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Elderly patients with multiple myeloma: towards a frailty approach?

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Purpose of review
To describe how to better identify frail multiple myeloma patients and to treat them appropriately.

Recent findings
Proteasome inhibitors, such as bortezomib, carfilzomib, and ixazomib, and immunomodulatory agents (IMiDs), such as thalidomide, lenalidomide, and pomalidomide, have significantly improved the outcome of multiple myeloma patients in the last decade. However, both in clinical trials and in daily clinical practice, elderly multiple myeloma patients have shown lesser benefit. This is mainly due to less stringent use of proteasome inhibitors and IMiDs, increased toxicity, and subsequent early discontinuation of therapy in elderly.

Summary
Multiple myeloma typically affects elderly patients. Approximately one-third of patients are older than 75 years at diagnosis. Moreover, at least 30% are frail, both due to disease-related symptoms and (agerelated) decline in physical capacity, presence of comorbidities, frailty, polypharmacy, nutritional status, and cognitive impairment. Treatment regimens that are investigated in clinical trials for transplant-ineligible patients have largely been investigated in fit, rather than frail patients, the latter being typically excluded or highly underrepresented therein. Data on the feasibility and efficacy of current standards of care are therefore lacking in frail patients. Preliminary data suggest a higher toxicity and discontinuation rate, loss of efficacy, and impaired quality of life in frail patients. Geriatric assessment helps to identify frail patients according to their functional and cognitive status. Both the International Myeloma Working Group (IMWG)- frailty index and Revised Myeloma Comorbidity Index constitute recently proposed algorithms that easily identify intermediate-fit and frail patients. Ongoing and future clinical trials, specifically designed for frail patients, will hopefully define frailty-directed treatment selection.

INTRODUCTION

The introduction of proteasome inhibitors and IMiDs combined with standard chemotherapy, has changed the management of multiple myeloma patients and has substantially extended both progression- free survival (PFS) and overall survival (OS), also in elderly patients [1]. However, the added value of proteasome inhibitors and IMiDs are generally less pronounced in the oldest patients more than 75 years of age, as has been shown in several clinical trials as well as population based registries (PBR) [2–4].

These data are highly relevant, because the global population is rapidly aging in all European countries. Particularly the population aged more than 80 years is expected to rise to almost triple [5]. The elderly population is highly heterogeneous, consisting of fit, intermediate-fit and frail patients. Geriatric impairment is prevalent in elderly patients, may not be easily detectable, but impacts patients' ability to complete treatment. Identification of such impairment is important, as omitting geriatric assessment will result in the fact that intermediate- fit and frail patients receive regimens that were initially tested in fit patients. This may cause substantial toxicity, early treatment discontinuation, lower efficacy, and impaired quality of life (QoL) [6]. The aim of this review is to clarify how to better categorize older multiple myeloma patients, thereby identifying fit, intermediate-fit and frail cohorts and to treat them appropriately based on current available knowledge.

Elderly patients more than 75 years of age have been shown to benefit from anti-multiple myeloma treatment; however, the benefit was less pronounced than in patients aged less than 75 years

Multiple myeloma accounts for 1% of all types of cancer and for 2% of all cancer deaths. These numbers represent approximately 13% of all hematological malignancies, and 20% of hematological malignancy-related deaths [4,7]. Multiple myeloma is a disease of the elderly reflected by a median age at diagnosis of approximately 70 years, with 35–40% of patients being older than 75 years [8]. For the past 10 years, the prognosis of elderly patients has improved due to the introduction and use of IMiDs (thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib and recently the oral proteasome inhibitor ixazomib). In first-line treatment of transplantineligible patients, the addition of bortezomib to melphalan and prednisone (VMP) improved both PFS and OS, as compared to melphalan and prednisone alone, therefore VMP advanced to one standard of care in Europe [9,10]. Accordingly, the addition of thalidomide to melphalan and prednisone (MPT) resulted in superior PFS and OS as compared to melphalan and prednisone [11]. Recently, the results from the FIRST-trial showed superiority of lenalidomide/dexamethasone over MPT both with respect to PFS and OS [12]. Importantly, VMP and lenalidomide/dexamethasone result in a median OS of almost 5 years. When assessing patients at least 75 years of age, elderly patients were also found to benefit from VMP and lenalidomide/ dexamethasone, although this benefit was less pronounced than in patients less than 75 years. The median OS with VMP was 43.3 months vs. not reached in patients 75 or older and less than 75 years, respectively [13]. Likewise, the median OS with lenalidomide/dexamethasone was 52.3 vs. 60.9 months in patients 75 or older and 75 years or less, respectively [3].

Also in PBR, reflecting real life, the eldest patients appear to benefit less: both in Italian and Dutch PBR, the OS of older patients at least 75 years was found to be similar over time, without an improvement in OS after the introduction of IMiDs and proteasome inhibitors after 2006 [4] (Verelst, personal communication). This lack of improvement does not seem to be explained by a biologically different, more aggressive disease in the elderly. Although data on cytogenetic analyses in the elderly patients are generally scarce [14] and differences in cytogenetic abnormalities have been observed between younger and older patients [15], there is currently no evidence of a higher incidence of biologically high-risk disease in the latter. The French Intergroupe Francophone du Mye´lome (IFM) showed that the incidence of t(4;14) was even decreased in patients more than 75 vs. 66–74 and 65 years or less with 8.3, 10.9, and 14.3%, respectively. The incidence of del17p was

similar in patients more than 75 vs. 66–74 and less than 65 years with 6.1, 5.9, and 6%, respectively. Data on del1p and ampl1q were not available [16]. In addition, no increase in the percentage of prognostic adverse hypermethylation of the tumor modulating genes GPX3, RBP1, SPARC, and TGFBI was found with age [17].
The lesser benefit of treatment in the very elderly might be better explained by the fact that in general practice the majority of elderly patients do either not receive therapy, or therapy is given but without the addition of proteasome inhibitors or IMiDs or with a lower dose of novel agents [18]. That this fact at least partly explains the difference in outcome between clinical trial and PBR is, indeed, supported by several observations showing that if novel therapy is given to the elderly outside of clinical trials, there is an increase in OS, even in the oldest patients. Data analysis of elderly patients actually receiving lenalidomide and/or bortezomib from the Mayo Clinic (89% of all patients used novel agents during the time period 2006–2010 vs. 29% in the period 2001–2005) showed an increase in OS over time, specifically in those aged over 65 years (median OS 5 vs. 3.2 years). Improved survival was also seen in those over 75 years of age [19,20]. Of course such data analyses are biased by the fact that the reasons for either or no treatment are unknown; however, these data indicate that at least a subgroup of elderly patients benefit from novel therapies. The challenge therefore is to determine who will benefit from therapy, as the higher incidence of organ dysfunction, leading to toxic effects of standard treatment regimens requiring treatment discontinuation probably negatively affects the benefit of treatment and might even be deleterious. Indeed, a meta-analysis of 1435 patients at least 65 years treated in four European clinical trials showed that the risk of death was increased in patients at least 75 years, in patients with renal failure, in those who experienced grade 3–4 infections, cardiac or gastrointestinal adverse events during treatment and in those who required drug discontinuationdue to adverse events. This increased risk was restricted to the first 6 months after occurrence of adverse events or drug discontinuation and declined over time [6]. This supports the need for tailored personalized medicine in elderly patients.

Are there tools available to define the subpopulation of elderly multiple myeloma patients who will benefit from treatment?

Since there is an urgent need to determine in whom effective antimyeloma therapy is feasible and in whom treatment will not only fail but might even compromise patients' QoL, comprehensive geriatric assessment (CGA) tools have been used to identify patients' general health status, including functional, cognitive, social, nutritional, and psychological parameters. These have been found to predict OS and adverse events during chemotherapy [21,22]. However, extensive data on the value of CGA in multiple myeloma patients are as yet incommensurate. Recently, the International Myeloma Working Group (IMWG) retrospectively assessed the IMWGfrailty index. This index is based on age (_75, 75–80, >80 years, score 0, 1, 2, respectively), Charlson Comorbidity Index (CCI; _1 or _2, score 0 or 1) and (Instrumental) Activities Daily Life score (ADL >4 or _4, score 0 or 1, instrumental activities of daily living (IADL) >5 or _5, score 0 or 1), and was found to predict nonhematological toxicity in 869 patients at least 65 years treated within three randomized clinical trials. Frail patients (score _2) had a 1.8 times higher discontinuation rate as compared to fit patients (score 0). In a multivariate analysis frailty [hazard ratio (HR) 1.64, 1.24–2.17], ISS III (HR 1.49, 1.17–1.89) and high-risk cytogenetics by fluorescence in situ hybridization analysis defined as del17p, t(4;14) or t(14;16) (HR 1.75, 1.38–2.22) equally predicted PFS, whereas for OS, the HR increased most with frailty (HR 3.11, 1.97–4.90) as compared to ISS III (1.77, 1.26–2.63 and high-risk cytogenetics (1.83, 1.26–2.63) [23&]. Importantly, in patients less than 75 years, frail and intermediate-fit patients were found in 17 and 44%, respectively, revealing that comorbidities also occur in 'younger' cohorts and suggesting that frailty scores are of added value to patients' numerical age. The IMWG-frailty index has been validated in the IMF FIRST-trial comparing lenalidomide/dexamethasone continuously, lenalidomide/dexamethasone for 18 and MPT for 12 cycles. However, as the investigators did not assess the ADL and IADL, they used the

EQ5D instead and confirmed an inferior outcome in frail vs. fit patients: the median PFS was 20.3 vs. 43.7 months and median OS 52.3 months vs. not reached, respectively [23&]. Additional preliminary analyses from a Dutch HOVON study also support the prognostic value of the IMWG-frailty index [24,25&].

The most extensive prospective validation of the IMWG-frailty index was performed by Engelhardt et al. in a German cohort of newly diagnosed multiple myeloma patients. Moreover, the IMWG-frailty index was compared with the Revised Myeloma Comorbidity Index (R-MCI) and other well known other comorbidity indices, such as CCI, Hematopoietic- Cell-Transplantation Comorbidity Index, and Kaplan Feinstein Index (KFI). Validation of the IMWG-frailty index in this prospective cohort demonstrated a 3-year-OS of 91%, 77% and 47% for fit, intermediate-fit and frail patients, respectively. The CCI, Hematopoietic-Cell-Transplantation Comorbidity Index, Kaplan Feinstein Index and the RCMI also defined fit and frail patients with distinct PFS and OS. The most pronounced differences in PFS and OS were found using the IMWG-frailty indes, CCI and R-MCI. As the CCI is included in the IMWG-frailty index, the latter and R-MCI were proposed for future frailty measurements, which is ongoing in a joint European Myeloma Network collaboration [26&&]. Subsequently, the value of the R-MCI was shown in 801 consecutive German multiple myeloma patients, this cohort being examined within a training and validation set. As multivariate analysis had determined renal, lung, Karnofsky performance Status (KPS) impairment, frailty, and age as independent risk factors for OS and high-risk cytogenetics to complement this R-MCI, these parameters were included in the weighted R-MCI, allowing identification of fit [R-MCI 1–3 (n¼247, 30.8%)], intermediate- fit [R-MCI 4–6 (n¼446, 55.7%)], and frail patients [R-MCI 7–9 (n¼108, 13.5%)]: these subgroups showed median OS rates of 10.1, 4.4, and 1.2 years, respectively. Advantages of the R-MCI are its accurate assessment of patients' physical conditions and simple clinical applicability [27&&]. Both the IMWG-frailty index and R-MCI have demonstrated validity as straightforward prognostic instruments in large clinical studies and patients cohorts treated according to current standards. As determination of comorbidity, frailty, and disability evaluation in multiple myeloma can be time-consuming, both the IMWG-frailty index and the R-MCI have been implemented within web-based technology applications, which allows to perform the scores expeditiously (http://195.88.6.191/Frailtyscore/Geriatric. asp andwww.myelomacomorbidityindex.org). These data showing the association between the IMWG-frailty score and R-MCI with clinical outcome underscore the importance of CGAs in the identification of intermediate-fit and frail patients. However, as treatment has not been modified according to the comorbidity index results, the next step is to include these indexes in prospective randomized clinical studies designed to adapt the therapeutic approaches.

Furthermore, it is important to investigate whether current indexes can be improved further. In both the Dutch HOVON study and German studies the value of objectively measured functional geriatric assessments, such as gait speed, handgrip strength, 'Timed Up and Go'-test, physicians' and patients' rating of fitness and others, are determined. In addition, more detailed information on nutrition and mental status are currently investigated. Finally, the value of biomarkers reflecting biological age, such as the senescence marker p16INK4a [28] and sarcopenia are explored [24,25&].

How to treat elderly multiple myeloma patients in clinical practice?

There is evidence, that in patients at least 65 years, and especially in those at least 75 years, the toxicity of antimyeloma treatment and subsequently the discontinuation rate is higher, negatively affecting outcome. On the other hand, as described above, increasing treatment possibilities paved the way for improving the outcome also of elderly multiple myeloma patients. Given the first data on the predictive value of geriatric scores to define fit, intermediate- fit, and frail patients determined by simple geriatric assessment and scores (e.g. IMWG-frailty index, R-MCI), these should be implemented in clinical practice. As yet, there are no RCT results available that prospectively investigate the clinical outcome with and without antimyeloma treatment adaptions

according to these assessments. The UK MRC, IFM, HOVON, and German DSMM study groups will or have already initiated studies based on the outcome of the IMWG-frailty index and R-MCI. Awaiting the result of these studies, based on the results of the Italian, French, German and Spanish clinical trials in which also patients more than 75 and patients more than 80 years of age (by definition intermediate-fit and frail, respectively, according to the IMWG-frailty index) were included and from preliminary data of the HOVON 123 study trial, practical guidelines can already be given (Table 1) [3,6,8,13,29&&,30–33]. Concerning VMP, the PETHEMA study group investigated a 'VMP light regime' with 5 cycles of once-weekly dosing of bortezomib following the first cycle of twice-weekly dosing, followed by 3 years of maintenance with bortezomib (either in combination with prednisone or thalidomide) [2,33]. The GIMEMA study group investigated bortezomib maintenance every 2 weeks, in combination with thalidomide, for 2 years following induction with an intense VMPT induction [30]. From the PETHEMA GEM05 study, it can be concluded that a limited, less intense induction, followed by maintenance, results in a comparable OS of 61.3 months vs. 61 months, respectively (even though being no head-to-head comparison). Moreover, toxicity was limited allowing a higher cumulative dose of bortezomib. The incidence of severe peripheral neuropathy (PNP) was significantly reduced from 14% in VISTA to 7%. Accordingly, the discontinuation rate due to SAEs was lower as compared to VISTA (17% vs. 34%) [2,33]. From the GIMEMA MM03-05 study, it was concluded that maintenance with bortezomib was feasible; during maintenance: only 4% of patients developed grade 3 PNP, and no grade 4 PNP was reported [30]. Preliminary results from the HOVON 123 trial showed that in frail patients, nine cycles of adjusted VMP were feasible in only 54%; however, six cycles were achieved in 69%. Moreover, overall response and VGPR or better were comparable after six and nine cycles [25&]. In view of these results a shorter induction therapy followed by maintenance therapy is an attractive alternative in frail patients, in order to not only make antimyeloma therapy feasible but also maintain its efficacy.

Concerning lenalidomide/dexamethasone, Hulin et al. [3] showed that by decreasing the dose of dexamethasone from 40 to 20 mg/week, lenalidomide/ dexamethasone was well tolerated without additional toxicity in patients more than 75 years of age. The treatment duration, exposure for more than 2 years and discontinuation rate in patients 75 or less and more than 75 years were comparable with 20 vs. 24 months, 35 vs. 41% and 26 vs. 21%, respectively [3].

CONCLUSION

The growing number of elderly multiple myeloma patients is increasing and thereby the need for practical strategies to recognize and appropriately manage frail patients. The efficacy and safety results suggest that full-dose can be applied in fit patients, whereas reduced therapy is preferred in frail patients (Table 1). Awaiting the results of clinical trials specifically designed for intermediate-fit and frail patients, practical guidelines have been published that can be used to personalize therapy in elderly patients [7,8]. In order to realize continuation of treatment by minimizing toxicity, we propose the algorithm that is deduced from these guidelines and from myeloma expert opinions (Table 1) [7,34].

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& of special interest
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Table 1. Patient-frailty index and frailty index-defined risk factor assessment via International Myeloma Working Group-frailty index and Revised Myeloma Comorbidity Index, suggesting consideration of treatment adjustment based on patient fitness

Patient risk factors				
Age >75 years				
Mild, moderately, or severely frail (patients who need help with either household tasks, personal care, or are completely dependent)				
Comorbidities (pulmonary, renal, cardiac, and hepatic dysfunction) And/or Preferably with (a) IMWG-frailty index[1] and/or (b) R-MCI[2] define fit, intermediate-fit, and frail patients, in order to consider to adapt antimyeloma therapy; fit level 0, intermediate fit level -1, and frail level -2.				
Frailty index risk factors				
IMWG frailty index[1]	0	1	1 + occurrence of grade 3–4 hematological AE	≥2
R-MCI[2]	1–3	4–6	7–9	
Dose level	0	-1	-2	-2
Treatment doses	**Level 0**	**Level -1**	**Level -2**	
Prednisone	2 mg/kg days 1–4 of a 4–6 week cycle 60 mg/m^2 days 1–4 of a 6 week cycle	1 mg/kg days 1–4 of a 4–6 week cycle 30 mg/m^2 days 1–4 of a 6 week cycle	0.3–0.5 mg/kg days 1–4 of a 4–6 week cycle 10–15 mg/m^2 days 1–4 of a 6 week cycle	
Dexamethasone	40 mg day 1, 8, 15, 22 of a 28-day cycle	20 mg day 1, 8, 15, 22 of a 28-day cycle	10 mg day 1, 8, 15, 22 of a 28-day cycle	
Melphalan	0.25 mg/kg days 1–4 of a 4–6 week cycle 9 mg/m^2 days 1–4 of a 6 week cycle	0.18 mg/kg days 1–4 of a 4–6 week cycle 7.5 mg/m^2 days 1–4 of a 6 week cycle	0.13 mg/kg days 1–4 of a 4–6 week cycle 5 mg/m^2 days 1–4 of a 6 week cycle	
Thalidomide	100 (–200) mg/day	50 (–100) mg/day	50 mg qod (–50 mg/day)	
Lenalidomide	25 mg days 1–21 of a 28-day cycle	15 mg days 1–21 of a 28-day cycle	10 mg days 1–21 of a 28-day cycle	
Pomalidomide	4 mg days 1–21 of a 28-day cycle	3 mg days 1–21 of a 28-day cycle	2 mg days 1–21 of a 28-day cycle	
Bortezomib	1.3 mg/m^2 twice weekly Day 1, 4, 8, 11 every 3 weeks	1.3 mg/m^2 once weekly Day 1, 8, 15, 22 every 5 weeks	1.0 mg/m^2 once weekly Day 1, 8, 15, 22 every 5 weeks	
Carfilzomib[a]	20 mg/m^2 day 1, 2, 8, 9, 15, 16 cycle 1, 27mg/m^2 cycle 2 every 3 weeks	20 mg/m^2 cycle 1 → 27 mg/m^2 cycle 2, day 1, 8, 15, every 3 weeks	20 mg/m^2 day 1, 8, 15, every 4 (5) weeks	
Ixazomib	4mg day 1, 8, 15, every 4 weeks	3mg day 1, 8, 15, every 4 weeks	2.3 mg day 1, 8, 15, every 4 weeks	
Daratumumab[a]	16 mg/kg bw cycle 1–8: weekly; cycle 9–24: day 1þ15, from week 25: every 4 weeks	16 mg/kg bw cycle 1–8: weekly; cycle 9–24: day 1þ15, from week 25: every 4 weeks	16 mg/kg bw cycle 1–8: weekly; cycle 9–24: day 1þ15, from week 25: every 4 weeks	
Elotuzumab[b]	10 mg/kg day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	10 mg/kg bw day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	10 mg/kg bw day 1, 8, 15, 22 cycle 1+2, from cycle 3: day 1+15	
Panobinostat	20mg day 1, 3, 5, 8, 10, 12 every 4 weeks	15mg day 1, 3, 5, 8, 10, 12 every 4 weeks	10mg day 1, 3, 5, 8, 10, 12 every 5 weeks	

In the Endeavor study the dose of carfilzomib was 56mg/m^2, with 17% of patients of 75 years or older. No dose modification was applied. In the Aspire study where carfilzomib was combined with lenalidomide a lower dose of 27mg/m^2 was given, also not adapted according to age.

[1] http://195.88.6.191/Frailtyscore/Geriatric.aspx.
[2] http://www.myelomacomorbidityindex.org/en_about.html.
AE, adverse event; IMWG, International Myeloma Working Group; R-MCI, Revised Myeloma Comorbidity Index; qod: every 2 day; cy: cycle, d: day, bw: body weight.
a +.
b: No known dose adaptation in elderly and/or frail patients reported.
https://www.croh-online.com/article/S1040-8428(18)30014-3/abstract