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REVIEW ARTICLE

Multiple myeloma gammopathies

Patient-centered practice in elderly myeloma patients: an overview and consensus from the European Myeloma Network (EMN)

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Abstract

Multiple myeloma is a disease typical of the elderly, and, because of the increase in life expectancy of the general population, its incidence is expected to grow in the future. Elderly patients represent a particular challenge due to their marked heterogeneity. Many new and highly effective drugs have been introduced in the last few years and results from clinical trials are promising. Besides the availability of novel agents, a careful evaluation of elderly patients showed to be a key factor for the success of therapy. A geriatric assessment is a valid strategy to better stratify patients. In particular, different scores are available today to appropriately assess elderly patients and define their fitness/frailty status. The choice of treatment—transplantation, triplets, doublets, or reduced-dose therapies including novel agents—should depend on the patient's fitness status (fit, intermediate-fit or frail). Second-generation novel agents have also been evaluated as salvage therapy in the elderly, and these new agents certainly represent a further step forward in the treatment armamentarium for elderly patients with multiple myeloma.

Introduction

The incidence of Multiple Myeloma (MM) is strongly related to age: ~70% of MM diagnoses occur in patients older than 65 years and 40% in those older than 75 years [1]. Since the worldwide population is rapidly ageing, the

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number of elderly people is considerably increasing, with those older than 80 years projected to amplify from 137 million in 2017 to 425 million in 2050 [2]. As the prevalence of cancer including MM will increase, this urges us to designate therapies, including clinical trials, for elderly cohorts.

Due to first-generation novel agents, namely bortezomib, thalidomide and lenalidomide, progression-free survival (PFS) and overall survival (OS) have substantially improved in MM. Before 2000, the median OS in newly diagnosed MM (NDMM) was ~2.5 years, whereas this is now >5 years, depending on the risk and response status of patients [3, 4]. Such a remarkable survival improvement is now also evident in the elderly population. In fact, after 2000, the 6-year OS of patients over 65 years significantly improved from 35% to 56% ($p < 0.001$) [4]. Nevertheless, older people represent a heterogeneous population in terms of both physical and psycho-social functioning. In addition, it is now accepted that chronological and biological age may not correspond, and that the presence of frailty, comorbidities and disabilities can affect therapy endurance. Thus, the assessment of frailty is desirable, but sensitive tools need to be systematically tested and clinically validated. Moreover, therapy allocation and randomized studies are not yet tailored according to patients' frailty status.

Of note, MM patients ≥75 years treated upfront with novel agents may show similar PFS as compared with younger patients, although their OS is impaired. This is partially due to the fact that toxic side effects from first-line treatment may preclude second-line treatment, with third-line therapies in > 80-year old MM patients being extremely rare [5]. Therefore, it is essential to identify patients that may need specifically tailored strategies to optimize tolerability and efficacy of the different treatment lines [6].

Recently, second-generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) and monoclonal antibodies (MoAbs) have led to the development of multi-drug salvage combinations. In this context, the impacts of age and frailty have not been fully determined. Therefore, this paper aims to provide recommendations from the European Myeloma Network (EMN) on the management of elderly MM patients in the era of innovative agents.

Methods

An interdisciplinary panel of myeloma experts on behalf of the EMN evaluated randomized clinical studies, meta-analyses, systematic reviews and other clinical analyses on the treatment of elderly MM patients published until December 2017. The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to assign grades of recommendations (Suppl. Table 1) [7]. If no sufficient data were available, the expert panel reached a consensus after internal discussion and provided recommendations. Initial discussion took place at the 8th EMN Trialist meeting (Baveno, Italy, 25th–26th September 2016) and finalization of this paper during and after the 9th EMN meeting (24th–25th September 2017). The recommendations circulated among EMN panel members. The manuscript subsequently underwent revision until all EMN panel experts reached mutual consensus and it is also published as a consensus paper by the European Hematology Association (EHA).

Treatment of elderly patients with newly diagnosed MM (NDMM)

Six prospective randomized trials compared melphalan and prednisone alone (MP) with MP plus thalidomide (MPT) showing a significant improvement in PFS with MPT, while conflicting results were reported for OS. Although the trials differed in terms of patient characteristics and MP/MPT-schedules, a meta-analysis of all 1685 patients showed a significant benefit for MPT in terms of OS (HR 0.83, 95% CI 0.73–0.94, $p = 0.004$), which increased from 32.7 with MP to 39.3 months with MPT. Consistently, MPT was associated with superior PFS (20.3 months with MPT vs. 14.9 months with MP; HR 0.68, 95% CI 0.61–0.76, $p < 0.0001$). Nevertheless, a higher cumulative incidence of grade 3–4 hematologic and non-hematologic toxicities was documented with MPT, leading to a toxicity-related discontinuation of thalidomide in 35% of MPT patients, with peripheral neuropathy (PNP) being the main reason (15%) [8, 9].

The combination bortezomib-melphalan-prednisone (VMP) was introduced as another standard upfront combination: VMP (intravenous bortezomib twice-weekly for cycles 1–4 and once-weekly for cycles 5–9) showed to be superior to MP in terms of PFS (median: 21.7 vs. 15.2 months, respectively; HR 0.558; $p < 0.001$) [10] in the VISTA trial. Furthermore, after a median follow-up of 60.1 months, a 31% reduced risk of death was achieved with VMP vs. MP (median OS: 56.4 vs. 43.1 months; HR, 0.695; $p < 0.001$) [11]. The survival benefit with VMP was found across pre-specified patient subgroups including age ≥75 years, ISS stage III, and creatinine clearance <60 mL/min. The occurrence of PNP negatively affected long-term bortezomib use. However, once-weekly rather than twice-weekly dosing, subcutaneous rather than intravenous route, and prompt dose reductions are current effective strategies to significantly reduce bortezomib-induced PNP, without affecting efficacy [12, 13]. Furthermore, VMP could partly restore PFS in high-risk patients, leading to a non-statistically

Table 1 Trials with various new antimyeloma agents in newly diagnosed elderly multiple myeloma patients: efficacy and safety

	Schedule	ORR (%)	PFS (months)	OS (months)	AEs of interest (%)
MPT vs. MP Meta-analysis Fayers et al. [9]	M: 4 mg/m^2 d 1–7 every 4 weeks for 6 cycles or 0.25 mg/kg d 1–4 every 6 weeks for 12 cycles; P: 40 mg/m^2 p.o. d 1–7 every 4 weeks for 6 cycles or 2 mg/kg d 1–4 every 6 weeks for 12 cycles; T: 100 mg/d p.o. continuously until PD or intolerance or 200 mg/d continuously for 12 cycles of 6 weeks	59 vs. 37	20.3 vs. 14.9	39.3 vs. 32.7	—
MPT vs. MP Meta-analysis Palumbo et al. [8].		—	—	—	Cumulative incidence G3-4 hemat: 32 vs. 29 G3-4 non-hemat: 40 vs. 18 G3-4 PNP: 6 vs. 1
MPR-R vs. MPR vs. MP Phase 3 Palumbo et al. [19]	*9 4-week cycles* M: 0.18 mg/kg P: 2 mg/Kg d1-4 R: 10 mg/d d 1-21 Maint. R 10 mg until PD	77 vs. 68 vs. 50	31 vs. 14 vs. 13	45.2 vs. NR vs. NR	G3 neutropenia: 67 vs. 64 vs. 29 G3 thrombocytopenia: 35 vs 38 vs. 12 G3 infection: 9 vs. 13 vs. 7
VMP vs. MP VISTA Phase 3 San Miguel et al. [10]	*9 6-week cycles* M 9 mg/m^2 d 1–4 P 60 mg/m^2 d 1–4 V 1.3 mg/m^2 d1, 4, 8, 11, 22, 25, 29, 32 cycles 1–4 + d1, 8, 22, 29 cycles 5–9	71 vs. 35	24 vs. 17	56.4 vs. 43.1	G3–4 PNP: 13 vs. 0
DARA-VMP vs. VMP ALCYONE Phase 3 Mateos et al. [18].	*9 6-week cycles* Dara 16 mg/kg d 1, 8, 15, 22, 29, 36 cycle 1 + d 1, 22 cycles 2–9, every 4 weeks thereafter M 9 mg/m^2 d 1–4 P 60 mg/m^2 d 1–4 V 1.3 mg/m^2 d1, 4, 8, 11, 22, 25, 29, 32 cycle 1+d1, 8, 22, 29 cycles 2–9	91 vs. 74	NR vs. 18	NR in both arms	G 3–4 neutropenia: 40 vs. 39 G 3–4 infections: 23 vs. 15 G 3–4 PNP: 1 vs. 4 G3-4 IRRs: 4 vs. –
Rd vs. Rd18 vs. MPT FIRST Phase 3 Benboubker et al. [14]	*4-week cycles* R: 25 mg/d d1-21 d: 40 mg d 1,8,15,22 *6-week cycles* M: 0.25 mg/kg d 1–4 P: 2 mg/kg d 1–4 T: 200 mg/d	75 vs. 73 vs. 62	25.5 vs. 20.7 vs. 21.2	4–yr: 59% vs. 56% vs. 51%	G3-4 neutropenia: 28 vs. 26 vs. 45 G3-4 infections: 29 vs. 22 vs. 17 G3-4 rash: 6 vs. 5 vs. 5
VRd vs. Rd SWOG-S0777 Phase Durie et al. [17]	*8 3-week cycles* V: 1.3 mg/m^2 d 1, 4, 8,11 R: 25 mg/d d 1-14 d: 20 mg/d d1, 2, 4, 5, 8, 9, 11, 12 *6 4-week cycles* R: 25 mg/d d 1-21 d: 40 mg/d d 1, 8, 15, 22	82 vs. 72	43 vs. 30	75 vs. 64	G ≥ 3 hematol:47 vs. 46 G ≥ 3 neurologic: 33 vs. 11
KMP vs. VMP CLARION Phase 3 Facon et al. [16]	*7-week cycles* K: 36 mg/m^2 IV d 1, 2, 8, 9, 22, 23, 29, 30 (20 mg/m^2 d 1, 2, cycle 1 only) over 30 min V: 1.3 mg/m^2 d 1,4,8,11,22,25,29,32 (d 4,11,25,32 omitted for cycles 5–9) M: 9 mg/m^2 d 1–4 P: 60 mg/m^2 d 1–4	84 vs. 78	22 in both arms	NR in both arms	G ≥ 3 PNP: < 1 vs. 8 G ≥ 3 renal failure: 7 vs. 2 G ≥ 3 cardiac failure: 8 vs. 3 G ≥ 3 hypertension: 10 vs. 4

ORR overall response rate, *PFS* progression-free survival, *OS* overall survival, *AEs* adverse events, *MP* melphalan-prednisone, *MPT* melphalan-prednisone-thalidomide, *MPR* melphalan-prednisone-lenalidomide, *MPR-R* melphalan-prednisone-lenalidomide followed by lenalidomide maintenance, *VMP* bortezomib-melphalan-prednisone, *Dara* daratumumab, *Rd* lenalidomide-dexamethasone continuously, *Rd18* lenalidomide-dexamethasone for 18 courses, *VRd* bortezomib-lenalidomide-dexamethasone, *KMP* carfilzomib-melphalan-prednisone, *G* grade, *NR* not reached, *IRRs* infusion related reactions, *PNP* peripheral neuropathy, *PD* progressive disease, — not applicable.

different PFS in high-risk vs. standard-risk cytogenetics, although numbers were low [10].

In the FIRST trial, continuous treatment with lenalidomide and dexamethasone (Rd) significantly improved PFS compared to fixed duration MPT for 12 cycles or Rd for 18 cycles (Rd 18) [14]. Indeed, continuous Rd significantly reduced the risk of progression compared to MPT (HR 0.69; $p < 0.00001$) and Rd 18 (HR 0.70), whereas no significant PFS difference between Rd 18 and MPT was determined. Median PFS with continuous Rd, Rd 18 and MPT was 26, 21, and 21.9 months, respectively. The PFS benefit of continuous Rd vs MPT was confirmed in various

subgroups, including age, ISS stage and ECOG PS, but not with increased lactate dehydrogenase (LDH), high-risk cytogenetics or severe reduction in renal function (creatinine clearance <30 ml/min). Continuous Rd was associated with fewer hematologic and neurologic adverse events (AEs) (grade 3–4 PNP 1% vs 9%), a moderate increase in infections (grade 3–4: 29% vs 17%) and fewer second primary hematologic cancers as compared with MPT.

To test the feasibility and activity of these 2 efficient regimens at diagnosis, the Spanish group evaluated both VMP and Rd regimens in 2 different schemes: 9 cycles of VMP (intravenous bortezomib twice-weekly for cycle 1 and once-weekly for cycle 2–9) followed by 9 cycles of Rd (sequential scheme) vs. VMP directly followed by Rd in an alternate fashion for up to 18 cycles (alternating scheme) [15]. Both arms induced similar median PFS (32 vs. 34 months, $p = 0.65$) and 3-year OS (72% vs. 74%, respectively $p = 0.63$). The greatest benefit of this approach was observed in patients aged 65–75 years. Moreover, the sequential and alternating groups showed similar hematologic and non-hematologic toxicity. However, since this PETHEMA trial did not directly compare VMP with Rd, the superiority of one regimen over the other and/or preference in different subgroups remained unanswered.

Recently, the CLARION study evaluated the combination of carfilzomib with melphalan-prednisone (KMP) vs. standard VMP for 9 cycles, showing comparable PFS (22.3 vs. 22.1 months, HR, 0.91; 95% CI, 0.75–1.10). Median time-to-progression (TTP) was 27.5 vs. 23.5 months (HR 0.84; 0.68–1.04, $p = 0.05$), and median OS was not reached in both arms (HR 1.08; 95% CI, 0.82–1.43). Grade ≥3 hypertension, dyspnea, acute renal failure, and cardiac failure were higher in the KMP vs. VMP group. Moreover, KMP showed a slightly higher incidence of treatment discontinuation (17.5% vs. 15.5%) due to adverse events (AEs) and deaths (6.5% vs. 4.3%) [16]. The failure of KMP to improve outcome may be due to a lower PNP rate with VMP than expected, thus prolonging VMP therapy; melphalan being used as a less suitable combination partner; and lesser endurance of twice weekly carfilzomib treatment in elderly patients, leading to a slightly higher frequency of AEs.

Moreover, to further improve response and outcome, the role of intravenous bortezomib combined with lenalidomide-dexamethasone (VRd) vs. Rd in NDMM patients was evaluated in the phase 3 SWOG-S0777 study [17]. That study included both younger and elderly patients (≥65 years: 43%), stratified according to the intent to transplant. Median PFS was significantly improved in the VRd vs. Rd group (43 vs. 30 months, respectively; HR 0.712, 96% CI 0.56–0.906; $p = 0.0018$). Median OS was also improved in the VRd vs. Rd group (75 vs. 64 months, respectively, HR 0.709, 95% CI 0.524-0.959; $p = 0.025$). Survival was unchanged when patients off study (with intent for ASCT) were censored. The advantage of VRd over Rd remained significant for both PFS and OS in an age-adjusted multivariate analysis (age ≥65). Grade ≥3 toxicities were reported in 82% with VRd and 75% with Rd, and discontinuation rate due to toxicity was 23% with VRd vs. 10% with Rd. No treatment-related deaths occurred in the Rd group, while 2 were reported in the VRd group. Therefore, VRd significantly improved PFS and OS with an acceptable risk profile.

Recently, in the ALCYONE trial, the anti-CD38 monoclonal antibody daratumumab combined with VMP (subcutaneous bortezomib twice-weekly for cycle 1 and once-weekly for cycles 2–9) followed by daratumumab maintenance significantly improved PFS compared to VMP alone (HR 0.50; 95% CI 0.38–0.65; $p < 0.001$) after a median follow-up of 16.5 months. The advantage was evident in patients with renal impairment, age ≥75 years, ISS stage III or high-risk cytogenetics. AEs included infusion-related reactions in 28% of daratumumab-treated patients (grade 3–4: 4%) and infections (grade ≥3: 23% vs 15%) with daratumumab-VMP compared with VMP, although treatment discontinuation due to infections was low in both arms (0.9% and 1.4%, respectively) [18].

Safety and efficacy results of these trials are summarized in Table 1.

Continuous treatment

The goal of maintenance treatment is to maintain or improve the depth and quality of response achieved during induction treatment in order to prolong PFS and ultimately OS. Nevertheless, a major concern is drug-related toxicity that may limit the long-term use of maintenance and affect patients' quality of life (QoL).

In a phase 3 trial, melphalan–prednisone–lenalidomide induction followed by lenalidomide maintenance (MPR-R) was compared with melphalan–prednisone–lenalidomide (MPR) or MP-placebo. Median PFS was significantly longer with MPR-R (31 months) than with MPR (14 months; HR 0.49; $p < 0.001$) or MP (13 months; HR 0.40; $p < 0.001$) [19]. No significant difference in OS was reported between treatment arms. The PFS benefit associated with MPR-R was seen in patients 65–75 years of age, but not in those older than that. After induction, a landmark analysis showed a 66% reduction in the rate of progression with MPR-R (HR for the comparison with MPR: 0.34; $p <$ 0.001) that was age-independent. Second primary malignancies (SPMs) were increased in the lenalidomide-arms: 3-year SPM rate was 7% with MPR-R or MPR vs. 3% with MP. Nevertheless, the benefit associated with MPR-R was judged to outweigh the increased risk of SPMs.

Table 2 Frailty Assessment in Myeloma

	IMWG-FRAILTY INDEX [31]	REVISED MYELOMA COMORBIDITY INDEX (R-MCI) [32]	MAYO FRAILTY INDEX [34]
N	869	801	351
Median age	74 (46% ≥75)	63 (13% ≥75)	65 (33% ≥75)
Factors	Age ADL IADL CCI	KPS Renal function (eGFR) Lung (PFTs) Fragility Age ±Cytogenetics	Age ECOG PS NT-Pro-BNP
Patient population	Selected clinical trial patients from 3 studies: Rd: MPR: CPR; VP: VCP: VMP; CCd	Unselected	Unselected
First-line-treatment	Len-based 76% PI-based 24% SCT: 0%	Novel-agent-based: 59% SCT: 50%	Len-based 63% Bortezomib-based 22% ASCT 39%
Weighted vs. unweighted score	Unweighted	Weighted	Unweighted
Validation assessment	Non-validated	Validated	Non-validated
Access	www.myelomafrailtyscorecalculator.net/	www.myelomacomorbidityindex.org	—
Summary	- Well cited - Well published	- Generated via test- and validation analysis, - Compelling statistics, - Simple clinical applicability	- Use of NT-pro-BNP as laboratory parameter to add risk to performance status and age

IMWG International Myeloma Working Group, *Rd* lenalidomide-dexamethasone, *MPR* melphalan-prednisone-lenalidomide, *CPR* cyclophosphamide-prednisone-lenalidomide, *VP* bortezomib-prednisone, *VCP* bortezomib-cyclophosphamide-prednisone, *VMP* bortezomib-melphalan-prednisone, *CCd* carfilzomib-cyclophosphamide-dexamethasone, *ADL* Activity of Daily Living, *IADL* Instrumental Activity of Daily Living, *CCI* Charlson Comorbidity Index, *KPS* Karnofsky Performance Status, *eGFR* estimated glomerular filtration rate, *PFTs* pulmonary function tests, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *NT-proBNP* N-terminal natriuretic peptide type B.

In another phase 3 trial, MPR-R was not significantly superior over melphalan-prednisone-thalidomide followed by thalidomide maintenance (MPT-T) in terms of PFS (HR, 0.84; $p = 0.06$) or OS (HR, 0.79; $p = 0.06$) [20]. Moreover, MPT-T induced a significantly higher PNP and MPR-R was associated with higher myelosuppression. Similar data were reported in a previous trial, where the use of MPT-T or MPR-R in elderly patients with untreated MM demonstrated no statistical or clinically relevant difference in response rates, PFS and OS; however, improved QoL and lower toxicity were reported with MPR-R [21].

In the FIRST trial, continuous Rd improved clinically relevant health-related QoL (HRQoL) measurements as compared to MPT [22]. HRQoL improved with treatment and was generally maintained while subjects were progression-free; however, these QoL results were influenced by the fact that only patients responding and staying on treatment were included in subsequent analyses. As expected, progressive disease was associated with worsening HRQoL across all evaluated domains, and MPT was associated with worse treatment-induced side effects as compared with Rd. Median OS was longer with continuous Rd than with MPT (59.1 vs 49.1 months; HR 0.78), including a 14-month difference in patients >75 years [23]. However, median OS with continuous Rd was comparable to Rd 18 arm (59.1 vs 62.3 months; HR 1.02). Continuous Rd prolonged PFS compared with MPT and Rd18 in patients with standard-risk cytogenetics, whereas no statistical difference was found in patients with high-risk cytogenetics; yet patients with high-risk cytogenetics did not experience OS benefits with continuous Rd vs MPT [23]. Furthermore, continuous Rd extended time-to-next-treatment (TTNT) compared with Rd18 and MPT, particularly in patients who achieved complete response (CR) or very good partial response (VGPR) (69.5 vs. 39.9 vs 37.7 months, HR 0.47 for continuous Rd vs Rd18, HR 0.42 for continuous Rd vs MPT). Rates of grade 3–4 AEs with continuous Rd were similar for patients ≤ or >75 years old; however, older patients required lenalidomide dose-reductions more frequently [24].

The Myeloma XI study explored the role of lenalidomide maintenance in both transplant-eligible and ineligible

patients [25]. Lenalidomide maintenance reduced the risk of progression or death by 54% as compared with no maintenance (median PFS: 39 vs. 20 months, respectively, HR: 0.46, $p < 0.0001$). The PFS benefit persisted across risk subgroups and was independent of induction, response and cytogenetic risk groups. For transplant-ineligible patients, median PFS was 26 vs. 11 months, respectively (HR 0.44, $p < 0.0001$). At a median follow-up of 30.6 months no difference in OS between lenalidomide maintenance vs no maintenance was observed in transplant-ineligible patients (50.8 vs 57.8 months, HR 1.02). Lenalidomide maintenance improved OS irrespective of cytogenetic risk in transplant-eligible patients, but there was no benefit in transplant-ineligible patients.

The GIMEMA group compared VMP-thalidomide followed by continuous VT (VMPT-VT) with VMP. After a median follow-up of 54 months, median PFS was significantly longer with VMPT-VT than with VMP (35.3 vs. 24.8 months; respectively; HR 0.58; $p < 0.001$) and the 5-year OS was greater (61% vs. 51%; HR 0.70; $p < 0.01$). High-risk and standard-risk cytogenetic patients in both arms had similar outcome. Nevertheless, the absence of a second randomization after induction made the maintenance vs. no maintenance comparison challenging [26].

The PETHEMA trial compared VMP with bortezomib-thalidomide-prednisone (VTP) followed by maintenance with bortezomib-thalidomide (VT) or bortezomib-prednisone (VP): PFS from the start of maintenance was 32 months for patients receiving VT and 24 months for those receiving VP (HR 1.4, 95% CI 0.8–2.1; $p = 0.1$), without a difference in OS (HR 1.2, 0.6–2.4), albeit side effects, especially arrhythmia and cardiac events, were more prominent with VT than VP [27].

Geriatric assessment (GA)

Age and PS are the most frequently used criteria to select patients for standard full-dose therapy, but the final decision is generally left to the physician's clinical judgment [28]. Indeed, these parameters may not be sufficient to describe the heterogeneity of elderly patients, and a large body of geriatric literature tries to address this challenge by designing specific geriatric scores.

Comprehensive [29] GA is a procedure developed by geriatricians to evaluate patients' functional and global health status, to identify and manage age-related problems allowing clinicians to select therapy appropriately, avoiding over- and undertreatment [30], thus allowing categorization of patients into groups with different age-related conditions and risks of toxicity/drop-out. However, full GA is a time- and manpower-consuming procedure, and it is challenging to perform in everyday clinical practice; thus, more feasible approaches including a limited number of indicators have been proposed (Table 2).

In 2015, the IMWG developed an effective method to detect and grade the severity of frailty. An additive scoring system (range 0-5), based on age, comorbidities and functional conditions (evaluated with Charlson Comorbidity Index (CCI), Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)), was developed to identify 3 groups of MM patients at diagnosis: fit (score = 0, 39%); intermediate (score = 1, 31%), and frail patients (score ≥2, 30%) [31]. This IMWG-frailty index predicted mortality and PFS in elderly patients. The prognostic impact of the frailty profile on OS was independent from ISS stage, chromosomal abnormalities, type of treatment and PS in multivariate analysis. Grade 3 or higher non-hematologic toxicity and treatment discontinuation due to toxicity were also higher in frail patients. To help users, the IMWG score is available online (http://www.myelomafrailtyscorecalculator.net/).

This IMWG-frailty index was prospectively validated and compared with the revised myeloma comorbidity index (R-MCI) in a German cohort of NDMM patients [32]. This validation demonstrated a 3-year-OS of 91%, 77%, and 47% for fit, intermediate-fit and frail patients, respectively. Using the CCI, Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI), Kaplan–Feinstein Index (KFI) and R-MCI also allowed to define fit and frail patients with distinct PFS and OS, albeit most pronounced differences resulted via R-MCI and IMWG-frailty index. Moreover, the relevance of the R-MCI was demonstrated in 801 consecutive German MM patients, this cohort being examined also prospectively within a training and validation set. Multivariate analysis determined 5 risk factors (renal, lung, KPS-impairment, frailty, age) as highly significant for OS. These were combined in the weighted R-MCI, allowing identification of fit (R-MCI 1-3), intermediate-fit (R-MCI 4-6) and frail patients (R-MCI 7-9): these subgroups showed median OS rates of 10.1, 4.4, and 1.2 years, respectively. The R-MCI was again compared to the CCI, HCT-CI and KFI: if each were divided in risk groups, highest HRs, best prediction and Brier scores were achieved with the R-MCI. Advantages of the R-MCI included its prospective validity, accurate assessment of patients' physical conditions, score-robustness due to repeated test- and validation analyses and its simple clinical applicability. To expedite its use, a web-based application was implemented (www.myelomacomorbidityindex.org) (Table 2).

The IMWG-frailty index was also validated in the FIRST-trial. However, ADL and IADL were not available, instead the EQ5D was used. Results confirmed an inferior outcome in frail vs. fit patients, with median PFS of 20.3 vs. 43.7 months and median OS of 52.3 months vs. not reached, respectively [33].

Table 3 Frailty status definition and related treatment goals in elderly NDMM patients

IMWG-FRAILTY INDEX: Age, CCI, ADL, IADL		
FIT	**INTERMEDIATE**	**FRAIL**
0 IMWG-frailty index points *CCI ≥ 2: 1* *IADL < 5: 1* *ADL < 4: 1* *Age 76–80: 1, > 80: 2*	1 IMWG-frailty index point	2-5 IMWG-frailty index points
REVISED MYELOMA COMORBIDITY INDEX (R-MCI): Age, KPS, renal function, lung function, frailty ± cytogenetics		
FIT	**INTERMEDIATE**	**FRAIL**
0–3 R-MCI points *Age 60–69: 1, ≥ 70: 2* *KPS: 80-90%: 2, < 70%: 3* *Renal disease: eGFR < 60: 1* *Lung disease: moderate/severe: 1* *Frailty: moderate or severe: 1 ± cytogenetics: unfavorable: 1*	4-6 R-MCI points	7-9 R-MCI points
MAYO FRAILTY INDEX: Age, ECOG PS, NT-proBNP		
STAGE I	**STAGE II/ STAGE III**	**STAGE IV**
0 Mayo frailty index points *Age ≥ 70: 1* *ECOG PS ≥ 2: 1* *NT-proBNP ≥ 300 ng/L: 1*	1 (STAGE II) Mayo frailty index point 2 (STAGE III) Mayo frailty index points	3 Mayo frailty index points
GOAL OF TREATMENT		
FIT	**INTERMEDIATE**	**FRAIL**
Efficacy: deep response	Balance efficacy and toxicity	Conservative approach, low toxicity
TREATMENT		
Full-dose therapy	**Full- or reduced-dose therapy**	**Reduced dose therapy**
ASCT TRIPLET REGIMENS VMP VRD DOUBLET REGIMENS Rd	DOUBLET REGIMENS Rd Vd Reduced-dose triplet	REDUCED-DOSE DOUBLET REGIMENS rd Vd Palliative + supportive care

NDMM newly diagnosed multiple myeloma, *ADL* Activity of Daily Living, *IADL* Instrumental Activity of Daily Living, *CCI* Charlson Comorbidity Index, *KPS* Karnofsky Performance Status, *ECOG PS* ECOG Performance Status, *ASCT* Autologous Stem Cell Transplantation, *VMP* bortezomib-melphalan-prednisone, *VRD* bortezomib-lenalidomide-dexamethasone, *Rd* lenalidomide-dexamethasone, *Vd* bortezomib-dexamethasone

Moreover, the N-terminal natriuretic peptide type B (NT-proBNP) was used as a laboratory risk parameter and predictor of survival independent of age and performance status in another large group of NDMM patients, it was therefore proposed as an additive biomarker of frailty (Table 2) [34]. Other biomarkers of frailty (such as sarcopenia, which predicts outcomes in patients with solid tumors) are under evaluation [35].

The use of standardized minimum datasets of tools and biomarkers to define frailty is an advantage to permit comparisons between different studies. More efficient methods are under development. Clinical trials designed for tailored treatment according to frailty status are ongoing. Preliminary analyses from a Dutch-HOVON study support the prognostic value of the IMWG-frailty index; prospective use of the R-MCI is also ongoing in and outside clinical trial MM patients. Objectively measured tests (gait speed and handgrip strength) and biomarkers (senescence marker and sarcopenia) are therein investigated. In the ongoing German

prospective studies, comorbidity scores and defined functional fitness tests are combined to determine most powerful frailty tools for MM, for effective treatment and toxicity-avoidance [36].

Recommendations

Both IMWG-frailty index and R-MCI are recommended instruments to identify fit, intermediate and frail patients, the latter showing an inferior outcome and a higher treatment discontinuation rate (1B).

Fit, elderly patients may receive full-dose therapy, including VMP (grade 1A), Rd (1A) or VRD (2B). Solid data recently published on the addition of the monoclonal antibody daratumumab to VMP will probably change the scenario in the near future. Patients with intermediate-fitness can benefit from doublets and/or even low-dose triplets (2C), whereas frail patients may require doublet treatment at lower doses (2C). Bortezomib-based induction may be preferred in patients with impaired renal function. Once-weekly subcutaneous bortezomib schedule may be applied due to the lower AE incidence. Rd may be preferred, if oral administration and lack of inducing or aggravating PNP are major considerations (Table 3).

In transplant-ineligible patients, continuous lenalidomide treatment (e.g. Rd) prolongs PFS (1A). Continuous Rd does not produce an OS advantage vs fixed duration Rd but prolongs TTNT, especially in patients achieving a high-quality response (at least VGPR).

Baseline cytogenetic data should be obtained in all elderly MM patients in whom a palliative approach is not planned. In the presence of high-risk cytogenetics, bortezomib-based treatment may be beneficial (2C), but confirmatory, well-designed trials are lacking [37]. Continuous treatment with lenalidomide remains uncertain in patients with high-risk cytogenetics and still needs to be confirmed

Autologous stem-cell transplantation (ASCT)

The benefit of high-dose therapy and ASCT in older patients has been controversially discussed [38]. Several retrospective single-center and transplant-registry analyses demonstrated that ASCT is possible in elderly and fit MM patients [39–42]. However, patients undergoing ASCT need particular attention and should meet strict selection criteria [43–45], at best via comorbidity tests, which take into account biological rather than chronological age [31, 32, 46–49].

Tandem-ASCT and even full-dose melphalan (Mel) 200 mg/m^2-conditioning are possible in elderly-fit patients; the DSMM XIII study is assessing continuous Rd treatment vs. Rd induction, tandem melphalan 140 mg/m^2-ASCT consolidation and lenalidomide maintenance in 60-75 year-old MM patients, and long-term results are eagerly awaited [50].

Especially in patients aged > 70 years, the risk of toxicities may counteract the potential benefits of ASCT. In a phase 2 study, bortezomib-pegylated liposomal doxorubicin-dexamethasone (PAD) induction followed by melphalan 100 mg/m^2 and ASCT, lenalidomide-prednisone consolidation and lenalidomide maintenance was highly effective (median PFS: 48 months; 5-year OS: 63%) [51]. However, for patients > 70 years a significantly higher rate of treatment-related AEs was observed in comparison with younger patients (19% vs. 5%).

Recently, criteria for patient selection and melphalan dose-reduction in the elderly have been proposed by the EMN [38]. However, future trials are needed to define selection criteria and potential benefit for ASCT as compared with innovative combinations including IMiDs plus PIs and MoAbs.

Recommendations

MM patients without prohibitive comorbidities and adequate organ function, thus transplant-eligible, may benefit from high-dose melphalan followed by ASCT (1A). In fit or intermediate-fit (rather than frail) patients up to the age of 70 (or even 75 years), ASCT with melphalan conditioning 140-200 mg/m^2 is feasible, and the selection of suitable patients should at best be performed via comorbidity tests (2C) [38].

Lenalidomide maintenance after ASCT prolongs PFS and OS in younger patients. Although phase 3 trials in the elderly are lacking, maintenance therapy after ASCT is advisable (2C).

How to select and choose treatment

The achievement of CR [52] and minimal residual disease (MRD) [53] negativity is a relevant endpoint of MM treatment. However, an optimal balance between treatment efficacy and toxicity is of utmost importance. Yet, standard treatment may induce a higher rate of AEs, translating into a higher discontinuation rate and an inferior survival benefit, particularly in frail patients [54, 55].

The assessment of fitness and frailty can thus be used to determine the treatment goals and select the most appropriate option. In fit patients, the priority of treatment should be the efficacy and the goal of therapy is the achievement of a deep remission (CR or MRD negativity). In intermediate patients, the priority of treatment should be a balance between efficacy and safety and the goal is the achievement of a deep response while maintaining a good safety profile. In frail patients, the priority of treatment should be to not

Table 4 Suggested frailty-adjusted dose reduction in patients with myeloma using standard and novel agents

Risk factors			
Age > 75 years			
Comorbidities (pulmonary, renal, cardiac and hepatic dysfunction) or Preferably with **a) IMWG-FRAILTY INDEX**[a] and/or **b) R-MCI**[b] define intermediate and frail patients, in order to consider to adapt antimyeloma therapy			
	FIT	**INTERMEDIATE**	**FRAIL**
IMWG-FRAILTY INDEX[a]	**0**	**1**	**≥ 2**
R-MCI[b]	**1–3**	**4–6**	**7–9**
DOSE LEVEL	**0**	**–1**	**–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	0.5 mg/kg days 1-4 of a 4-6 week cycle 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	0.18 mg/kg days 1-4 of a 4-6 week cycle	0.13 mg/kg days 1-4 of a 4-6 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 1-21of a 28-day cycle	10 mg days 1-21of 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°*	20 mg/m^2 d 1, 2, 8, 9, 15, 16 cycle 1, 27 mg/m^2 cycle 2 every 4 weeks	20 mg/m^2 cycle1 - > 27 mg/m^2 cy2, d 1, 8, 15, once weekly every 4 weeks	20 mg/m^2 d 1, 8, 15, once weekly every 4 (5) weeks
Ixazomib*	4 mg d 1,8,15, every 4 weeks	3 mg d 1,8,15, every 4 weeks	2.3 mg d1,8,15, every 4 weeks
Daratumumab*	16 mg/kg bw cy 1-8: weekly; cy9-24: d1 + 15; week 25 onwards: every 4 weeks	16 mg/kg bw cy 1-8:weekly; cy9-24: d1 + 15, week 25 onwards: every 4 weeks Consider splitting the dose on 2 consecutive days in the first cycle.	16 mg/kg bw cy 1-8:weekly; cy9-24: d1 + 15, week 25 onwards: every 4 weeks Consider splitting the dose on 2 consecutive days in the first cycle.
Elotuzumab*	10 mg/kg bw d 1,8,15,22, cy 1 + 2, cy 3: d 1 + 15	10 mg/kg bw d 1,8,15,22, cy 1 + 2, cy3: d 1 + 15	10 mg/kg bw d1,8,15,22 cy 1 + 2, cy 3: d1 + 15
Panobinostat*	20 mg d1,3,5,8,10,12 every 4 weeks	15 mg d1,3,5,8,10,12 every 4 weeks	10 mg d1,3,5,8,10,12 every 5 weeks

qod: every 2.day; cy: cycle, d: day, bw: body weight

[a] http://195.88.6.191/Frailtyscore/Geriatric.aspx

[b] http://www.myelomafrailtyscorecalculator.net

*no known dose adaptation in elderly and/or frail patients were reported

°Carfilzomib dose in the ENDEAVOR study was 56 mg/m^2 weekly, no dose modifications according to age were reported

Table 5 Selected phase 3 trials in RRMM patients

Trials	ENDEAVOR (Kd vs. Vd) [61]	ASPIRE (KRd vs. Rd) [62, 63]	TOURMALINE-MM1 (IRd vs. Rd) [64]	CASTOR (Dara-Vd vs. Vd) [68]	POLLUX (Dara-Rd vs. Rd) [67]	ELOQUENT-2 (Elo-Rd vs. Rd) [71]
Median age (range)	65 (30–89)	64 (31–91)	66 (30–90)	64 (30–88)	65 (34–89)	66 (37–91)
Patients ≥ 75 years (%)	15.4%	12.1%	15%	11.6%	11.2%	20%
Key inclusion criteria	1–3 prior lines, PI refractory excluded	1–3 prior lines, Bor and Len refractory exlcuded	1–3 prior lines, PI and Len refractory excluded[a]	≥ 1 prior line, primary refractory and PI refractory excluded	≥ 1 prior line, primary refractory and Len refractory excluded	1–3 prior lines, Len refractory excluded
ORR (%)	77% vs. 63%	87% vs. 67%	78% vs. 72%	83% vs. 63%	93% vs. 76%	79% vs. 66%
Median PFS (months)	18.7 vs. 9.4 h 0.53 (95% CI, 0.44–0.65)	26.3 vs. 17.6 h 0.69 (95% CI, 0.57–0.83)	20.6 vs. 14.7 h 0.74 (95% CI, 0.59–0.94)	NR vs. 7.2 h 0.39 (95% CI, 0.28–0.53)	NR vs. 18.4 h 0.37 (95% CI, 0.27–0.52)	19.4 vs. 14.9 h 0.70 (95% CI, 0.57–0.85)
HR in patients ≥ 75 years	HR 0.38 (95% CI, 0.23-0.65)	HR 0.62 (95% CI, 0.36-1.08)	HR 0.87 (95% CI not reported)[b]	NA. In patients with ≥ 65 years HR 0.35 (95% CI 0.22-0.57)	HR 0.11 (95% CI, 0.02-0.51)	NA. In patients with ≥ 65 years HR 0.65 (95% CI 0.50-0.85)
Grade ≥ 3 hematological AEs	Anemia 14% vs. 10% Neutropenia 2% vs. 2% Thromocytopenia 8% vs. 9%	Anemia 18% vs. 17% Neutropenia 30% vs. 26% Thrombocytopenia 17% vs. 12%	Anemia 9% vs. 13% Neutropenia 23% vs. 24% Thrombocytopenia 19% vs. 9%	Anemia 14% vs. 16% Neutropenia 13% vs. 4% Thrombocytopenia 45% vs. 33% Lymphopenia 10% vs. 3%	Anemia 12% vs. 20% Neutropenia 52% vs. 37% Thrombocytopenia 13% vs. 13% Lymphopenia 5% vs. 4%	Anemia 19% vs. 21% Neutropenia 34% vs. 44% Thrombocytopenia 19% vs. 20% Lymphopenia 77% vs. 49%
Grade ≥ 3 non-hematological AEs	Pneumonia 7% vs. 8% Hypertension 9% vs. 3% PNP (G ≥ 2) 6% vs. 32% Cardiac failure 5% vs. 2%	Hypokalemia 9% vs. 5% Dyspnea 3% vs. 2% Hypertension 4% vs. 2% Cardiac failure 4% vs. 2%	Diarrhea 6% vs. 3% Rash 5% vs. 2% PNP 2% vs. 2%	Pneumonia 8% vs. 10% PNP 5% vs. 7% Diarrhea 4% vs. 1% Hypertension 7% vs. 1% Infusion related reaction 9% vs. NA	Pneumonia 8% vs. 8% Fatigue 6% vs. 3% Dyspnea 3% vs. 1% Infusion related reaction 5% vs. NA	Diarrhea 5% vs. 4% Infusion related reaction 1% vs. NA

G grade, *PI* proteasome inhibitors, *KD* carfilzomib-dexamethasone, *VD* bortezomib-dexamethasone, *KRD* carfilzomib-lenalidomide-dexamethasone, *RD* lenalidomide-dexamethasone, *IRD* ixazomib-lenalidomide-dexamethasone, *Dara-RD* daratumumab- lenalidomide-dexamethasone, *Dara-VD* daratumumab-bortezomib-dexamethasone, *Elo-RD* elotuzumab-lenalidomide-dexamethasone, *PNP* peripheral neuropathy, *NA* not available, *NR* not reached, *Bor* Bortezomib, *Len* lenalidomide

[a] primary refractory patients included

[b] median progression-free-survival 18.5 vs 13.1 months in patients with ≥ 75 years

harm but to preserve QoL by lowering toxicity (Table 3). Two independent trials demonstrated that triplets did not offer an advantage over doublet combinations, especially in frail patients [56, 57]. The community-based, phase 3 UPFRONT trial compared three frontline bortezomib-containing regimens in transplant-ineligible patients (42% of the patients were aged ≥ 75 years, and 18% were aged ≥ 80 years) [57]. After a median follow-up of 42.7 months, median PFS and OS with bortezomib-dexamethasone (VD), bortezomib-thalidomide-dexamethasone (VTD) or VMP were 14.7, 15.4 and 17.3 months and 49.8, 51.5 and 53.1 months, respectively, with no significant differences among treatments (global $p = 0.46$ and $p = 0.79$, respectively). AEs were more common with VTD than VD or VMP. Bortezomib maintenance was feasible without producing cumulative toxicity. In another trial including 25% of frail patients, the triplet lenalidomide-based regimens (MPR, CPR) did not induce any advantage over doublet Rd, which was associated with the lowest toxicity in elderly frail patients [56, 58].

Suggested frailty-adjusted dose reduction in patients with MM using standard and novel agents can be considered (Table 4).

Treatment of relapsed/refractory elderly MM patients

Treatment of elderly MM patients at relapse is often challenging, in part due to the fact that the number of therapeutic lines that can be endured is limited compared to younger and fitter patients [59]. Advanced age, coexisting comorbidities, toxicities from previous therapies and an aggressive pattern of relapse may also reduce the spectrum of feasible salvage therapies [6]. The analysis of the risk/benefit ratio of each agent is therefore pivotal to individualize treatment. In fit patients, treatment should aim at achieving response, since there is evidence that even among elderly relapsed and/or refractory MM (RRMM) patients, the achievement of CR significantly prolongs OS [60]. In frail patients the major goal of treatment is preserving QoL and minimize toxic complications [31]. Unfortunately, data on GA in RRMM patients are lacking and there is currently limited evidence on how to adapt treatment intensity other than using clinical judgment. Here, we describe the results of selected trials in RRMM patients assessing regimen features that can be relevant in elderly patients (Table 5).

Carfilzomib

In the ENDEAVOR study patients who were not refractory to PIs were randomized to receive either carfilzomib-dexamethasone (Kd) or bortezomib-dexamethasone (Vd) [61]. Median age was 65 years, and 15.4% of patients was ≥75 years of age. In the overall population, Kd led to a clinically meaningful prolonged PFS compared to Vd (median PFS 18.7 vs. 9.4 months, respectively; HR 0.53, 95% CI 0.44–0.65) and this advantage was evident also in patients ≥75 years (HR 0.38, 95% CI 0.23–0.65). Treatment discontinuation due to AEs was similar in the Kd vs. Vd group (14% vs. 15.7%). A lower PNP incidence was reported in the Kd group, while this adverse event frequently led to treatment discontinuation in the Vd group. Yet, higher grade ≥3 hypertension, dyspnea and cardiac failure rates were reported with Kd compared to Vd.

In the ASPIRE study, patients who were neither refractory to bortezomib nor lenalidomide were randomized to carfilzomib-lenalidomide-dexamethasone (KRd) or Rd alone. Median age was 64 years (12.1% were ≥75 years). KRd induced a longer PFS compared with Rd (median PFS: 26.3 vs 17.6 months respectively; HR 0.69, 95% CI 0.57–0.83), this benefit was also maintained in patients ≥75 years (median PFS: 30.3 vs. 16.6 months, respectively; HR 0.62, 95% CI 0.36–1.08) [62, 63]. In the safety analysis according to age, the rates of grade ≥3 cardiovascular AEs (hypertension, heart failure, ischemic heart disease, pulmonary embolism), neutropenia and thrombocytopenia were higher among patients ≥70 years vs. younger patients, and so was also the rate of carfilzomib discontinuation due to cardiovascular AEs (6.8% vs. 1.4%).

Ixazomib

The oral PI ixazomib has been tested in combination with Rd (IRd) vs. Rd in RRMM patients who were not refractory to PIs and lenalidomide [64]. Median PFS in the IRd group was 20.6 vs. 14.7 months in the Rd group (HR 0.74, 95% CI 0.59–0.94). A trend toward an advantage of IRd compared to Rd was reported also in 15% of enrolled patients aged ≥75 years (median PFS: 18.5 vs. 13.1 months; HR 0.87, 95% CI not reported). A subgroup analysis revealed that patients with high-risk cytogenetics did benefit from IRd vs. Rd (median PFS: 21.4 vs. 9.7 months; HR 0.54, 95% CI 0.32–0.92) although the cutoff points for defining the presence of high-risk abnormalities were lower compared to other trials (5% positive cells for del(17p), 3% positive cells for t(4;14),3% positive cells for t(14;16)). Grade ≥3 thrombocytopenia (19% vs. 9%) and diarrhea (6% vs. 3%) were higher with IRd, but toxicities were manageable and led to treatment discontinuation in only <2% of patients.

Daratumumab

The anti-CD38 MoAb daratumumab as single-agent was tested in two trials in heavily pretreated RRMM patients

[65, 66]. ORR ranged from 29% to 36% and median PFS from 3.7 to 5.6 months in the overall population. The drug was well-tolerated and the only safety concern was represented by infusion-related reactions (IRRs) (ranging from 42 to 71%), which were manageable and rarely severe. The number of elderly patients enrolled was low and overall in the 2 trials only 16 patients with ≥75 years could be evaluated for response. The ORR of these elderly patients was 25%, which was comparable to the overall population.

In the POLLUX trial, RRMM patients (not refractory to lenalidomide) were treated with Rd with or without daratumumab (Dara-Rd vs. Rd) [67]. Dara-Rd showed a significantly better PFS as compared with Rd (HR 0.37, 95% CI 0.27–0.52). This benefit was even more pronounced in elderly patients (≥75 years: HR 0.11, 95% CI 0.02–0.51). AEs leading to treatment discontinuation were limited and comparable between treatment groups (6.7% and 7.8% with Dara-Rd vs. Rd, respectively). Higher rates of neutropenia, diarrhea, fatigue, nausea, and dyspnea were reported in the Dara-Rd group, however they were clinically manageable. IRRs were usually limited to the first infusion and improved with inclusion of the leukotrien antagonist montelukast.

In the CASTOR trial, RRMM patients (not refractory to bortezomib) were treated with Dara-Vd vs. Vd. Dara-Vd showed an improved PFS (HR 0.39, 95% CI 0.28–0.53) [68]. The Dara-Vd advantage was consistent in patients ≥65 years (HR 0.35, 95% CI 0.22 to 0.57), whereas no data are available on older patients. No difference in treatment discontinuation due to AEs was reported between Dara-Vd vs. Vd. Dara-Vd led to a higher rate of hematological toxicity (thrombocytopenia, neutropenia, lymphopenia). IRRs were reported in 45%, almost all occurring during the first infusion and rarely being severe (≥3 grade: <10%).

The combination of daratumumab with pomalidomide plus low-dose dexamethasone (Pd) has been explored in the phase 1 EQUULEUS study in RRMM patients [69]. ORR was 60% and median PFS was 8.8 months. No differences in ORR were noted in patients younger or older than 65 years of age. The incidence of grade ≥3 neutropenia was 78%, however the rate of infections was quite similar to published data on Pd alone [70].

Elotuzumab

The anti-SLAMF7 MoAb elotuzumab was evaluated in the phase 3 ELOQUENT-2 trial [71]. RRMM patients (not refractory to lenalidomide) were randomized to elotuzumab-Rd (Elo-Rd) vs. Rd. Notably, 20% of patients were ≥75 years. Median PFS with Elo-Rd vs. Rd was 19.4 vs. 14.9 months, respectively (HR 0.70, 95% CI 0.57–0.85). Elotuzumab was very well tolerated and IRRs were rare and mild. Lymphocytopenia was the only AE, occurring significantly more frequently in the Elo-Rd vs. Rd group and leading to an increased incidence of herpes zoster reactivation but no other opportunistic infections. No efficacy data are available in patients ≥75 years, however the benefit of Elo-Rd was confirmed in ≥65 year-old patients (HR 0.65, 95% CI 0.50–0.85).

A smaller phase 2 randomized trial also evaluated the combination Elo-Vd vs. Vd, showing a trend for a better PFS with Elo-Vd (HR 0.72, 95% CI 0.49–1.06), with similar results between patients ≥65 years and the overall population [72].

Pomalidomide

The IMiD pomalidomide combined with dexamethasone was compared to high-dose dexamethasone in heavily pretreated RRMM patients. More than 90% of enrolled patients were refractory to lenalidomide and 75% were refractory to lenalidomide and bortezomib. Pd significantly prolonged PFS (median PFS 4 vs. 1.9 months, HR 0.48, 95% CI 0.39–0.60) and OS (median OS 13 vs 8 months, HR 0.74, 95% CI 0.56–0.97). Patients receiving Pd, either younger or older than 65 years, showed similar PFS (3.9 and 4 months, respectively). The analysis of patients aged ≥75 years was limited by the low numbers of patients (24/302 in the Pd arm). The main grade ≥3 AEs included neutropenia (48%), infections (34%) and anemia (33%) [70].

The addition of oral cyclophosphamide to Pd, particularly in lenalidomide-refractory RRMM patients, prolonged median PFS compared to Pd (9.5 vs. 4.4 months, HR 0.54; 95% CI 0.29–1.00). A slight increase of myelosuppression was observed with the addition of cyclophosphamide, although not significant. No data in subgroups by age were available [73].

Recommendations

Trials specifically designed for elderly RRMM patients are lacking and only ~50% of patients enrolled in phase 3 clinical trials are >65 years of age, and ~10-20% of patients older than 75 years. Patients with meaningful comorbidities are often excluded from clinical trials, leading to a selection bias compared to real life patients and making recommendations in elderly patients a challenge [74]. The following recommendations are therefore expert-opinion-based, derived from subgroup analyses and real life experience.

In RRMM patients not refractory to PIs, Kd is more effective than Vd (1B); however, the results reported in the control arm might be affected by previous bortezomib treatment. In the same patient population Dara-Vd is superior to Vd alone (1B). Thus, PI-sensitive patients progressing during or following lenalidomide could receive both Kd or Dara-Vd.

In patients who are not refractory to bortezomib and lenalidomide, carfilzomib could be added to Rd, if tolerated (2B). Caution is advised when using carfilzomib in elderly patients with preexisting hypertension and cardiac comorbidities (2B). The careful assessment and correction of cardiovascular risks and appropriate management of underlying cardiac conditions (cardiac failure and hypertension) need to be ensured before starting carfilzomib treatment. The addition of ixazomib to Rd is beneficial in the same patient population (2B).

In patients not refractory to lenalidomide, and/or progressing during or following bortezomib, Dara-Rd or Elo-Rd are recommended over Rd alone (1B).

Novel combinations do improve but do not overcome high-risk cytogenetics (2B).

Fit patients may receive full-dose treatments. Intermediate-fit patients may benefit from Elo-Rd or IRd, particularly in non-aggressive relapse (2C). Kd may be an option in patients who have no cardiac contraindication and with ensured cardiovascular work-up (1B). Dara-Rd or Dara-Vd may be beneficial, without additional toxicity as compared to both doublets Rd and Vd (1B). Among the different options, frail patients may benefit from daratumumab, elotuzumab, and ixazomib (2C).

High quality data after third-line therapy in elderly patients are lacking, making it hard to make formal recommendations. The expert panel agrees that, in fit elderly patients refractory to lenalidomide and PIs, Pd [70], Pd plus cyclophosphamide, single-agent daratumumab [65, 66], and inclusion in clinical trials are reasonable options (2C). In frail patients, low-dose combinations including oral cyclophosphamide or melphalan with or without low-dose thalidomide, if tolerated, can help to control disease symptoms (2B).

Conclusions

Despite recent advances in the treatment of MM patients thanks to novel effective agents, the choice of therapy in elderly patients remains a challenge. To make a sensible choice, physicians should take into account different fundamental aspects. First, a thorough assessment of patients' characteristics, including age, frailty status, compliance and social support, should be performed. Second, disease characteristics are essential to appropriately choose therapy, thus disease stage, cytogenetics, tumor burden and aggressiveness of the disease need to be considered. Third, the goal of care in the specific patient should be established: whether therapy should aim at achieving a deep response (CR and MRD negativity), or disease control (Tables 3 and 4). Finally, drug characteristics are crucial: cardiovascular, renal and pulmonary comorbidities, previous PNP and prior thromboembolic events are determinant factors in the selection of proper treatment and concomitant therapy; moreover, route of administration of a drug—orally, intravenously, subcutaneously—based on patient compliance can influence the choice of treatment. A careful GA (Table 2), interdisciplinary approaches, and the availability of new, different molecules have provided clinicians with a wide variety of possible treatment options, allowing more personalized therapies, with an appropriate balance between efficacy and safety [75].

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Compliance with ethical standards

Conflict of interest AL has received honoraria from Amgen, BMS, Celgene, and Janssen-Cilag; ET has received honoraria from Amgen, Celgene, Genesis, Janssen, Novartis, Takeda, Abbvie, BMS, and GSK; research funding from Celgene, Janssen, Amgen; has participated in DMC for Celgene and in SC for Amgen, Takeda and Janssen; HG has received research support from Amgen, BMS, Celgene, Chugai, Janssen, Sanofi, Mundipharma, Takeda, Novartis, honoraria from Celgene, Janssen, Novartis, Chugai, BMS, ArtTempi, and served on the advisory boards of Adaptive Biotechnology, Amgen, BMS, Celgene, Janssen, Sanofi, Takeda; FG has participated in the advisory board of Takeda, Seattle Genetics, Mundipharma, Janssen, and received honoraria from Takeda, Amgen, Celgene, Janssen, BMS; SB has received honoraria from BMS, Celgene, Janssen-Cilag, and participated in the advisory board of Amgen, Mundipharma, Karyopharm; JC has participated in the advisory board of and received honoraria from Amgen, Celgene, Janssen and research funding from Celgene. MO has received honoraria from and participated in advisory board of Celgene, Janssen, Takeda, Amgen, BMS; HWA has received research support from Amgen, participated in the advisory board of and honoraria from Amgen, Takeda, Karyopharm, Chugai, Novartis; HE has received honoraria, research support from and served on the advisory board of Janssen, Celgene, Amgen, BMS, Novartis; MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Abbvie, BMS, and research funding from Celgene, Janssen, Amgen, BMS, Mundipharma, Novartis, Sanofi; PS has participated in the advisory board of and received honoraria from Amgen, Celgene, Janssen, Karyopharm, Takeda-Millennium, and research support from Amgen, Celgene, Janssen, Takeda-Millennium, SkylineDx.

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