Frailty in multiple myeloma: the need for harmony to prevent doing harm

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In the last decade, an extended treatment armamentarium has led to an impressive improvement in the prognosis of older patients with multiple myeloma (MM) ineligible for autologous stem-cell transplantation. The extent by which however, is less than compared to younger patients, probably due to biological aging. Aging is characterized by a progressive loss of physiological reserve, leading to impaired organ function, of which frailty is the phenotype.[1] In frail MM patients, anti-MM drugs cause more side effects and subsequent discontinuation of therapy, with a negative impact on outcome.[2] The International Myeloma Working Group (IMWG) developed an index to identify frail patients with inferior overall survival (OS) and progression-free survival (PFS), higher incidence of grade III-IV non-hematological toxicity and discontinuation rate. The score is based on age (≤75, 76-80 or >80 years), the Charlson Comorbidity Index (≤1 or >1), the Activities of Daily Living (ADL, >4 or ≤4) and instrumental ADL (IADL, >5 or ≤5) and has been validated in a separate cohort of patients.[3,4] Patients who were defined frail using the IMWG frailty index, have more functional impairments and loss of muscle mass compared to non-frail patients, indicating that the index reflects biological frailty indeed.[5]

However, data on ADL/IADL are lacking in many studies, which precludes validation of the IMWG frailty score in clinical trials and in population-based registries. Therefore, Cook and colleagues made an important effort to create an easy-to-define prediction model for outcome and treatment feasibility, including the largest patient cohort analyzed so far in MM. The model consists of World Health Organization performance status (PS), International Staging System, age and C-reactive protein concentration and defined three risk groups (low, intermediate and high) with a 35-month difference in median OS between the low- (60 months) and high-risk group (25 months). In addition, the model predicted PFS, early mortality and treatment compliance. Importantly, the prognostic value of this model was independent of treatment and cytogenetic risk profile. Because these parameters are available in the majority of studies, comparisons of the outcome of frail patients using different treatment regimens are now possible and pave the way for frailty-adapted treatment.[6]

Yet, this score does not necessarily reflects frailty as originally defined by Fried et al, namely based on the presence of at least 3 of 5 criteria: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.[7] In fact, PS reflects the physical activity of patients, however the assessment is made by physicians and it does not provide functional data and it has been reported that PS score did not reflect objective physical activity levels.[8] In addition, CRP, being produced by senescent cells, has been described as a parameter of 'inflammaging', however, with low specificity.[1]

Unfortunately, the authors did not compare their score with the current gold standard, the IMWG frailty score. Therefore, it is unknown whether both scores are equal in discriminating outcome, and whether they identify an identical frail population who would benefit less from treatment.[3]

That brings us to the main issue of defining older patients who will not benefit from treatment and who might even experience early mortality due to treatment. Although frailty is generally perceived as the underlying cause, there is currently no uniform definition of frailty in clinical practice. In addition, the discriminative power of current scores is still insufficient to select patients who are suitable for therapy or in whom benefit will be negligible, leading to the decision not to start treatment. Therefore, further improvement of a frailty score is of critical importance.

Of note the value of a frailty score might be dependent on the treatment, as novel treatments, including immune-therapy, could overcome the negative impact of frailty on the clinical outcome. Indeed, a recent trial evaluating bortezomib-melphalan-prednisone with or without the monoclonal antibody daratumumab found no difference in outcome between patients over 75 and below 75 years of age. However, the IMWG frailty score was not performed in that study and thus it is difficult to draw conclusions.[9] Preliminary data in IMWG-defined frail patients do support feasibility of ixazomib and daratumumab in unfit and frail patients.[10]

Cook et al. provided an easy-to-use prognostic risk model. Like others, they did not only implement patient- but also disease-characteristics, known to increase the discriminative power. It is clear that, in order to guide physicians in the treatment of older MM patients, the different frailty scores should be further improved and harmonized. This will allow to compare outcome of frail patients and to develop novel, effective and feasible treatment regimens. As frailty is a consequence of biological aging, it would be interesting to explore the added value of biomarkers for aging.[1]

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