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Do older patients truly benefit from advances in myeloma care?

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The survival of patients with multiple myeloma (MM) has increased dramatically during the last two decades, alongside with the advent of novel anti-myeloma treatments and their incorporation into the frontline therapy. Recent studies report 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 whether the improved outcomes reported are truly reflecting real-world data, and whether this elderly population benefits as well from the advances seen in the field.

In their study, Moore et al [2] not only present data on a very large Nordic registry of over 4600 elderly patients (≥ 75 years), thus capturing close to 100% of the population of two countries, but further compare their outcomes with younger patients, and with parallel data from key clinical trials.

The authors highlighted differences in baseline parameters between younger and older patients, with higher ISS 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 does confirm that survival has significantly increased over time also among older patients. The population-based design of this study has enabled the assessment of relative survival rates as opposed to overall survival, taking into account competing mortality causes. 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, this observed benefit in terms of relative survival was larger for the older compared with younger patients. Even in the octogenarians, while mortality rates remain relatively high, a net survival benefit was observed, highlighting that age by itself is not a reason to withhold treatment with novel agents.

Compared with key clinical trials in the transplant ineligible population (i.e., a relatively older population), this population-based study reports a higher proportion of patients ≥ 75 years, and a higher frequency of advanced international scoring system (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 the cytogenetic risk had more influence on survival, while in older patients the effect of outcome was considerably weaker.

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

Performance status commonly predicted survival at all ages, suggesting that physical frailty rather than the numerical age is more predictive of outcome. In view of the latter observation, it is less surprising that age of ≥ 70 years was not associated with worse outcomes in MM patients who underwent autologous transplant in a large report of the Center for International Blood and Marrow Transplant Research (CIBMTR), as long as melphalan 200mg/m² was given [4]. This observation probably reflects the fitness of older patients who were judged to be eligible for this therapy, and highlights the importance of a comprehensive functional and frailty assessments.

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 age-related major 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 more 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 possible that the excess mortality in older patients may be partially explained by underutilization of novel agents, as well as incomprehensive assessments of frailty, leading to suboptimal selection of older patients to frontline regimens of various intensities.

Last but not least, in this Nordic population study, Moore et al. have found that despite more effective treatment, and the decline if not disappearance of conventional chemotherapy from usage, early mortality has not decreased in the older patients, and remained 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 lower risk for 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

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 of early reduction in the mortality rate.

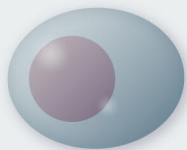
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Figure legend:

Figure 1- Suggested steps to improve survival of older patients with multiple myeloma

Improved risk assessment



Compared to younger patients,
ISS more predictive,
Cytogenetics less predictive

Frailty assessment



Utilizing valid scales

Improving survival of
elderly myeloma
patients



Novel agents'-based induction



Reduction of early mortality

