocytic leukemia patients for clinical presentation and prognosis. A retrospective study of 53 cases. Eur J Haematol. 1994;52(4):216-21.
9. Montserrat E, Gomis F, Vallespi T, Rios A, Romero A, Soler J, et al. Presenting features and prognosis of chronic lymphocytic leukemia in younger adults. Blood. 1991;78(6):1545-51.
10. Dhodapkar M, Tefferi A, Su J, Phyliky RL. Prognostic features and survival in young adults with early/intermediate chronic lymphocytic leukemia (B-CLL): a single institution study. Leukemia. 1993;7(8):1232-5.
11. De Rossi G, Mandelli F, Covelli A, Luciani M, Martelli M, Resegotti L, et al. Chronic lymphocytic leukemia (CLL) in younger adults: a retrospective study of 133 cases. Hematol Oncol. 1989;7(2):127-37.
12. Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol. 2007;25(35):5616-23.
13. Knauf WU, Lissichkov T, Aldaoud A, Liberati A, Loscertales J, Herbrecht R, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27 (26):4378-84.
14. Wierda WG, Kipps TJ, Durig J, Griskevicius L, Stilgenbauer S, Mayer J, et al. Chemoimmunotherapy with O-FC in previously untreated patients with chronic lymphocytic leukemia. Blood. 2011;117(24): 6450-8.
15. Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJS, Bezares RF, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet. 2007;370 (9583):230-9.
16. Eichhorst BF, Busch R, Hopfinger G, Pasold R, Hensel M, Steinbrecher C, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood. 2006;107(3):885-91.
17. Flinn IW, Neuberg DS, Grever MR, Dewald GW, Bennett JM, Paietta EM, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. J Clin Oncol. 2007;25(7):793-8.
18. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164-74.
19. Tam CS, O'Brien S, Wierda W, Kantarjian H, Wen S, Do KA, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008;112 (4):975-80.
20. Dreger P, Corradini P, Kimby E, Michallet M, Milligan D, Schetelig J, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia. 2007;21(1): 12-7.
21. Sorror ML, Storer BE, Sandmaier BM, Maris M, Shizuru J, Maziarz R, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol. 2008;26(30):4912-20.
22. Grever MR, Lucas DM, Dewald GW, Neuberg DS, Reed JC, Kitada S, et al. Comprehensive assessment of genetic and molecular features predicting outcome in patients with chronic lymphocytic leukemia: results from the US Intergroup Phase III Trial E2997. J Clin Oncol. 2007;25 (7):799-804.
23. Byrd JC, Gribben JG, Peterson BL, Grever MR, Lozanski G, Lucas DM, et al. Select high-risk genetic features predict earlier progression following chemoimmunotherapy with

fludarabine and rituximab in chronic lymphocytic leukemia: justification for risk-adapted therapy. J Clin Oncol. 2006;24(3): 437-43.
24. Ding W, Ferrajoli A. Evidence-based mini-review: the role of alkylating agents in the initial treatment of chronic lymphocytic leukemia patients with the 11q deletion. Hematology Am Soc Hematol Educ Program. 2010;90-2.
25. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;481-8.
26. Maddocks-Christianson K, Slager SL, Zent CS, Reinalda M, Call TG, Habermann TM, et al. Risk factors for development of a second lymphoid malignancy in patients with chronic lymphocytic leukaemia. Br J Haematol. 2007;139(3):398-404.
27. Shanafelt TD, Rabe KG, Kay NE, Zent CS, Jelinek DF, Reinalda MS, et al. Age at diagnosis and the utility of prognostic testing in patients with chronic lymphocytic leukemia. Cancer. 2010;116(20):4777-87.
28. Shanafelt TD, Geyer SM, Bone ND, Tschumper RC, Witzig TE, Nowakowski GS, et al. CD49d expression is an independent predictor of overall survival in patients with chronic lymphocytic leukaemia: a prognostic parameter with therapeutic potential. Br J Haematol. 2008;140(5):537-46.
29. de Lima M, O'Brien S, Lerner S, Keating MJ. Chronic lymphocytic leukemia in the young patient. Semin Oncol. 1998;25(1):107-16.
30. Pamuk G, Pamuk O, Soysal T, Ongören S, Başlar Z, Ferhanoğlu B, et al. An overview of young CLL patients: a single-centre experience from Turkey. Haematologia (Budap). 2002;31(4):303-11.
31. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood. 1996;87(12):4990-7.
32. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999;17(12):3835-49.
33. Shanafelt TD, Witzig TE, Fink SR, Jenkins RB, Paternoster SF, Smoley SA, et al. Prospective evaluation of clonal evolution during long-term follow-up of patients with untreated early-stage chronic lymphocytic leukemia. J Clin Oncol. 2006;24(28):4634-41.
34. Moreira J, Rabe KG, Cerhan JR, Kay NE, Wilson JW, Call TG, et al. Infectious complications among individuals with clinical monoclonal B-cell lymphocytosis (MBL): a cohort study of newly diagnosed cases compared to controls. Leukemia. 2012;27(1):136-41.
35. Thurmes P, Call T, Slager S, Zent C, Jenkins G, Schwager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2008;49(1):49-56.
36. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12): 5446-56.
37. Therneau TM GP. Modeling Survival Data, Extending the Cox Model. Springer, New York, NY. 2000:274-5.
38. Therneau T OJ. Technical Report Number 63: Expected Survival Based on Hazard Rates. Technical Reports Rochester, MN: Mayo Clinic. 1999;1:26.
39. Rai K, Sawitsky A, Cronkite E, Chanana A, Levy R, Pasternack B. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-34.