Do older patients truly benefit from advances in myeloma care?

Moshe E. Gatt[1,2] and Eyal Lebel[1,2]
[1]Faculty of Medicine, The Hebrew University of Jerusalem and [2]Hematology Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Correspondence: M. Gatt
rmoshg@hadassah.org.il

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The survival of patients with multiple myeloma (MM) has increased dramatically during the last two decades, alongside the advent of novel anti-myeloma treatments and their incorporation into front-line therapy. Recent studies document a significant increase in the prevalence of MM, especially in the elderly,[1] highlighting the importance and relevance of real-world reports of this population. As the elderly population is regularly underrepresented in clinical trials, questions arise about whether the improved outcomes reported truly reflect the real-world situation, and whether the elderly population does indeed benefit from the advances seen in the field.

In their study, published in this issue of *Haematologica*, Moore *et al.*[2] not only present data from a very large Nordic registry of over 4,600 elderly patients (≥75 years) with MM, thus capturing close to 100% of the elderly, affected population of the two countries, but further compare their outcomes with those of younger patients, and with parallel data from key clinical trials.

The authors highlighted differences in baseline parameters between younger and older patients, with higher International Staging System (ISS) stage and higher frequency of anemia and kidney dysfunction in the elderly. Overall, and not surprisingly, older age was confirmed as a predictor of worse outcome. However, the analysis confirmed that survival has improved significantly over time also among older patients. The population-based design of this study enabled the assessment of relative survival rates as opposed to overall survival, taking into account competing causes of mortality. The improved relative survival over time among the older patients points to better myeloma care as a key contributing factor, and rules out the general improved survival of the whole population as the sole explanation. This improvement in survival coincided with a dramatic increase in the use of novel agents, and with improved response rates achieved with these agents. Moreover, the observed benefit in relative survival was greater for the older patients than for the younger ones. Even in the octogenarians, although mortality rates remained relatively high, a net survival benefit was observed, highlighting that age itself is not a reason to withhold treatment with novel agents.

Compared with key clinical trials in transplant-ineligible patients (i.e., a relatively older population), the population-based study by Moore *et al.* included a larger proportion of patients ≥75 years, and a higher frequency of those with advanced ISS stage. These differences limit the external validity of key clinical trials, and myeloma physicians as well as health care authorities should be aware of them. An analysis of the relative importance of different outcome predictors in different ages confirmed notable differences between younger and older patients.[3] In younger patients cytogenetic risk had more influence on survival, while in older patients the effect of cytogenetics on outcome was considerably weaker.

Specifically, while 17p deletion was associated with adverse prognosis in patients of all ages, t(4:14) and 1q gain were associated with adverse outcomes only in younger patients. On the other hand, ISS stage was a stronger predictor in older patients than in younger ones.

Performance status commonly predicted survival at all ages, suggesting that physical frailty rather than numerical age is more predictive of outcome. In view of this observation, it is less surprising that age ≥70 years was not associated with worse outcomes in MM patients who underwent autologous transplant, as long as melphalan 200 mg/m^2 was given, as shown in a large report from the Center for International Blood and Marrow Transplant Research (CIBMTR).[4] This observation probably reflects the fitness of older patients who were judged to be eligible for this therapy, and highlights the importance of comprehensive assessments of function and frailty.

Recent studies confirmed that frailty status is predictive of outcomes,[5] can be objectively assessed using validated scoring systems, and can influence treatment decision-making.[6] Puyade *et al.* described major age-related disparities in adherence to guidelines,[7] and concluded that older patients are less likely to undergo all necessary diagnostic procedures and to receive adequate therapy in accordance with guidelines. These conclusions are complex to interpret considering, as discussed above, that the validity of guidelines for the older population is uncertain, given the underrepresentation of this group in clinical trials. Taken together, it is poss-

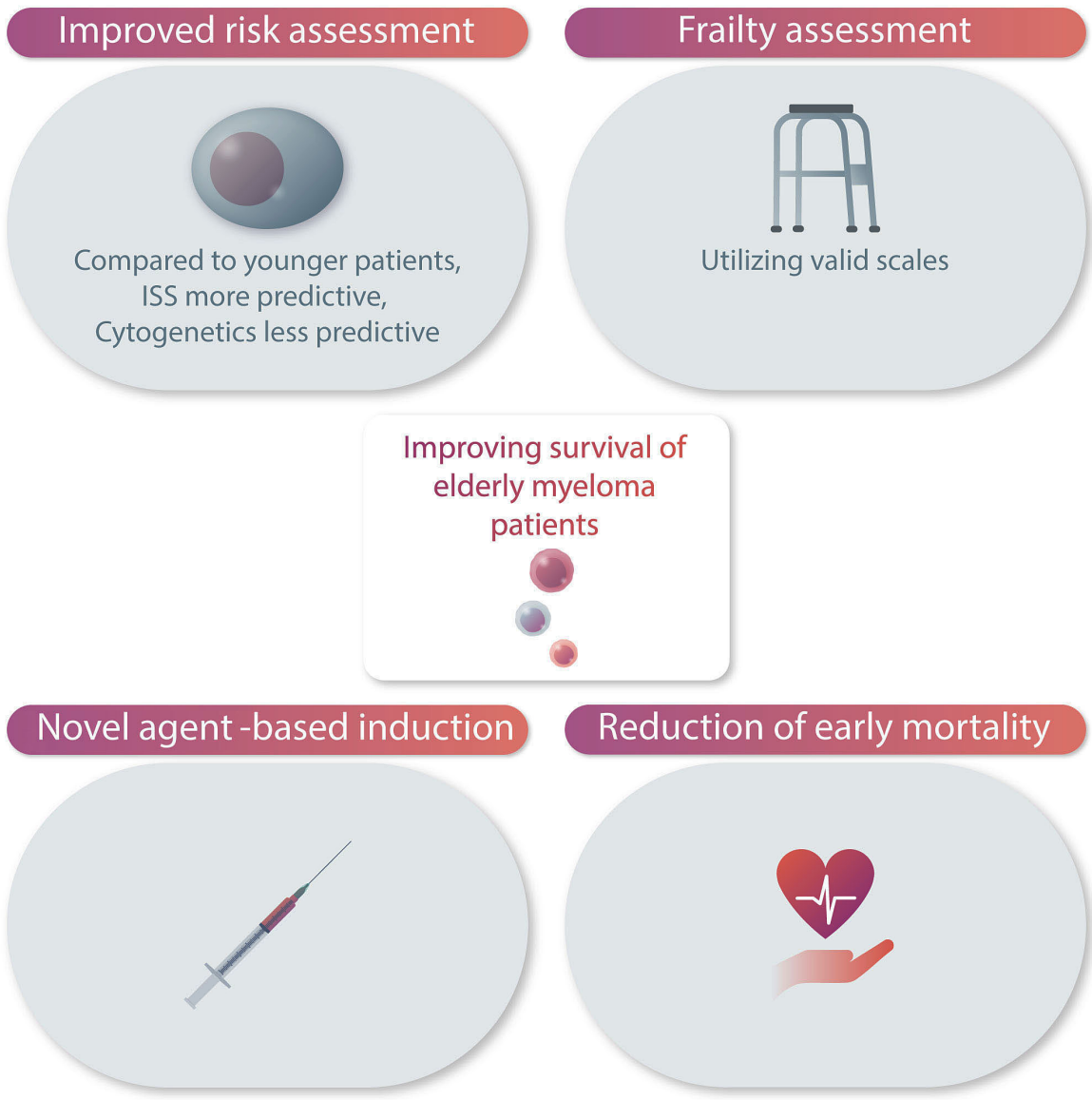

Figure 1. Suggested steps to improve survival of older patients with multiple myeloma. ISS: International Staging System.

ible that the excess mortality in older patients may be partially explained by underutilization of novel agents, as well as limited assessments of frailty, leading to suboptimal selection of older patients for front-line regimens of various intensities.

Last, but not least, in this Nordic population study, Moore *et al.* found that despite more effective treatment, and the decline if not disappearance of conventional chemotherapy from usage, early mortality has not decreased in older patients, and remains strikingly high.[2] As expected, age is an established predictor of early mortality in many cancers, including MM. However, the incorporation of novel agents was consistently associated with a lower risk of early mortality.[8] This finding should highlight the importance of close monitoring of older patients, as well as consideration of dose reduction (particularly of steroids), in order to reduce infection rates and mortality.[9]

In conclusion, older patients ≥75 years, accounting for about 40% of all patients with MM, do indeed benefit from the recent advances in the field, as they more often nowadays receive novel agents, achieve deeper responses and survive longer. However, there are still gaps (highlighted in Figure 1) in the incorporation of better assessments of fitness and frailty, adherence to guidelines, understanding of the relative importance of different risk factors and, most importantly, in the critical need for early reduction in the mortality rate.

Disclosures

No conflicts of interest to disclose.

References

1. Turesson I, Bjorkholm M, Blimark CH, Kristinsson S, Velez R, Landgren O. Rapidly changing myeloma epidemiology in the general population: increased incidence, older patients, and longer survival. Eur J Haematol. 2018;101(2):237-244.
2. Moore KLF, Turesson I, Genell A, et al. Improved survival in myeloma patients–a nationwide registry study of 4,647 patients ≥75 years treated in Denmark and Sweden. Haematologica. 2023;108(6):1640-1651.
3. Pawlyn C, Cairns D, Kaiser M, et al. The relative importance of factors predicting outcome for myeloma patients at different ages: results from 3894 patients in the Myeloma XI trial. Leukemia. 2020;34(2):604-612.
4. Munshi PN, Vesole D, Jurczyszyn A, et al. Age no bar: a CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma. Cancer. 2020;126(23):5077-5087.

5. Patel BG, Luo S, Wildes TM, Sanfilippo KM. Frailty in older adults with multiple myeloma: a study of vs veterans. JCO Clin Cancer Inform. 2020;4:117-127.
6. Grant SJ, Freeman CL, Rosko AE. Treatment of older adult or frail patients with multiple myeloma. Hematology Am Soc Hematol Educ Program. 2021;2021(1):46-54.
7. Puyade M, Defossez G, Guilhot F, Leleu X, Ingrand P. Age-related health care disparities in multiple myeloma. Hematol Oncol. 2018;36(1):224-231.
8. Galli M, Paris L, Pavoni C, Delaini F, Rambaldi A. Effect of novel agents on the risk of early death of newly diagnosed symptomatic multiple myeloma patients: a single centre retrospective analysis. Am J Hematol. 2019;94(1):E11-E13.
9. Diamond E, Lahoud OB, Landau H. Managing multiple myeloma in elderly patients. Leuk Lymphoma. 2018;59(6):1300-1311.