Chronic lymphocytic leukemia in young individuals revisited

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The median age of patients at the time of diagnosis of chronic lymphocytic leukemia (CLL) is 71 years and the incidence of this hematologic malignancy increases steadily with age.[1] In studies from Europe and USA only 5%-11% of patients with CLL are younger than 50-55 years at diagnosis.[2,3] However, in view of the high incidence (4-5 cases per 100,000 inhabitants/year) and prevalence of CLL in Western countries, the absolute number of young patients with CLL is significant. Good knowledge of the factors associated with disease evolution and outcome of such patients is needed in order to be able to provide these patients appropriate management. Our knowledge of the clinical picture and behavior of CLL diagnosed at a young age does, however, come from studies conducted in the late 1980s[4,5] and 1990s,[6-9] a time when most biomarkers currently analyzed in CLL patients had not yet been discovered,[10-13] therapy was still based on alkylating agents,[14] and the role of allogeneic stem cell transplantation was not well established.[15]

In this issue of Haematologica, Parikh *et al.*[16] have reviewed the clinical and biological characteristics, and outcome of CLL patients diagnosed at ≤55 years of age. They compared the clinical and biological characteristics of 844 CLL patients ≤55 years, 55% of them with biomarkers available, with those of 2324 older patients followed-up at the Mayo Clinic from January 1995 to April 2012, and with the sex- and age-matched general population. To avoid a possible bias due to the inclusion of referred patients, the authors also compared the clinico-biological characteristics of young patients residing within 120 miles (193 Km) of the Mayo Clinic with those of patients who resided beyond this distance. For both groups of patients the median time from diagnosis to evaluation at the Mayo Clinic was ≤3 months.

In this study the gender distribution was similar in CLL patients ≤55 and >55 years, whereas a male predominance had been noted in previous analyses of young CLL patients[7,17] and in general series of CLL patients.[2,3] Patients ≤55 years old at diagnosis were more likely to be in intermediate Rai stage disease (Rai I and II) than were older patients (53% *versus* 37%, respectively). This feature was rarely detected previously[4] and should be confirmed in further studies. Additionally, young CLL patients more frequently had several adverse biological features such as unmutated *IGHV* (54% *versus* 45%), positivity for ZAP-70 (45% *versus* 38%), and higher values of clonal B cells. In contrast, young CLL patients had significantly higher values of hemoglobin, although this difference was clinically non-relevant, lower values of beta2-microglobulin, lower expression of CD49d, and better performance status. Finally, fluorescence *in situ* hybridization (FISH) risk category and CD38 expression by CLL cells did not differ according to age. The paradox of having simultaneously favorable and adverse risk features deserves further confirmation, even though some of these results could be associated with age-related factors (e.g. the lower incidence of renal failure in young patients would result in lower beta2-microglobulin concentration despite having a higher tumor burden). The higher frequency of intermediate Rai stages and of unmutated *IGHV* in young CLL patients was maintained when the analysis was restricted to local patients and when the patients were subdivided further by age (≤45, 46 to 50, and 51 to 55 years old). In keeping with this, the time to first treatment was shorter in younger patients. It could be argued that physicians looking after older ("slow go"[18]) patients may delay treatment initiation due to co-morbidities, impaired performance status or patients' desire. However, a multivariate analysis confirmed that Rai stage and *IGHV* mutation status rather than age accounted for this difference in time to first treatment. In summary, younger patients with CLL followed up at the Mayo Clinic had a significantly more aggressive and advanced disease at diagnosis and, importantly, this was not due to referral bias.

The long period of analysis and the observational nature of this study resulted in heterogeneity in the treatment given to patients. Moreover, young CLL patients were more likely than older patients to receive chemoimmunotherapy or purine analogs in monotherapy or in combination. Although the causes of the differential treatment applied to both groups of patients were not explored, the better performance status and the use of a treatment approach with curative intent in the subgroup of young patients could underlie the difference. In fact, the proportion of patients submitted to allogeneic transplantation was 14%, 5% and 1% for patients ≤45, 46 to 55, and >55 years old, respectively. Unfortunately, the authors did not provide information on response to treatment and outcome after treatment in these subgroups of young patients.

CLL patients ≤55 years old at diagnosis had a longer overall survival than older patients (12.5 years *versus* 9.5 years), even if the comparison was restricted to patients 56 to 65 year old. At the same time, no differences in overall survival were observed among age subgroups of young patients. As different treatment modalities were given according to age subgroups, an analysis of their impact on overall survival could have helped in the interpretation of the results. More importantly, the median overall survival of young CLL patients reported in this series was very similar to the median overall survival observed in some historical studies.[6,9] In addition, the overall survival of young CLL patients was clearly shorter than that of the general sex- and age-matched population. A median reduction of life expectancy for CLL patients <50 years of nearly 20 years compared with that of the general population was already reported 20 years ago.[9] Previous analyses showed that early clinical stage and other features associated with a favorable outcome (i.e. long lymphocyte doubling time, bone marrow patterns, smoldering CLL[19]) were able to identify young patients with a longer overall survival.[7-9] The present analysis showed that the same biological parameters reported to have an impact on outcome in non-selected CLL cohorts of patients (i.e. ZAP-70 and CD38 expression, *IGHV* mutational status and FISH cytogenetic

abnormalities) applied to patients ≤55 years, and that these factors retained their independent impact in this subgroup of patients individually stratified according to age, gender and Rai stage. In the study by Parikh *et al.*, the authors found that patients in Rai 0 stage with mutated *IGHV* genes or patients in Rai stage 0 with either 13q deletion or normal FISH had an overall survival comparable to that of the sex- and age-matched population. Indeed, the overall survival was significantly longer in young patients with no adverse factors (median overall survival not reached), one adverse factor (13 years), or two adverse factors (7.7 years). Bearing in mind that most young CLL patients die of their disease[7,17] and that their relative survival is definitely shortened, there is clear room for improvement in the therapeutic options for these patients.

In summary, Parikh *et al.*[16] reported the clinical and biological characteristics of the largest series of CLL patients ≤55 years old at diagnosis published so far and included for the first time the analysis of the biomarkers identified in the last 15 years. They showed that patients ≤55 years with CLL frequently had high-risk disease resulting in a shorter time to first treatment and a significantly reduced overall survival compared to that of a sex- and age-matched population. A comparison with historical series did not show a significant improvement in overall survival through the decades for this subgroup of patients. The authors, nevertheless, identified a subgroup of patients ≤55 years with good risk CLL who had an overall survival comparable to that of a sex- and age-matched population in the 10 years following diagnosis. A longer follow-up is required to confirm this comparable overall survival in the long-term because of the long life expectancy of individuals of this age. Furthermore, the retrospective nature of the study resulting in variable availability of biomarker data, heterogeneity in the treatment given to patients, and lack of information on recently described recurrent mutations in CLL necessitates additional studies that could improve the management of patients diagnosed with CLL at a young age.

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References

1. Ferrajoli A. Treatment of younger patients with chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:82-9.
2. http://seer.cancer.gov/statfacts/html/clyl.html.
3. Marcos-Gragera R, Allemani C, Tereanu C, De AR, Capocaccia R, Maynadie M, et al. Survival of European patients diagnosed with lymphoid neoplasms in 2000-2002: results of the HAEMACARE project. Haematologica. 2011;96(5):720-8.
4. 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.
5. 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.
6. 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.
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. Crespo M, Bosch F, Villamor N, Bellosillo B, Colomer D, Rozman M, et al. ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. N Engl J Med. 2003; 348(18):1764-75.
11. Damle RN, Wasil T, Fais F, Ghiotto F, Valetto A, Allen SL, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood. 1999;94(6):1840-7.
12. Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-6.
13. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6):1848-54.
14. Tefferi A, Phyliky RL. A clinical update on chronic lymphocytic leukemia. II. Critical analysis of current chemotherapeutic modalities. Mayo Clin Proc. 1992;67(5):457-61.
15. 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.
16. Parikh SA, Rabe KG, Kay NE, Call TG, Ding W, Schwager S et, al. Chronic lymphocytic leukemia in young (≤ 55 years) patients: a comprehensive analysis of prognostic factors and outcomes. Haematologica. 2014;99(1):140-47.
17. Pamuk GE, Pamuk ON, Soysal T, Ongoren S, Baslar Z, Ferhanoglu B, et al. An overview of young CLL patients: a single-centre experience from Turkey. Haematologia (Budap). 2002;31(4):303-11.
18. Hallek M. Chronic lymphocytic leukemia: 2013 update on diagnosis, risk stratification and treatment. Am J Hematol. 2013;88(9):803-16.
19. Montserrat E, Vinolas N, Reverter JC, Rozman C. Natural history of chronic lymphocytic leukemia: on the progression and progression and prognosis of early clinical stages. Nouv Rev Fr Hematol. 1988;30(5-6):359-61.

Bortezomib just for induction or also for maintenance in myeloma patients with renal impairment?

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In this issue of Haematologica Scheid *et al.* report on a prospective multicenter clinical trial conducted by the GMMG and Hovon groups which evaluated the prognostic role of renal impairment in patients with multiple myeloma treated with bortezomib before and after autologous stem cell transplantation.[1]