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Managing multiple myeloma in elderly patients

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Abstract

Multiple myeloma (MM) is a plasma cell neoplasm that affects elderly individuals with two-thirds of patients over 65 years at diagnosis. However, data available are derived from clinical trials conducted in younger patients. Fewer studies investigated treatment options in the elderly. This review summarizes the clinical outcomes and toxicities associated with therapeutic regimens in older patients including doublet, triplet and high dose therapyin newly diagnosed patients and relapsed patients with MM. We highlight the importance of an approach tailored to individuals, incorporates the geriatric frailty assessment, considers comorbiditiess and commits to early recognition and management of toxicities ranging from myelosuppression to polypharmacy. To date, no trial has prospectively investigated a tailored treatment paradigm in older patients based on frailty and/or comorbidities. As the population ages, the proportion of MM patients with advanced age will grow. Studies are indicated to determine optimal treatment approaches in this increasingly heterogeneous geriatric population.

Keywords

Geriatric; dose modification; dose adjustment; dose reduction; toxicity; transplant ineligible

Introduction

Multiple myeloma (MM) is a malignant neoplasm of the elderly. The National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) Program has estimated 30,280 new MM cases in the United States in 2017, making it the third most frequent hematologic malignancy and 14th leading cancer [1]. With an improvement in treatments, the 5-year survival rate of patients with MM reported in the SEER database has increased from 26.3% in 1975 to 34.5% in 2000, to 52.7% in the 2009–2014 period [1]. The global population is rapidly aging and the number of people greater than 80 years old is expected to quadruple between 2000 and 2050 [2]. With greater than 60% of diagnoses and nearly 75% of deaths occurring in those over 65 years of age, it is essential to critically evaluate the data available to guide management of elderly patients with MM [3].

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Patient assessment and prognostic tools

The management of older individuals with MM can be challenging due to increased frailty, comorbid conditions and physical disabilities related to aging [4]. Frailty results from the cumulative decline in many physiological systems, which ultimately leads to diminished resistance to stressors, such as cancer and its treatment [4]. Thus, the International Myeloma Working Group (IMWG) conducted a pooled analysis of 869 patients from three prospective trials with newly diagnosed MM in order to develop a scoring system based on age, comorbidities, cognitive and physical status, evaluating their prognostic role on overall survival (OS) [5]. The frailty score ranged from 0 to 5 to classify patients as fit (score of 0; 39%), intermediate fitness (score of 1; 31%), or as frail (score ≥2; 30%), as summarized In Table 1.

In the multivariate analysis, advanced age, functional decline on activities of daily living (ADL), instrumental activities of daily living (IADL) and the presence of comorbidities showed a trend towards a progressive worsening of OS, regardless of International Staging System (ISS) stage and treatment. The IMWG also took into consideration factors including functional ability, comorbidity, nutrition, cognition, psychological health, social support and economic resources as an additional way to help minimize toxicity and improve outcomes. With a median follow-up of 18 months, the 3-year OS was 84% in fit patients compared with 76% in intermediate fitness patients (hazard ratio (HR) = 1.61, 95% CI; 1.02–2.56, $p = .042$) and 57% in frail patients (HR = 3.57, 95% CI; 2.37–5.39, $p < .001$) [5]. By applying the proposed frailty score, the 3-year progression-free survival (PFS) was 48% in fit, 41% in intermediate-fitness and 33% in frail patients. Grade 3 or higher non-hematologic adverse events (AE) were reported in 18% of fit patients, 22% of intermediate fitness patients and 30% of frail patients which led to twice as many frail compared with fit patients who discontinued drug. Of the 869 patients, 143 (16%) died: 34 (10%) in the fit, 39 (14%) in the intermediate group and 70 (27%) in the frail group. Increased mortality in the frail group was associated with a higher incidence of toxicity, drug discontinuation and disease progression. Unexpectedly, the performance status alone did not affect OS, whereas the frailty status increased the risk of death by threefold [5].

The IMWG scoring system for frailty was recently validated in a German study that included 125 patients with a median age of 63 years, which is lower than the original publication [6]. Among these patients, the incidence of functional decline and differences in 3-year OS based on frailty score were demonstrated with 91, 77 and 47% surviving for fit, intermediate-fit and frail patients, respectively [6]. Thus before starting the therapy, the frailty score combining age, functional status and comorbidities is useful to determine the appropriateness of a treatment regimen. Ideally, this information should also be included in clinical trials in order to have a better understanding as how known and novel treatment strategies affect more specific subsets of patients.

The IMWG recommends that very fit patients could receive full-dose, triplet therapies or high-dose therapy followed by autologous hematopoietic stem cell transplantation (HDT-ASCT); intermediate or fit patients may benefit from doublet treatments or less intense

triplets and frail patients should receive a gentler, reduced dose doublet approach or palliative treatment [7].

Treatment of older adults with MM

In general, most medical oncology practices are largely based on results of large, multicenter, randomized clinical trials. However, despite efforts from cooperative groups, patients enrolled in trials are generally younger and presumably healthier than the typical geriatric, frail patient with the same cancer. Among patients who receive treatment of a malignancy, about 10% of patients are >75 years of age and 40% are frail [8]. With very few exceptions, there is no evidence that cancer is more or less resistant to treatment in older patients, such that age alone should theoretically not preclude any therapeutic approach.

Treatment of newly diagnosed patients

HDT-ASCT is an effective and widely-used treatment option for those MM patients that are less than 65 years of age [9] and prior to the introduction of novel agents, this was thought to be responsible for improving OS [10]. Although HDT-ASCT is recommended for patients less than 65 years old with newly diagnosed MM (NDMM), in patients older than 65 years, the only prospective, randomized data yielded conflicting results [11,12]. However, with more judicious patient selection and better supportive care, more recent data suggests that elderly patients with a good functional status and low frailty score derive similar benefit as younger patients (<65 years) with HDT-ASCT [13–16], even in patients older than 70 years [17–19]. A retrospective study reported on 53,675MM patients who underwent a first HDT-ASCT in 31 European countries between 1991 and 2010 [20]. In this series, the number of patients undergoing ASCT increased for all groups (<40, 40–49, 50–59, 60–64, 65–69, and >70) with the highest increase in patients aged >65 who accounted for 3% of ASCTs in 1991–1995 and for 18.8% of ASCTs in 2006–2010. Survival improved considerably more in older than in younger patients in recent years. In 2006–2010, median two- and five-year post-transplant survival respectively ranged from 85.9 and 61.5% in patients <40 to 80.2 and 49.7% in those >70. All cause day-100 mortality decreased throughout the observation period to <2.4% for all age groups in 2006–2010. The results of this study highlight increased utilization and safety of ASCT with improved post-transplant survival particularly in elderly patients in recent years in Europe.

However, since most MM patients are >65 with multiple comorbidities and higher frailty scores, it is of particular relevance to consider novel agents for frontline treatment of the elderly population with MM [21]. Table 2. illustrates the reported outcomes from studies investigating various induction regimens in elderly patients with MM, including response rates, PFS, OS, as well as AE and dose modifications and/or discontinuation, when available.

Prior to 2007, frontline chemotherapy with melphalan and prednisone (MP) was considered a standard of care in the treatment of elderly patients with MM who are ineligible for HDT-ASCT [10]. In the past decade with the introduction of thalidomide, bortezomib and lenalidomide, as part of frontline treatment there has been an improvement in the rate of complete response (CR), without substantially increasing toxicity. Prospective, randomized,

phase 3 studies comparing MP with or without novel agents such as bortezomib (VMP regimen) or thalidomide (MPT regimen) have demonstrated that MPT and VMP are superior to MP in terms of time to progression (TTP), progression-free survival (PFS) and OS [10,12,22–24]. More recently the FIRST trial, showed that continuous lenalidomide-dexamethasone (Rd) was superior to 18 cycles of MPT with longer PFS (25.5 vs. 21.2 months; $p < .001$) and was better tolerated [25]. Over half of the patients (54%) were categorized as 'frail' according to the IMWG geriatric assessment and continuous Rd improved PFS and OS in these frail patients compared to MPT.

VMP has been compared with bortezomib-dexamethasone (Vd) and bortezomib-thalidomide-dexamethasone (VTd) in the UPFRONT trial and to bortezomib-thalidomide-prednisone (VTP) in the GEM2005 study [23,26,27]. There was no difference in PFS or OS across treatment arms in the UPFRONT study, suggesting that a bortezomib-based doublet (Vd) may be an acceptable frontline therapy for transplant-ineligible patients. However, PFS was shorter than expected in all arms and likely reflects the high proportion of patients who discontinued treatment for AE, most notably peripheral neuropathy in the setting of intravenous, twice-weekly dosing of bortezomib. Similarly, in the GEM2005 trial, there was more toxicity and treatment discontinuations in the VTP arm compared with the VMP arm, especially in patients >75 years, which likely contributed to the longer PFS and OS in the VMP arm. Both trials suggest that improving tolerability of treatment in order to maintain dosing exposure is imperative. This is consistent with the FIRST trial (continuous Rd) as well as with the several studies indicating that maintenance therapy following HDT-ASCT improves PFS and OS in MM [28–31].

More recently, the SWOG S0777 trial compared bortezomib-lenalidomide-dexamethasone (VRd) versus Rd as frontline treatment in 525 patients with MM. In all comers, VRd demonstrated both a PFS (43 vs. 30 months, HR 0.71) as well as OS (75 vs. 64 months, HR 0.70) which is anadvantage over Rd [32]. These data have established modern triplet therapy as a new standard. It is notable that over 40% of patients enrolled in the trial were age 65 years or older. Dose-adjusted bortezomib-lenalidomide-dexamethasone, the so-called 'RVD lite' regimen utilizing weekly bortezomib (1.3mg/m^2 on days 1, 8, 15 and 22), reduced lenalidomide (15 mg, days 1–21) and modified dexamethasone was designed to balance efficacy and toxicity in older patients [33]. In 48 NDMM patients with a median age of 72 years (range 65–91 years), the ORR was 90% and 1-year PFS was >95%. With this regimen, grade 3 or higher toxicity was minimal and suggests an effective way to deliver the three drug combination.

The second-generation proteasome inhibitor, carfilzomib, has also been investigated in combination with MP (CMP) in elderly patients with NDMM in a phase I/II dose-escalation study conducted by the Intergroupe Francophone du Myelome [34]. Based on the preliminary results, CMP combination appeared to be well tolerated and resulted in 90% ORR with estimated PFS of 21 months and 80% OS at 3-years. Carfilzomib, lenalidomide and dexamethasone (KRD) is another modern triplet which has a significant activity in both newly diagnosed and relapsed patients with MM [35,36]. Among 23 elderly patients with NDMM (median age 72 years, range 65–81) treated with KRD, the ORR was 100 (91% very good partial respose (VGPR)) with 3-year PFS of 80 and OS 100%,respectively [37].

Notably, only four patients discontinued therapy prior to 24 cycles, with only one due to toxicity suggesting safety and tolerability of this regimen, even in this population.

Other induction regimens have been investigated in elderly patients with MM, either consisting of a simple doublet combination with lenalidomide plus dexamethasone, or incorporating alkylating agent such as cyclophosphamide with bortezomib and dexamethasone (VCD, also called CyBorD), or sometimes combining even more agents either synchronously and/or sequentially [25,38–40]. The results from these various induction regimens options are summarized in Table 2. Interestingly, Magarotto et al. demonstrated that the doublet therapy lenalidomide plus dexamethasone regimen is non-inferior to a triplet-combination of an alkylator with lenalidomide and prednisone in elderly, but with significantly less toxicity [41]. As such, less aggressive induction treatment options are often preferred in older patients with MM.

Treatment of relapsed patients

For second or third-line therapy, recent data suggests that triplet therapy extends the duration of remission when compared to doublet therapy [36,42]. In the ASPIRE trial [36], KRD (for 18 cycles) followed by RD was compared with RD in 792 patients with relapsed MM. 50% of patients who enrolled onto the study were 65 years or older (range 31–91) although the overwhelming majority (~90%) had a performance status of 0–1 on the Eastern Cooperative Oncology Group (ECOG) scale. KRD significantly improved outcomes with a 31% reduction in disease progression and an improved median PFS by 8.7 months (26.3 months in KRD arm vs. 17.6 months in the RD arm). Although more AEs occurred in the carfilzomib arm, the median duration of treatment was considerably longer in patients receiving KRD, 88 weeks vs. 57 weeks in the RD arm. Similar numbers of patients (15 and 18%) discontinued treatment in both arms due to AE. Patients in the carfilzomib group reported superior health-related quality of life than those in the control group, based on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Global Health Status and Quality of Life questionnaire.

Ixazomib, the first in class oral proteosome inhibitor, has also been combined with lenalidomide and dexamethasone (IRD) and compared to RD in patients with relapsed MM [42]. Among 722 patients enrolled, 52% were 65 years or older (range 30–91) and had favorable performance status (ECOG 0–1 in 94%). Overall response rates were higher in the IRD arm compared to the RD arm (78 vs. 72%, $p = .04$). The median PFS was extended by six months in the ixazomib group (20.6 vs. 14.7 months) and the hazard ratio for disease progression or death was 0.74 (95% CI, 0.59–0.94, $p = .01$) in favor of IRD. AEs were similar in both arms with the exception of a higher incidence of rash (36 vs. 23%) and more frequent gastrointestinal symptoms, which were almost exclusively low grade and manageable. Patient-reported for quality of life outcomes, as indicated by EORTC QLQ-C30 and the QLQ-MY20 scores, were similar in both arms.

Most recently, daratumumab, a fully human IgG kappa monoclonal-antibody targeting CD38 has been used in combination with bortezomib and dexamethasone (DVd) in the Castor study and lenalidomide and dexamethasone (DRd) in the Pollux trial [43,44]. In the Castor

trial, daratumumab, bortezomib and dexamethasone were compared to bortezomib plus dexamethasone (BD). In both arms the BD was for a fixed duration such that after eight cycles the comparison was of continuous daratumumab versus no therapy. The three-drug regimen was found to be superior with an ORR of 83 vs. 63% and median PFS that was not reached in the Dvd arm versus 7.2 months (HR 0.39). The Pollux trial also showed a higher response in the DRd arm compared to Rd (93 vs. 76%, respectively) and longer median PFS which was not reached in the DRd arm versus 18.4 months (HR 0.37) in the Rd group, despite both arms continuing on Rd until progression. In both trials, approximately 50% of patients were 65 years or older and over 10% were ≥75 years. Although daratumumab-related infusion reactions occurred in almost half of patients in both studies, they were grade 1–2 and occurred during the first infusion in the overwhelming majority of patients. On the basis of these studies, both regimens were approved by the United States Food and Drug Administration (FDA) in November 2016 for the treatment of patients with relapsed MM who have been treated with at least one prior therapy.

Pomalidomide, the newest immune modulating drug was granted FDA approval as a treatment for patients with MM following two prior therapies including lenalidomide and bortezomib in 2013 [45]. Compared to thalidomide and lenalidomide, pomalidomide was more potent preclinically and has a more favorable toxicity profile clinically. The combination of pomalidomide, bortezomib and dexamethasone is now being studied in a randomized phase III trial in patients who have received 1–3 previous therapies [46]. Patients with lenalidomide-refractory MM may benefit from the combination of pomalidomide, cyclophosphamide and dexamethasone which was found to be superior to pomalidomide and dexamethasone alone in a randomized phase II study [47]. Although myelosuppression was greater when cyclophosphamide was added, the differences were not statistically significant and the incidence of febrile neutropenia was similar. When pomalidomide and cyclophosphamide were combined with prednisone, older age was associated with a shorter PFS, suggesting that dose adjustments are necessary in vulnerable patients.

Elotuzumab is an immunostimulatory monoclonal-antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7). This was recently FDA-approved in the second-line setting based on ELOQUENT-2, a randomized phase III trial comparing the efficacy and safety of lenalidomide and dexamethasone with or without Elotuzumab [48]. In that study, after a median follow-up of 24.5 months, the median PFS in the elotuzumab group was 19.4 months versus 14.9 months in the control group (HR for progression or death in the elotuzumab group was 0.70; 95% CI 0.57–0.85; $p < .001$). The ORR in the elotuzumab group was 79 vs. 66% in the control group ($p < .001$). The median duration of treatment was 17 months in the elotuzumab group and 12 months in the control group; 65 and 79% of patients, respectively, discontinued treatment, most commonly owing to disease progression. In the elotuzumab group, the AEs were lower when compared to the control group for ≥ grade 3 neutropenia (34 vs. 44%) but were higher for≥ grade 3 infections (81 vs. 74%), and incidence of herpes zoster (4.1 vs. 2.2 per 100 patient-years). The benefit of adding elotuzumab to Rd was observed across most prespecified subgroups, including patients with resistance to the most recent line of therapy and those who had previous exposure to immunomodulatory drugs (IMIDs) or bortezomib or had a high-risk cytogenetic profile,

particularly the presence of the del(17p) variant. The addition of elotuzumab had no significant effect on patients pain or health-related quality of life, despite being a three-drug regimen that included an intravenous drug and a premedication regimen [48].

High dose therapy followed by a second salvage ASCT has been utilized in MM patients relapsing after a prior ASCT [49]. In one randomized study, 174MM patients (median age 61 years) relapsing after a prior ASCT underwent a bortezomib-based re-induction therapy before a second ASCT with 200mg/m^2 of Mel (n = 89) or low-dose consolidation with weekly cyclophosphamide for 12 weeks (n = 85). Both time to progression and OS were significantly longer in the autologous transplant cohort compared to the nontransplant cohort: 19 vs. 11 months (p < .0001) and 67 vs. 52 months (p = .022), respectively [50]. Other series also suggest activity of high dose melphalan as salvage therapy but most include younger patients, less than 65 and indicate the greatest benefit in patients with a long response duration after first ASCT [51]. Therefore the use of second salvage transplant may be a valuable option in selected patients with a favorable response to initial transplant and a good performance status.

Overall the same treatment paradigm should be applied when treating elderly patients for relapsed disease as for frontline therapy. While the biology of the disease in the relapsed setting in older patients is not distinct from their yourger counterparts, individual characteristics may be. Considering comorbidities and frailty and tailoring therapy with the goals to minimize toxicity and improve delivery of any regimen is paramount to controlling disease and preserving quality of life.

Treatment toxicity in older patients with MM

The availability of highly effective and tolerable drugs offers alternative treatment strategies to those who are unsuitable for alkylators or early generation combination therapies. Each treatment regimen for MM should be tailored to individuals based on their frailty score as well as their susceptibility to particular toxicities. Potential side effects including fatigue, hematologic, gastrointestinal and cardiopulmonary toxicities, infections, peripheral neuropathy, edema and thromboembolic events may be more significant in patients with certain comorbidities and dose reductions must be considered promptly to reduce the risk of significant AEs.

Myelosuppression

Myelosuppression is commonly induced by standard chemotherapy but is also seen commonly with novel MM treatments. Bortezomib, lenalidomide, carfilzomib and alkylating agents all cause thrombocytopenia, especially in combination, whereas it rarely occurs with thalidomide. In the VISTA trial, patients with NDMM who were not candidates for HDT-ASCT received induction treatment with VMP, which was associated with 40% grade 3–4 neutropenia and 37% grade 3–4 thrombocytopenia [22]. In an updated analysis of treatment-emergent AEs by treatment cycle, bortezomib given weekly rather than twice weekly was noted to reduce the frequency of grade 3–4 AE to comparable levels as MP alone, but the regimen was associated with deeper responses and improved outcomes [23]. In general, bortezomib should be given weekly in fragile populations.

In newly diagnosed patients not eligible for ASCT, lenalidomide in combination with melphalan and prednisone (MPR) was associated with a trend towards improved PFS and OS ($p = .06$) compared with MP plus thalidomide (MPT) [52]. However MPR had significantly more grade 3–4 hematologic toxicities (anemia 14 vs. 5%; thrombocytopenia 30 vs. 8%; neutropenia 64 vs. 27%, all had a $p < .01$). Patients >75 years of age had increased rates of hematologic toxicities in both arms. Lenalidomide in combination with bortezomib and dexamethasone (RVd) resulted in 19% grade 3–4 neutropenia and 18% grade 3–4 thrombocytopenia [32].

In general, with lenalidomide-based regimens or any associated with myelosuppression, dose reduction and growth factor support to minimize the risk of neutropenic infection and bleeding in predisposed patients is warranted. G-CSF can be used to prevent febrile neutropenia or when grade 3/4 neutropenia occurs; if grade 4 thrombocytopenia occurs, treatment should be withheld and can be resumed when the event resolves to grade 2 [53]. In addition, sensitive patients with hemoglobin less than 10 g/dL during chemotherapy should be considered for erythropoietin [53,54].

Peripheral neuropathy

Peripheral neuropathy (PN) in patients with MM may be caused by the disease itself or by treatment, particularly by thalidomide and bortezomib. Patients receiving these drugs require close monitoring for subtle signs and symptoms of neuropathy which often develop gradually with thalidomide but may escalate quickly with bortezomib. Up to a quarter of patients develop grade 3–4 neuropathy while receiving MPT which precludes continual administration [12,54,55]. Even in the short-term, dose reductions (from 100 to 50 mg per day) are essential to avoid irreversible damage. When bortezomib is delivered intravenously on a twice-weekly schedule, 22% of patients receiving MPV developed grade 3–4 PN and up to 80% of patients receiving RVd developed neuropathy although the majority were grade 1 and 2 [22–24]. While less severe PN may not even be captured in studies, in frail patients even modest PN is not inconsequential and must be taken seriously in clinical practice. Weekly rather than twice-weekly and subcutaneous instead of intravenous bortezomib is essential for patients at risk for PN. For treatment emergent symptoms, bortezomib at 1.3 mg/m^2 should be reduced to 1.0 mg/m^2 and subsequently to 0.7 mg/m^2 per week [55]. In studies using lenalidomide combinations without bortezomib, far fewer patients reported PN [7,52,55–57]. Thus, lenalidomide-containing regimens should be considered in patients with pre-existing neuropathy or comorbidities that would make PN intolerable.

Venous thromboembolism

Patients with MM are at high risk of venous thromboembolism (VTE) based on individual and disease characteristics as well as exposure to particular therapies [58]. Advanced age, obesity, immobility and the need for surgery increase an individual’s risk of VTE. The diagnosis of myeloma itself, the disease burden it brings and hyperviscocity are all myeloma related factors leading to VTE. Patients treated with immune modulating agents (thalidomide, lenalidomide or pomalidomide) in combination with steroids or multiagent chemotherapy are at greatest risk of VTE [12,38,52,56,59]. Thus, patients with MM should receive appropriate thromboprophylaxis [60,61]. During thalidomide or lenalidomide

treatment, ASA (81–325 mg) should be administered as the standard of care with no other significant risk factors for VTE [62]. However, in high risk patients with two or more additional risk factors for VTE, prophylactic low molecular weight heparin (enoxaparin 40 mg once daily) or dose adjusted therapeutic warfarin should be administered [63–65]. For patients who develop VTE, treatment should be temporarily interrupted and they should receive anticoagulation therapy indefinitely as long as they are on an IMID [66].

Renal failure

Renal failure is a common problem in MM usually due to light chain deposition and damage of proximal tubules along with nephrotoxic drugs [67]. High dose dexamethasone is a rapid intervention to assure a fall in light chain load. In the case of acute renal failure or for patients requiring dialysis, bortezomib can be safely used without dose modifications [5]. In the case of chronic renal impairment, lenalidomide and pomalidomide can be administered but with dose reductions based on creatinine clearance [6]. Appropriate lenalidomide dose reductions are mandatory: 10 mg per day when creatinine clearance (CrCl) is 30–50 mL/min; 15 mg every other day when CrCl is less than 30 mL/min and 5 mg per day after dialysis when the patient requires dialysis.

Polypharmacy

The term ‘polypharmacy’ has a definition that is multifaceted. Polypharmacy can refer to prescribing a number of medications (some inappropriate) to a single individual, which can increase the risk for adverse drug reactions [68]. The underuse or duplication of medications may also constitute polypharmacy. Older adults with cancer are particularly vulnerable to polypharmacy because of comorbid conditions requiring medical management at the same time they require chemotherapy and adjunctive or supportive medications [69]. A study of 100 consecutive hospitalized cancer patients found that patients received an average of eight medications with 63% having the potential for an adverse drug interaction; more than half of these interactions were classified as moderate-to-severe risk [70]. The Beers criteria for potentially inappropriate medication use in older adults were updated in 2015 and may be a valuable tool to evaluate polypharmacy in older adults with cancer [71,72].

Additional toxicity considerations

Other toxicities that occur less frequently or are considered less troublesome in the general population can be threatening to a frail patient. Grade 1 fatigue or grade 2 diarrhea are tolerable in patients with some reserve but can result in criticial deficits in a vulnerable population with longterm consequences. Side effects from corticosteroids including sleeplessness, mood disturbance and muscle weakness can be similarly debilitating in elderly or compromised patients. With durable disease control and not cure the reality and goal for most patients, quality of life must be considered throughout the patients course.

General considerations and reccomendations

Randomized phase III studies in elderly patients provide the best insight into the most appropriate treatment regimens to minimize toxicity and improve outcomes but are not always available. It is also important to recognize that patients participating in trials are

often fitter than a less selected population of MM patients. While the most recent data suggests that triplet drug regimens are safe and more effectively control disease, unselected elderly patients treated in community settings may be less able to withstand the AEs associated with combinations of multiple drugs. Declines in quality of life on therapy, reduces treatment adherence and impacts disease related outcomes. It is therefore critical that these patients are closely monitored and any emergent AEs are promptly and appropriately managed. Table 2 summarizes the reported grade 3–4 AEs and dose adjustments (when available) for induction regimens studied in elderly patients with MM. Decisions for treatment discontinuation or dose reductions should be individualized for each patient, depending on grade of toxicities, comorbidities and other risk factors for complications. For very elderly and/or frail patients, tailored reduced intensity regimens are necessary from treatment initiation to encourage treatment adherence and reduce discontinuation [73]. Improving tolerability of treatment regimens and lengthening progression-free survival has been shown to improve health-related quality of life (QOL) for patients living with MM.

With these considerations, we offer the following recommendations. For fit elderly patients without comorbidities or disabilities, VRd induction for up to eight cycles is an appropriate option [32]. Weekly and subcutaneous administration of bortezomib should be considered and VRd should be followed by Rd maintenance until progression [28,32]. However, if either bortezomib or lenalidomide is not tolerated, the dose should be reduced or discontinued. An alternative in fit patients is the use of high dose therapy and ASCT following a non-alkylator based induction regimen [74,75]. Lenalidomide maintenance following ASCT extends time to disease progression and OS [76] but is associated with more toxicity and secondary cancers [28,77]. Patients over seventy years of age were not included in post-transplant maintenance studies. Therefore, the benefit of lenalidomide maintenance in this population is uncertain but is presumed given the advantage of lenalidomide maintenance in the elderly in other settings.

Unfit or frail patients are rarely studied and few clinical trials have been dedicated to patients over the age of 75 years. No studies have been prospectively designed based on frailty [4,5,6]. However, given the higher incidence of toxicity and discontinuation of treatment, dose adjustments upfront are fundamental. Bortezomib should always be given weekly with low-dose steroids; lenalidomide can be given at a standard dose with low-dose dexamethasone. Initial doublet therapy is reasonable in this population although RVD lite can also be considered. We favor Rd over Bd for most of these patients with the exception of those who present with cast nephropathy, have baseline renal insufficiency or myelosuppression from other causes. The oral regimen is preferred when traveling back and forth to appointments is difficult but subcutaneous administration may be favored in patients whose compliance is questionable.

In all patients efficacy and toxicity of treatment should be evaluated every cycle in order to identify toxicity, avoid ineffective therapies or alternately overtreatment. While some side effects will be ameliorated by dose reductions, holding treatment may be necessary to facilitate adequate recovery and to identify the offending agent. Steroids alone, even at low doses, can cause significant toxicity in frail and/or elderly patients. While often essential,

supportive measures such as antimicrobial prophylaxis, anti-emetics and analgesics can also be harmful. With careful attention to toxicity in the frontline setting, there should be several options for second line therapy and beyond. The anti CD-38 antibody, daratumumab in combination with either lenalidomide or bortezomib may be particularly effective in those who are lenalidomide or bortezomib naïve, respectively. Elotuzumab in combination with lenalidomide is another option, particularly in patients treated with upfront bortezomib. With the exception of the high incidence of infusion reactions that occur with the first dose but not beyond that, the favorable safety profile of both monoclonal antibodies makes their use especially appealing for elderly or frail patients.

In summary, the introduction of novel agents has improved outcomes for all patients with multiple myeloma, including the elderly [8,78]. However, despite the promise of newer therapies, multiple myeloma remains incurable in all but a few patients. Decisions regarding therapy in older adults with multiple myeloma must balance the burden of disease, the risks and benefits of therapy and the patients goals of care. Pretreatment assessment in elderly patients that combines age, functional status and comorbidities is useful to determine the appropriateness of a regimen. Tailored treatments based on an individual's functional status are imperative to limit treatment related toxicities while improving quality of life and overall survival.

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Table 1.

IMWG frailty score*.

Variable	Hazard ratio (CI 95%)	*p* value	Score
Age			
<75 years	1	–	0
75–80 years	1.37 (0.93–2.03)	0.114	1
>80 years	2.75 (1.81–4.18)	<0.001	2
Charlson index	1	–	0
≤1			
≥2	1.6 (1.07–2.39)	0.021	1
ADL score	1	–	0
>4			
≤4	1.76 (1.14–2.71)	0.01	1
IADL score	1	–	0
>5			
≤5	1.53 (1.03–2.27)	0.036	1
Additive total score	Patient status		
0	Fit		
1	Unfit		
≥2	Frail		

IMWG: The International Myeloma Working Group; ADL: activities of daily living; IADL: instrumental activities of daily living.

*Adapted from Palumbo et al. [5].

Table 2.

Selected induction regimens for elderly patients with reported outcomes and adverse events.

Reference	Patients	Median age (range)	Regimen	Response rate	Median PFS (months)	Median OS (months)	Grade 3–4 AEs	Notes/Dose adjustments
Palumbo et al., Blood, 2015 [5]	869 A: Fit 340 B: Int 269 C: Frail 260	74 (70–78)	Len-based 76%; Prot. inhib-based 24%	N/R	3-yr OS A: 48% B: 41% C: 33%	3-yr OS A: 84% B: 76% C: 57%	Hem/Non-hem A: 38%/18% B: 35%/22% C: 30%/30%	Reduced/Discontinued A: 21%/17% B: 22%/22% C: 16%/25%
Facon et al., Lancet, 2007 (IFM 99–06 trial) [12]	195	65–75	MPT	ORR 76% CR 13% VGPR 34% PR 29%	27.5	51.6	Hem: A 14%/N 48%/T 14% VTE 12% Peripheral neuropathy 6% Somnolence 8% Infections 13% Cardiac arrhythmia 2% Constipation 10%	TRM: 0%. Starting Thalidomide: 52% ≤200mg/d 48% >200mg/d Dose increased: 9%; Dose reduced: 40%; Discontinued: 45% due to AE.
San Miguel et al., NEJM, 2008; Mateos et al., Lancet Oncol, 2010; San Miguel et al., JCO, 2013 (VISTA trial) [22–24]	340	71 (57–90)	VMP	ORR 74% CR 34% VGPR 8% PR 33% SD 23% POD 1%	21.7	56.4; 3-yr OS 68.5%	Hem: A 19%/N 40%/T 37% GI: N/V 4% Diarrhea 8% Infections: PNA 7% Zoster 3% Pyrexia 3% CNS: Neuralgia 9% Peripheral neuropathy 13% Others: Fatigue 8% Anorexia 3% Asthenia 6% Dyspnea 4% Hypokalemia 7%	TRM 1%. Discontinuation due to AE: 15%; Bortezomib alone discontinued in 19%.
Mateos et al., Lancet Oncol, 2010 [23]	130	73 (69–76)	VTP	ORR 81% CR 28% VGPR 8% PR 45% SD 17% POD 2%	25	3-yr OS 65%	Hem: A 8%/N 22%/T 12% Cardiac 8% Neuropathy 9% Infections 1% GI 2% VTE 2%	TRM 5%. Discontinuation due to AE: 17%.
Benboubker et al., NEJM, 2014 [25]	535	73 (44–91)	Rd (continuous)	ORR 75% CR 15% VGPR 28% PR 32% SD 19% POD 1%	25.5	3-yr OS 70%	Hem: A 18%/N 28%/T 8% Infection 29% Cardiac 12% VTE 8% Asthenia 8% Fatigue 7% Back pain 7% Hypokalemia 7% Hyperglycemia 5% Rash 6% Cataracts 6% Dyspnea 6%	Multiple dose modifications per pre-determined protocol

Reference	Patients	Median age (range)	Regimen	Response rate	Median PFS (months)	Median OS (months)	Grade 3–4 AEs	Notes/Dose adjustments
							Constipation 2% 2nd cancer 3%	
Durie et al., Lancet, 2017 [32]	242	63 (IQR 56–70)	VRd	ORR 81% CR 16% VGPR 28% PR 38% SD 16% POD 3%	43	75	Hem: 47% Neuropathy 33% Infection 15% Constitutional 20% GI 22% Cardiac 7% Vascular 9% 2nd cancers 1%	23% discontinuation due to AE (others at time of achieving disease control); no discontinuation due to AE
Moreau et al., Blood, 2015 [34]	68	72 (66–86)	CMP	ORR 90% CR 12% VGPR 46% PR 32% SD 10% POD 0%	21	3-yr OS 80%	Hem: A 35%/N 38%/T 28% Infections 7% GI: Nausea 6% Elevated LFTs 4% Cardiovascular: CHF 4% Afib 1.5%, HTN 3% DVT 1.5% Peripheral neuropathy 1.5% AKI 3% Fatigue 3%	No treatment discontinuation in any patient; dose reduction not reported
Mateos et al., Blood, 2016 [38]	233	75 (65–89)	VMP-Rd Sequential or Alternating	ORR 78% CR 24% VGPR 22% PR 15% SD 3% POD 14%	33	3-yr OS 73%	Hem: A 3%/N 21%/T 21% Infections 6% GI 6% VTE 3% Rash 5% Peripheral neuropathy 3%	TRM 6%. Discontinuation 14% in sequential (6.4% SAE) vs. 18% in alternating (9.3% SAE) scheme.
Zepeda et al., Blood, 2014 (Abstract) [39]	20	76 (66–90)	CyBorD (VCD)	ORR 95% CR 15% VGPR 55% PR 25% SD 5% POD 25%	N/R	N/R	Hem: 10% Non-hem (20%): PNA Muscle weakness Sepsis	10% dose-reduction; 5% discontinuation cyclophosphamide due to cytopenia
Palumbo et al., JCO, 2014 [40]	250	71 (IQR 68–75)	VMPT-VT	ORR 89% CR 38% VGPR 21% PR 30% SD 6% POD 1%	35.3; 3-yr PFS 56%	3-yr OS 89%; 5-yr OS 61%	Hem: A 10%/N 38%/T 22% Fatigue 6% Cardiac (11%): CHF 3% Arrhythmia 4% MI/angina 2% CNS (21%): Neuralgia 4% Neuropathy 11% Both 4% Infections (13%): PNA 6% Neutrop fever 2% Sepsis 2% Other 2% GI 6% VTE 5% Others 11%	TRM 4%. Discontinuation due to AE: 28%; ≤75years: 25% had dose interruption due to AEs with 81% of planned bortezomib dose intensity given over median 24 months; >75years: 35% had dose interruption due to AEs with 58% of planned bortezomib dose intensity given over median 11 months.

Reference	Patients	Median age (range)	Regimen	Response rate	Median PFS (months)	Median OS (months)	Grade 3–4 AEs	Notes/Dose adjustments
Zweegman et al., Blood, 2016 [49]	319 318	73 (60–87) 72 (60–91)	MPR MPT	ORR 84% CR 11% VGPR 45% PR 39% ORR 81% CR 10% VGPR 37% PR 34%	23 20	3-yr OS 69%; 4-yr OS 56% 3-yr OS 64%; 4-yr OS 52%	Hem: A 14%/N 64%/T 30% Neuropathy 1% VTE 8% Hem: A 5%/N 27%/T 8% Neuropathy 7% VTE 8%	Discontinuations mostly due to AEs: 41% in MPR, 49% in MPT; mainly occurred in pts >75 (51 vs. 32%).

N/R: not reported; IQR: interquartile range; Hem: Hematologic; A/N/T: Anemia/Neutropenia/Thrombocytopenia; ORR: overall response rate; VGPR: very good partial response; PR: partial response; SD: stable disease; POD: progression of disease; PFS: progression free survival; OS: overall survival; AEs: adverse events; MPT: melphalan, prednisone, thalidomide; VMP: bortezomib, melphalan, prednisone; VTP: bortezomib, thalidomide, prednisone; Rd: lenalidomide, dexamethasone; VRd: bortezomib, lenalidomide, dexamethasone; CMP: carfilzomib, melphalan, prednisone; VMP-Rd: bortezomib, melphalan, prednisone - lenalidomide, dexamethasone; CyBorD(VCD): cyclophosphamide, bortezomib, dexamethasone; VMPT-VT: bortezomib, melphalan, prednisone - bortezomib, thalidomide; MPR: melphalan, prednisone, lenalidomide; MPT: melphalan, prednisone, lenalidomide; LFT: liver function tests; CHF: cardiac heart failure; Afib: atrial fibrillation; DVT: deep venous thrombosis; AKI: acute kidney injury; CNS: central nervous system.