The benefit of population-based studies for older patients with acute myeloid leukemia

Ulrike Bacher and Torsten Haferlach

MLL Munich Leukemia Laboratory, Germany

E-mail: ulrike.bacher@mll.com *doi:10.3324/haematol.2012.080242*

Considering the unsatisfactory outcomes of elderly patients with acute myeloid leukemia (AML), the discussion on the best suitable therapeutic strategy in this subgroup continues. The past two decades demonstrated clearly that AML in older patients is characterized by adverse biological features such as frequent occurrence of multidrug resistance, a high frequency of unfavorable karyotypes,[1,2] and a higher frequency of molecular markers with an unfavorable impact, such as the intrageneic *RUNX1* mutations,[3] as compared to younger patients. The spectrum of recommended therapeutic strategies for this age group is wide ranging from intensive induction chemotherapy over hypomethylating agents or compounds such as clofarabine, to supportive therapy alone.[4]

In the present issue of *Haematologica*, Oran and Weisdorf[5] investigated 5,480 older patients who were diagnosed with AML from 2000-2007 in the US by use of the population-based SEER program database and Medicare files. A minimum 2-year follow up was guaranteed. Median age of patients was 78 years (range 65-93 years), approximately 45% of the patients had comoribidities, and 17.5% had a history of a previous myelodysplastic syndrome (MDS). Despite the limitations of the SEER database, this registry allows the investigation of a large and unselected older AML population in the US, irrespective of therapy. Due to the availability of new drug therapies and the development of reduced intensity conditioning (RIC) for allogeneic hematopoietic stem cell transplantation (HSCT), the authors had hypothesized that the poor prognosis of older AML patients reported in the 1990s might have improved during the last decade.

First, the study showed that survival was significantly improved in patients receiving leukemia treatment as compared to patients without leukemia therapy [median overall survival (OS), 6 *vs*. 2 months; $P<0.001$]. The difference in survival outcomes between patients with and without leukemia treatment was significant in all age groups under 80 years. However, it should be noted that a lower rate of leukemia therapy was associated with older age, higher comorbidity scores, and a previous MDS diagnosis. Compared to earlier studies from the literature, the percentage of older AML patients receiving leukemia therapy (38.4% in the present study) showed a slight increase over the last decade. Use of hypomethylating agents was less frequent (16.3% of patients) in the period of investigation as compared to use of induction chemotherapy (38.4% of patients). Hypomethylating treatment resulted in a median overall survival of nine months with only 18.7% early deaths (ED), which was considered to be encouraging. HLA-testing was performed in only 2.5% of all patients, and the proportion of patients receiving allogeneic HSCT was very low in the cohort (only 0.8% of patients). However, median survival in 46 patients with HSCT was 22 months which exceeded the survival outcomes of any other leukemia therapy in the study. Compared with the remaining patients, the HSCT recipients were significantly younger (median age 67 *vs*. 78 years; $P<0.001$) and had a lower comorbidity index. Strikingly, only 34.9% of patients had cytogenetics tested in the study cohort that demonstrates that this important prognostic parameter is less frequently evaluated in this age group than in younger patients.

Therefore, the population-based study of Oran and Weisdorf shows that survival of older AML patients is markedly prolonged with leukemia therapy, when possible, and that a subgroup of patients from this age group benefits from allogeneic HSCT. This is in line with a study from the Swedish Adult Acute Leukemia Registry analyzing outcomes of 506 treated and untreated AML patients aged 70-79 years. Survival outcomes were significantly better in regions where more elderly patients were considered eligible for remission induction, so the remission intention rate had a significant impact on the prognosis.[6] In contrast, Pulsoni *et al*. investigated 1,005 patients aged over 60 years registered in the database of the GIMEMA cooperative group and found survival outcomes by multivariate analysis to be dependent on parameters such as age, white blood cell count, and heart function, whereas the intensity of treatment (aggressive *vs*. non-aggressive) had no independent significant prognostic impact.[7] On behalf of the German Acute Myeloid Leukemia Cooperative Group, Krug *et al.* verified the association of standard clinical and laboratory variables with complete remission (CR) and early death (ED), and developed a web-based application for risk assessment of intensive chemotherapy in these patients. Multivariate regression analysis was used to develop risk scores for a cohort of 1,406 patients aged 60 years and over with AML, but otherwise medically healthy. Patients were treated with two courses of intensive induction chemotherapy. Risk prediction was validated in an independent cohort of 801 older patients with AML who were given two induction courses. Body temperature, age, *de novo* leukemia *versus* secondary or therapy-related AML, hemoglobin, platelet level, fibrinogen, and serum LDH (lactate dehydrogenase) were significantly associated with CR or ED. Therefore, Krug *et al.* suggested that these scores could be used to predict the probability of CR and the risk of ED in older patients with AML, but otherwise medically healthy, for whom intensive induction chemotherapy was planned.[8] In a study of elderly patients with AML and low marrow blast counts ranging from 20% to 30%, Fenaux *et al.* found azacitidine to be associated with a median overall survival of 24.5 months, which was superior to the 16 months in patients receiving conventional care regimens ($P=0.005$). Furthermore, azacitidine was associated with fewer total

©Ferrata Storti Foundation

days in hospital compared to conventional care regimens.[9]

With regards to allogeneic HSCT in elderly patients with AML, reduced intensity conditioning (RIC) was reported to achieve overall survival rates as high as 45-50% at two years, and can be beneficial even in advanced stages beyond CR1 in this age group.[10] Lübbert *et al.* described 15 consecutive patients with AML and MDS aged 60-75 years who received first-line treatment with decitabine and subsequent RIC-HSCT from sibling or unrelated donors. Fourteen of 15 patients achieved a CR with a median duration of five months. Six of these 14 patients were alive at the time of their report; of these 4 had complete donor chimerism.[11] These studies all demonstrate that, in principle, the option of leukemia therapy should be considered in most elderly patients with AML, taking parameters such as comorbidity, general performance status, or the cytogenetic or molecular risk profile into account for the final decision. They further demonstrate that for distinct subgroups of older AML patients, alternative approaches such as demethylating agents (e.g. in case of lower bone marrow blasts) or RIC-HSCT (e.g. in case of an adverse genetic risk profile of the AML but a good general performance status) should be further evaluated.

Population-based registries may provide data complementary to that from basic science and clinical intervention studies, and are, therefore, helpful for establishing recommendations for the management of patients in the "real" world. Registries with high coverage of the target population reduce the impact of selection on outcome and the subsequent problem with extrapolating data to non-studied populations. Therefore, data that can help clinical decision-making in situations that are not well covered by clinical studies can be provided.[12] The SEER database study from Oran and Weisdorf is a further step in this direction, as it shows the reality of performance and treatment outcomes of older patients with AML. It further confirms that the approach of leukemia therapy for elderly patients with AML is justified and can improve survival in this subgroup of patients. Furthermore, the article encourages hematologists to expand diagnostic approaches in older patients with AML, considering the strikingly low percentage of patients investigated by cytogenetics (and probably also molecular genetics, although this was not the issue of the study) at present in this age group.

Ulrike Bacher is a hematologist at the MLL Munich Leukemia Laboratory, Germany. She is fascinated by diagnostic techniques and is highly interested in the interaction of different laboratory methods in hematology. Torsten Haferlach is one of the co-founders of the MLL Munich Leukemia Laboratory. He is dedicated to the optimization of diagnostic workflows and fosters the introduction of novel diagnostic techniques (e.g. high-throughput sequencing) into hematologic diagnostics.

Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

References

1. Schoch C, Kern W, Krawitz P, Dugas M, Schnittger S, Haferlach T, et al. Dependence of age-specific incidence of acute myeloid leukemia on karyotype. Blood. 2001;98(12):3500.
2. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, et al. Age and acute myeloid leukemia. Blood. 2006;107(9):3481-5.
3. Mendler JH, Maharry K, Radmacher MD, Mrozek K, Becker H, Metzeler KH, et al. RUNX1 Mutations Are Associated With Poor Outcome in Younger and Older Patients With Cytogenetically Normal Acute Myeloid Leukemia and With Distinct Gene and MicroRNA Expression Signatures. J Clin Oncol. 2012;30(25):3109-18.
4. Schiffer CA. "I am older, not elderly," said the patient with acute myeloid leukemia. J Clin Oncol. 2010;28(4):521-3.
5. Oran B, and Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica 2012;97(12):1916-24.
6. Juliusson G, Billstrom R, Gruber A, Hellstrom-Lindberg E, Hoglunds M, Karlsson K, et al. Attitude towards remission induction for elderly patients with acute myeloid leukemia influences survival. Leukemia. 2006;20(1):42-7.
7. Pulsoni A, Pagano L, Latagliata R, Casini M, Cerri R, Crugnola M, et al. Survival of elderly patients with acute myeloid leukemia. Haematologica. 2004;89(3):296-302.
8. Krug U, Rollig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet. 2010;376(9757):2000-8.
9. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2010;28(4):562-9.
10. Niederwieser D, Lange T, Cross M, Basara N, Al-Ali H. Reduced intensity conditioning (RIC) haematopoietic cell transplants in elderly patients with AML. Best Pract Res Clin Haematol. 2006;19(4):825-38.
11. Lübbert M, Bertz H, Ruter B, Marks R, Claus R, Wasch R, et al. Non-intensive treatment with low-dose 5-aza-2'-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. Bone Marrow Transpl. 2009;44(9):585-8.
12. Juliusson G, Lazarevic V, Horstedt AS, Hagberg O, Hoglund M. Acute myeloid leukemia in the real world: why population-based registries are needed. Blood. 2012;119(17):3890-9.

©Ferrata Storti Foundation