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

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In the past decade, an expanded treatment armamentarium has led to impressive improvements in the prognosis of older patients with multiple myeloma who are ineligible for autologous stem-cell transplantation. The extent of this improvement however, is more notable in younger patients than in older patients, probably because of biological ageing. Ageing is characterised by a progressive loss of physiological reserves leading to impaired organ function, of which frailty is the phenotype.[1] In frail patients with multiple myeloma, drugs cause more adverse events than in non-frail patients, sometimes leading to discontinuation of therapy, with a negative effect on outcome.[2] The International Myeloma Working Group (IMWG) has developed an index to identify frail patients who might have worse overall survival and progression-free survival, increased incidence of grade III–IV non-haematological toxicity, and discontinuation rate. The score is based on age (≤75 years, 76–80 years, 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 defined as frail with the IMWG frailty index have greater functional impairments and loss of muscle mass than non-frail patients, indicating that the index reflects biological frailty.[5]

However, data about ADL and IADL are absent in many studies, which precludes validation of the IMWG frailty score in clinical trials and in population-based registries. Therefore, the study by Gordon Cook and colleagues[6] in *The Lancet Haematology* represents an important effort to create an easy-to-define prediction model for outcome and treatment feasibility, in the largest patient cohort analysed so far in multiple myeloma. The model consists of WHO performance status, International Staging System, age, and C-reactive protein (CRP) concentration and defines three risk groups (low, intermediate, and high), with a 35-month difference in median overall survival between the low-risk (60 months) and high-risk group (25 months). Additionally, the model predicted progression-free survival, early mortality, and treatment compliance in the datasets analysed. Importantly, the prognostic value of this model was independent of treatment and cytogenetic risk profile. Because these data are available in most studies, comparisons of the outcome of frail patients with different treatment regimens are now possible and could pave the way for frailty-adapted treatment.[6]

Yet, this score does not necessarily reflect frailty as originally defined by Fried and colleagues, based on the presence of at least three of five criteria: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity.[7] Although performance status indicates the average daily physical activity of patients, this assessment is made by physicians, not by patients. Accordingly, it has been reported that performance status does not reflect objective levels of physical activity. Additionally, it does not provide functional data.[8] Furthermore, CRP, which is produced by senescent cells, has been described as a variable related to the chronic inflammation associated with ageing (so-called inflammaging), albeit 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 outcomes, 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 because of treatment. Although frailty is generally perceived as the underlying cause, there is currently no uniform definition of frailty in clinical practice. Additionally, 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 importance.

Notably, the value of a frailty score might be dependent on treatment, as novel treatments, including immune therapy, could overcome the negative effect of frailty on the clinical outcome. Indeed, a recent trial investigating bortezomib plus melphalan plus prednisone with or without the monoclonal antibody

daratumumab found no difference in outcome between patients aged 75 years and older and those younger than 75 years. However, the IMWG frailty score was not used in that study and drawing conclusions is therefore difficult.[9] Preliminary data from IMWG-defined frail patients do support the feasibility of ixazomib and daratumumab in unfit and frail patients.[10]

Cook and colleagues have provided an easy-to-use prognostic risk model. In the same way as others, they not only implemented patient characteristics but also disease characteristics, which are known to increase discriminative power. In order to guide physicians in the treatment of older patients with multiple myeloma, the different frailty scores should be further improved and harmonised. This will allow comparisons of outcomes of frail patients and development of novel, effective, and feasible treatment regimens. As frailty is a consequence of biological ageing, it would be useful to explore the added value of biomarkers for ageing.[1]

Sonja Zweegman, Alessandra Larocca
Department of Haematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands (SZ); and Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy (AL)
s.zweegman@vumc.nl

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