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Management of Newly Diagnosed Elderly Multiple Myeloma Patients

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Abstract

Purpose of Review Given the median age at diagnosis of 69, multiple myeloma (MM) is commonly identified among elderly individuals. Over-treatment of the frail may lead to unnecessary morbidity, while under-treatment of fit elderly patients may prevent improvement in organ function; both instances reducing quality of life. Here, we summarize assessments of frailty and include considerations in managing newly diagnosed elderly MM patients.

Recent Findings Eligibility criteria for studies of anti-myeloma agents have traditionally relied on performance status and comorbidities; however, geriatric and myeloma-specific frailty assessments are beginning to be incorporated for more accurate stratification of patients for treatment. The IMWG and R-MCI scores are validated metrics that predict survival in elderly MM patients. In addition, dose-attenuated induction regimens and conditioning before autologous transplant may decrease morbidity in elderly MM patients.

Summary Although MM remains incurable, multi-drug regimens have the ability to prolong survival of both untreated and relapsed elderly patients. Older patients require a highly individualized approach since they may have preexisting organ dysfunction, worse frailty scores, and variable goals of care.

Keywords Multiple myeloma · Elderly · Geriatric assessment · Frailty · Autologous stem cell transplantation

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy and results from clonal proliferation of neoplastic plasma cells in the bone marrow and production of monoclonal immunoglobulins, leading to end organ damage. MM and its asymptomatic precursor, MGUS, are generally considered diseases of the elderly with a median presentation at ages 69 and 72, respectively [1, 2]. In addition, the global proportion of elderly people is rapidly increasing, with the number of people over age 80 expected to quadruple between 2000 and 2050, and MM appears to be increasing in parallel [3, 4]. Considering nearly 40% of MM patients are older than 75 at diagnosis, one cannot stratify the elderly for treatment without considering factors associated with aging, such as comorbidities and functional status [5]. The complexity of caring for older adults with MM arises in part from the heterogeneity of aging, with patients ranging from extremely fit to severely frail, as well as the myriad comorbid conditions that may further impair organ function [6]. Patients older than 75 with reduced performance status have a shorter MM-specific survival; however, overall survival appears to be improving in older MM patients with the use of novel agents [7, 8].

The introduction of novel anti-myeloma drugs along with consolidation with high-dose melphalan followed by autologous stem cell transplantation (ASCT) has marked an era of significant therapeutic advancement [9]. Clinical trials of novel agents typically categorize elderly MM patients holistically according to whether they are considered fit for ASCT following initial induction treatment, rather than strictly according to age [10••, 11••]. The introduction of novel anti-myeloma agents, including proteasome inhibitors (PIs), immunomodulators (IMiDs), as well as monoclonal antibodies (mAbs) to the

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upfront setting has changed the treatment landscape and substantially extended both progression-free survival (PFS) and overall survival (OS) [10••, 11••]; these being common endpoints for regulatory approval [12]. In addition, these drugs are more effective and typically better tolerated, allowing older patients to be candidates for either full or attenuated doses. However, many clinical trials continue to under-enroll and sometimes exclude older patients based on age, performance status, or comorbidities, particularly if ASCT is included [13, 14••]. Most studies have characterized elderly patients as being older than 65 years, leading to a knowledge-gap in treatment strategies for those most often affected by the disease [15]. Older and frail adults remain at greater risk for early mortality and experience poorer survival than their younger counterparts, highlighting the need for further research to optimize treatment in older MM patients [16]. In this review, we discuss strategies to approach the initial management of elderly MM patients.

Challenges in Managing Elderly Myeloma Patients

Normal aging is associated with progressive decline in physiological systems, including but not limited to cardiovascular, renal, and hepatic function, and an overall decrease in physiological reserve [9]. As listed in Table 1, elderly MM patients often have concomitant disabilities and comorbidities. Thus, they require a different therapeutic approach compared to younger patients, making treatment decisions complex. For example, patients with chronic kidney disease and reduced creatinine clearance < 60 mL/min require dose reductions in drugs such as lenalidomide, an immunomodulatory drug (IMiD) commonly used with initial treatment, and zoledronic acid, a bone-modifying agent used to prevent skeletal events [17, 18]. The aging process can affect the pharmacokinetics/pharmacodynamics of anti-myeloma agents, altering clinical efficacy and potentially increasing toxicity [19]. Disease-related factors, such as high-risk cytogenetics, add additional complexity, as no regimen has shown consistent survival benefit in high-risk elderly patients [20].

Geriatric impairment is prevalent but not easily detectable without dedicated assessment. This increases the potential risk of undertreating the fit or over-treating the frail. Although it has been shown that OS is decreased in the elderly population compared to younger patients, there does not appear to be a significant difference in disease presentation [21]. In addition, the incidence of more aggressive high-risk cytogenetic findings such as t(4;14) and del(17p) have been noted to be less prevalent in patients older than 65 [22, 23].

For an elderly patient with newly diagnosed MM, the primary objective is to determine a treatment approach tailored to the disease biology as well as the patient's age, performance status, and comorbidities, while maintaining a meaningful quality of life (QOL). Although achieving a deep complete remission (CR) is an important goal irrespective of age [24], there is a substantial risk of treatment-related toxicity in elderly, less-fit patients, and it may be necessary to aim for a more modest remission such as a very good partial remission (VGPR) or partial remission (PR) for control of disease burden [25]. In addition, novel agents are associated with adverse events that may impair QOL, and premature discontinuation or the need for substantial dose reductions can diminish the reported efficacy [9, 26]. It is therefore important to establish at diagnosis whether the goal of treatment is palliation intended to prevent worsening end-organ function versus maximal disease control by achieving a deep remission, or a middle ground between these extremes. The art of managing elderly MM patients involves balancing competing disease-related and patient-specific factors (Fig. 1).

Table 1 Potential compromise of organ function with aging and MM

Organ system	Normal aging	Multiple myeloma	Converging complications	Multiple myeloma management
Bone health	Decreased bone density	Lytic bone disease	Fractures	Bone-modifying agents
Bone marrow reserve	Decreased cellularity	Cytopenias	Fatigue	Anti-myeloma treatment, transfusions as needed
Cardiovascular function	Coronary artery disease	Cardiac amyloid	Cardiomyopathy	Anti-myeloma treatment, autologous transplant
Immune system	Immunosenescene	Immunocompromise	Infections	Prophylaxis for specific anti-myeloma regimen
Renal function	Decreased renal mass	Acute renal failure	Reduced GFR	Avoid nephrotoxins, drug dose modifications

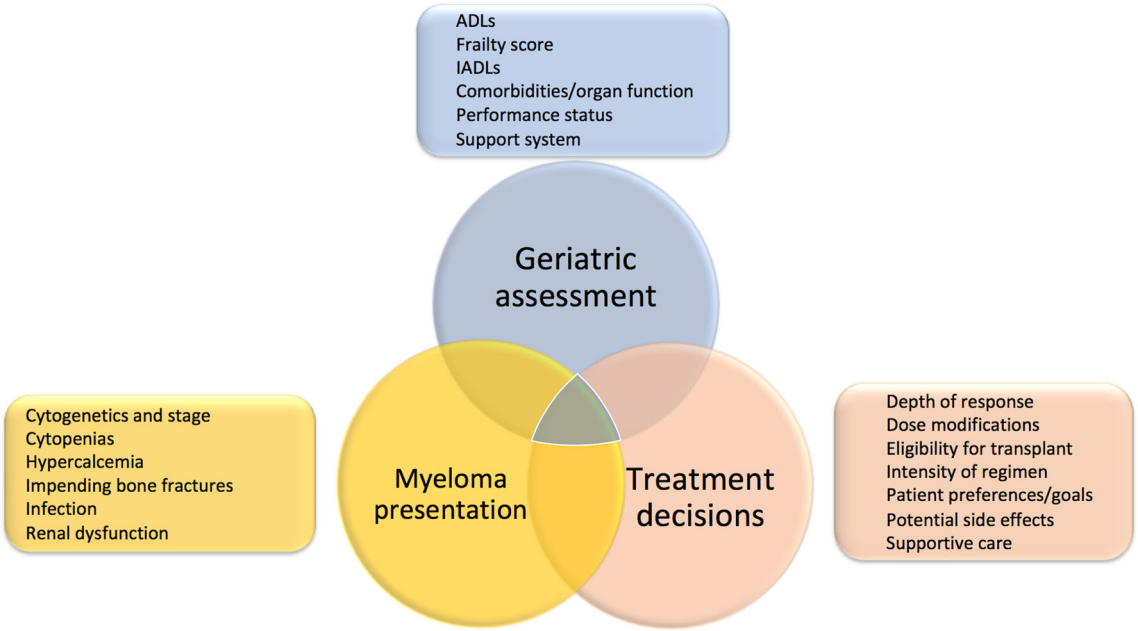

Fig. 1 Competing factors in managing elderly MM patients. ADLs activities of daily living, IADLs instrumental activities of daily living

Assessment Tools to Stratify Elderly Myeloma Patients

Frailty is a state of increased vulnerability, with cumulative deficits in several physiological systems, resulting in diminished resistance to stressors [27, 28]. It has been associated with poor therapeutic response, increased toxicity, and worse survival for patients with blood cancers [29], including MM [30]. Approximately one third of MM patients at diagnosis are frail, making the rigorous assessment for frailty increasingly important to improve outcomes. Simple measures of daily activity such as the Karnofsky performance status (KPS) or the Eastern Cooperative Oncology Group (ECOG) performance status scores have been predominantly used for considering patients for clinical trials and tailoring management. While easy to apply in a clinical setting, these are limited by their focus on daytime activity, are subjective measures, and do not accurately predict outcomes in MM [9].

Frail patients are at high risk of nonhematologic adverse events (AEs) and treatment discontinuation, regardless of other prognostic factors, and require a thorough evaluation of their ability to tolerate treatment [28]. Chronological age, performance status, and in-office assessments based on physical examination are imprecise and may not be sufficient to objectively distinguish patients who are more or less fit for intensive treatment. Thus, more accurate assessments of functional status incorporating comorbidities and other factors are needed [31]. Toward this goal, several groups have proposed scoring systems to more objectively assess frailty and stratify patients for treatment, as described below.

A number of comprehensive tools have been proposed to optimize clinical judgment of frailty in cancer patients, with geriatric assessment (GA) being a more sensitive predictor of frailty [19]. A comprehensive GA (CGA) is an interdisciplinary evaluation using validated tools that can quantify frailty [32••]. Domains of the CGA include comorbidities, function (including dependence on daily activities and falls), cognition, polypharmacy and inappropriate medications, social support, and depression or psychological distress, with the goal of identifying unrecognized determinants of frailty in the elderly [6]. Because a full CGA is a time-consuming procedure that is difficult to apply in everyday clinical practice, a simplified GA that includes Katz and Akpom's basic activities of daily living (ADL) scale [33], Lawton and Brody's instrumental ADL (IADL) scale [34], and the Charlson comorbidity index (CCI) [35], can be used to assess elderly patients. While each of these GA tools have shown value in distinguishing outcomes in various cancers, they are not myeloma-specific, and when used in isolation may not adequately stratify MM patients for treatment [36, 37••].

The International Myeloma Working Group (IMWG) evaluated the predictive role of a GA tool applied to MM patients in a study of 869 elderly newly diagnosed MM patients with a median age of 74 years, with 46% being older than 75 years. As shown in Table 2, age, performance status, and elements on the CCI lead to a scoring system indicating "fit," "intermediate-fit," and "frail." The resulting IMWG frailty score predicted both survival and risk for toxicity. The 3-year overall survival for fit, intermediate-fit, and frail patients was 84%, 76%, and 57%, respectively, and the cumulative incidence of

Table 2 Elements on of the MM-specific IMWG and R-MCI frailty indices

Factor	IMWG	IMWG points	R-MCI	R-MCI points
Link	www.myelomafrailtyscorecalculator.net		www.myelomacomorbidityindex.org	
Age	≤ 75 years	0	60–69 years	1
	76–80 years	1	≥ 70 years	2
	> 80 years	2		
Performance Status	ADL Katz (6-item) > 4	0	KPS 80–90	2
	ADL Katz (6-item) ≤ 4	1	KPS < 70%	3
	iADL Lawton (8-item) > 5	0		
	iADL Lawton (8-item) ≤ 5	1		
Comobidities	CCI index ≤ 1	0	Renal Disease, GFR < 60	1
	CCI Index ≥ 2	1	Moderate/severe pulmonary disease	1
Cytogenetic	–	–	Unfavorable	1
Other	–	–	Moderate/severe frailty phenotype	1
		Fit = 0 Intermediate = 1 Frall = 2		Fit = 0–3 Intermediate = 4–6 Frall = 7–9

grade ≥ 3 nonhematologic AEs at 1 year in these groups was 22%, 26%, and 34%, respectively [32••]. The impact of the IMWG score on clinical outcomes was validated in a well-characterized external cohort of 125 newly diagnosed MM patients [38•]. Both univariate and multivariate analyses found that cytogenetics, impaired renal function, lung function, and KPS were key factors that improved its prediction of fit, intermediate-fit, and frail patients. This led to the development of a "revised" myeloma comorbidity index (R-MCI) designed to incorporate these relevant risk factors, as well as MM-related cytogenetics, as shown in Table 2. The R-MCI was evaluated in a large cohort of 801 consecutive newly diagnosed MM patients with a median age of 63 years, 13% of which were older than 75 [37••]. Lastly, in a study of 351 MM patients ages 57–71, investigators at Mayo Clinic proposed a simpler frailty index, with age ≥ 70, ECOG performance status ≥ 2, and NT-pro-BNP ≥ 300 ng/L defining a scoring system of 1 point per risk factor [39•]. The median OS was not reached in absence of these risks and was significantly worse at 58, 28, and 18 months, with 1, 2, or 3 risk factors, respectively. Results from this study await validation, but further confirm the importance of incorporating multiple parameters of a GA to guide the determination of fitness in newly diagnosed MM patients. Given that MM primarily affects the elderly whose vulnerabilities can change over time, it is reasonable to incorporate serial geriatric assessments throughout treatment in order to potentially modify or escalate therapy over time, though this remains to be incorporated into standard practice. For those patients who are too frail to tolerate treatment and/or anticipated to have a short life-expectancy, the use of GA can also be helpful to facilitate end-of-life care discussions [40].

Considerations for Transplant-Eligible Patients

Upfront consolidation with ASCT following induction remains the standard of care in MM, particularly in patients with higher-risk disease. However, patients older than age 65 have historically been considered ineligible for ASCT due to the risk of transplant-related mortality (TRM) associated with impairment in organ function and reduced drug tolerance when challenged with high dose melphalan (200 mg/m^2, MEL200) [41]. Despite its cost-effectiveness, insurers may limit reimbursement for ASCT in the elderly [42, 43]. Data from several retrospective studies support the efficacy of ASCT in older MM patients considered fit enough for high-dose melphalan [44, 45]. As such, incorporation of stem cell transplantation appears to be increasing in the management of elderly MM patients, with favorable outcomes [46, 47•].

In order to decrease mortality associated with ASCT, the use of attenuated doses of melphalan was initially suggested by the Italian Multiple Myeloma Study Group (using melphalan 100 mg/m^2, MEL100) [48, 49] and the Little Rock Arkansas Group (using melphalan 140 mg/m^2, MEL140) [41, 50]. Palumbo and colleagues established the superiority of MEL100 in the context of ASCT compared to conventional doses of oral melphalan and prednisone alone [48]. In addition, MEL140 was associated with considerably lower TRM than MEL200 [41]. In contrast, the European IFM 99-06 study randomly assigned 447 newly diagnosed MM patients

ages 65–75 to oral melphalan (0.25 mg/kg) and prednisone (MP), MP plus thalidomide (MPT), or reduced-intensity conditioning (RIC) MEL100 with ASCT [51]. The primary endpoint, median OS, was significantly better for the MPT regimen (51.6 months) compared to MP (33.2 months, $p = 0.0006$) or RIC ASCT (38.3 months, $p = 0.027$). There was no survival difference between MP and RIC ASCT, and although there were imbalances between the groups favoring MPT, the authors concluded that the triplet MPT regimen was superior for newly diagnosed elderly MM patients.

While the majority of therapeutic studies examining untreated elderly MM patients above age 65 have considered them ineligible for ASCT [52, 53], several prospective studies have examined dose attenuated conditioning chemotherapy [47, 49, 54]. Using a more modern induction regimen containing the PI bortezomib, Gay et al. prospectively studied 102 newly diagnosed MM patients between ages 65 to 75 ineligible for MEL200 but treated with a combination of bortezomib, pegylated liposomal doxorubicin, and dexamethasone (PAD) for 4 cycles followed by two doses of MEL100 and ASCT; lenalidomide was also given as consolidation and maintenance [54]. The CR rate was higher after transplant (33%) and consolidation (49%) compared to after PAD (12%). Deaths related to AEs, primarily related to induction and transplant, were significantly higher in patients older than age 70 (19%) compared to younger patients (5%). The authors suggested that this regimen including modern agents and MEL100 ASCT might be suitable for fit elderly MM patients without comorbidities. In a study by Straka et al., 434 newly diagnosed MM patients between ages 60–70 were randomized to receive induction with conventional anthracycline-based chemotherapy (without modern agents) or no induction; all patients were planned to undergo double ASCT with MEL140 within a 3 month time frame, with no maintenance therapy given [55]. Eighty-five percent of patients received at least one ASCT and 69% completed a double transplant; fewer patients older than 65 completed tandem transplant (65 versus 73%). There was no difference in median PFS with or without induction chemotherapy (21.4 versus 20 months), and patients older than 65 (55%) did not have inferior outcomes following transplant. Patients 65–70 had a higher discontinuation rate than younger patients (18% versus 9%), but there were no differences in deaths following single or double ASCT (< 2%). This study provides additional support for the tolerability of attenuated dose melphalan in patients 65 or older undergoing ASCT.

Multiple parameters can be used as criteria to assess fitness for ASCT based on organ function (Table 3). For fit patients with comorbidities, the hematopoietic cell transplant comorbidity index (HCT-CI) can help predict nonrelapse mortality associated with stem cell transplant and gauge fitness for ASCT (http://www.hctci.org/Home/Calculator) [56, 57]. While the need for upfront ASCT in patients who achieve deep remissions following induction is debatable [58], prospective studies that include induction with modern anti-myeloma therapy and stratify patients by fitness measures are warranted to further delineate the evolving role of ASCT in elderly MM patients.

First-Line Treatment of Transplant-Ineligible Patients

There is no consensus on the optimal first-line induction regimen for older MM patients, and multiple evidence-based combination regimens have been described [19, 59]. Multiagent induction therapy is well established in managing MM, and the decision to pursue doublet, triplet, or even quadruplet therapy should be fitness- and disease-adapted (Fig. 2). At present predictive markers of response are lacking outside of established cytogenetic risk groups, leading to some confusion about the optimal first-line regimen [60]. Patients with high-risk cytogenetic features, such as deletion 17p [61], may benefit from triplet regimens that include a PI, IMiD, or mAb [62]. For example, in the phase II EVOLUTION study which enrolled 140 newly diagnosed MM patients, 31% of which were older than 65, the 1-year PFS was similar in high-risk ($n = 24$) and standard-risk patients treated with combination regimens containing a PI and/or IMiD [63].

Prior to the introduction of novel agents, MP was primarily used as the comparator group for treatment of elderly MM patients, with a median OS of 29–37 months [53]. The introduction of novel agents has demonstrated a PFS and OS benefit over conventional therapies, with favorable toxicity profiles, establishing these agents as preferable frontline options [64–67]. Thalidomide was the first IMiD used in MM and was evaluated in a meta-analysis which included 1685 previously untreated elderly patients with myeloma, demonstrating that the addition of thalidomide to MP (MPT) produced significantly longer PFS (20.3 versus 14.9 months, $P = 0.023$) and median OS (39.3 versus 32.7 months, $P = 0.004$), which was consistent across all prognostic subgroups. However, the incidence of adverse events was higher in the MPT arm [68]. Lenalidomide, a second-generation IMiD, has also been evaluated in multiple randomized studies as part of the backbone therapy in elderly myeloma patients. In the randomized phase III FIRST trial, lenalidomide and low-dose dexamethasone (Rd) was compared to MPT in transplant-ineligible patients [66]. In this landmark study, PFS and OS was improved with continuous Rd in elderly MM patients over age 75 (using modified doses of the drugs), allowing the achievement of better dose intensity rather than frequent interruptions with standard dosing [69•]. A randomized study comparing Rd to lenalidomide-based triplet regimens containing an alkylating agent and a steroid in elderly MM patients failed to show

Table 3 Common parameters used to assess fitness for ASCT

Assessment for ASCT	Test in MM patients	Criteria
Performance status	History and physical exam	ECOG 2 or better, or KPS > 70%
Transplant comorbidity index	HCT-CI	HCT-CI score 1 or better
Disease status	Reduction in M-spike at least 50%	At least partial remission
Cardiac function	Echocardiogram or MUGA scan	EF > 40%
Hepatic function	Liver function tests	Bilirubin < 2–3× upper limit of normal
Renal function	Creatinine clearance	GFR > 40 mL/min
Psychosocial/economic evaluation	Family support, insurance approval	Must be compliant and have caregiver/support throughout

superiority of the triplet regimens compared the Rd doublet [70].

PIs, such as bortezomib, have also shown to benefit elderly MM patients. Bortezomib was tested in the first-line setting in transplant-ineligible patients in the phase III VISTA study [64]. Six hundred eighty-two newly diagnosed MM patients with a median age of 71 (30% of the total were age ≥ 75) were randomized to bortezomib-melphalan-prednisone (VMP) versus MP alone. VMP was associated with higher response rates (CR of 30% versus 4%, $P < 0.001$), PFS (24 versus 16.6 months, $P < 0.001$), and OS (not reached versus 43 months, $P < 0.001$). Grade 3 or higher peripheral sensory neuropathy was more frequent with bortezomib (14 versus 0%); however, since the study was published, neuropathy has been diminished with administration of bortezomib subcutaneously instead of intravenously, which is now the convention. In the phase III UPFRONT trial, three bortezomib-based regimens (VD versus VTD versus VMP) followed by

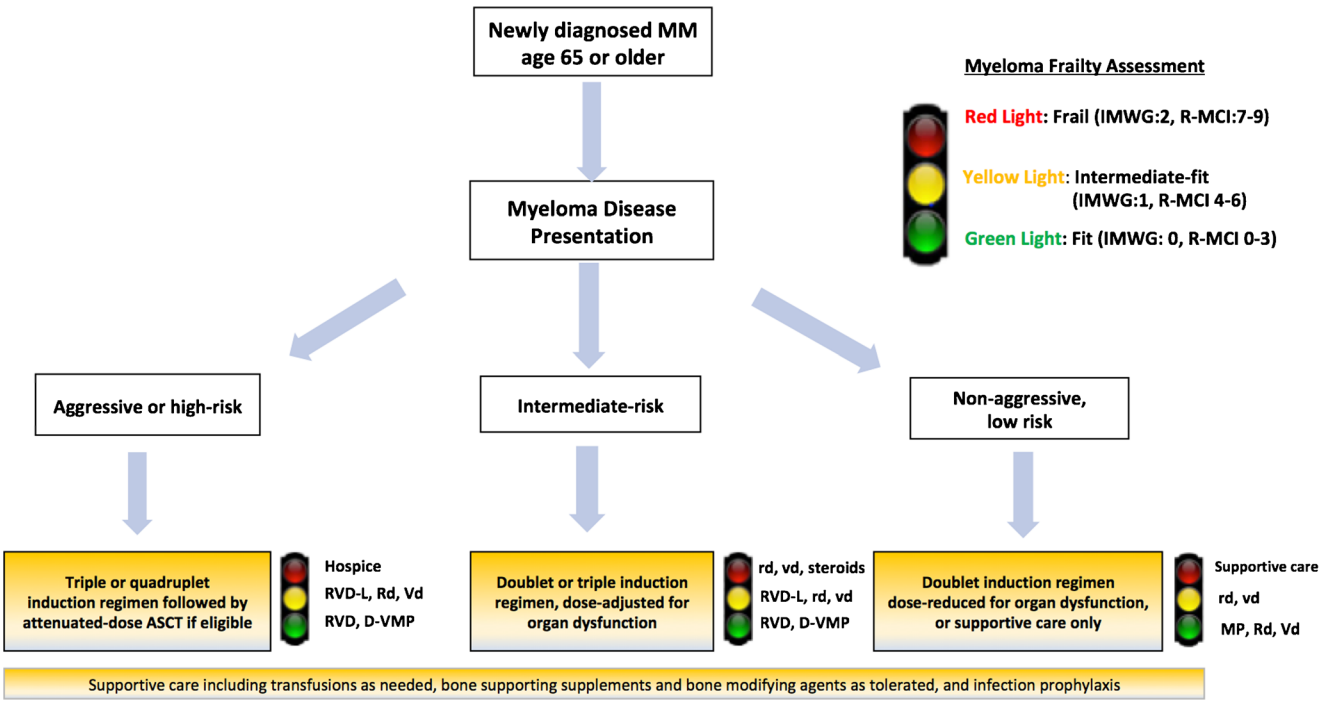

Fig. 2 Suggested approach to management of newly diagnosed elderly myeloma patients. While there is no consensus on the optimal first-line regimen, assessment of disease presentation is an important consideration. Regimens shown are suggested, but not validated, for high-risk disease or aggressive presentations with organ compromise, nonaggressive presentation or intermediate risk disease, or lower risk, nonaggressive disease. Degrees of frailty are shown as traffic lights for patients who are fit (green), intermediate-fit (yellow), and frail (red) defined by either IMWG or R-MCI indices. HDT-ASCT high-dose therapy autologous stem cell transplant, CCI Charlson comorbidity index, MP melphalan prednisone, MPR melphalan prednisone lenalidomide, RD lenalidomide dexamethasone, VD bortezomib dexamethasone, D-VMP daratumumab bortezomib melphalan prednisone, VRD-L bortezomib lenalidomide dexamethasone lite, VTD bortezomib thalidomide dexamethasone. Lowercase regimens suggest dose reductions from the start of treatment. See reference 60 for definition of risk groups

bortezomib maintenance therapy were evaluated for their efficacy and safety among 502 newly diagnosed elderly MM patients age 67–79 [67]. The investigators found no difference noted in OS between study arms, suggesting that a bortezomib-based doublet (VD) may be an acceptable frontline therapy for transplant-ineligible patients. Bortezomib doublet therapy has therefore emerged as an attractive upfront strategy for the treatment of older MM patients but has never been compared in randomized studies to RD in the upfront setting.

The benefit of combined PI and IMiD therapy in older patients was established in the randomized phase III SWOG S0777 study in which 529 patients, 43% of which were over age 65, were randomized to a triplet regimen of bortezomib, lenalidomide, and dexamethasone (VRD) versus RD alone [10••]. The median PFS was 43 months with VRD compared with 30 months in the control RD group (PFS HR 0.71, 96%, $P = 0.0018$); median OS was also significantly improved with triplet bortezomib arm (75 versus 64 months, HR 0.709, $P = 0.025$) [10••]. In the subgroup analysis, there was a significant OS difference in patients older than 75 years with median OS of 63 months with VRD versus 31 months with RD alone. In an effort to modify this regimen for older patients, O'Donnell and colleagues published results of a phase II study using a dose-attenuated "RVD-lite" regimen in newly diagnosed patients age 65–91 (median 73) [71•]. The primary outcome, overall response rate, was 86%, with a median PFS of 35.1 months; median OS was not reached at a median follow up of 30 months. Importantly, the discontinuation rate was low at 4%, and only 1 of 50 patients experienced grade 3 neuropathy. This is an attractive alternative regimen for patients who are less likely to tolerate standard dose VRD, such as those with intermediate frailty scores.

There have been a number of further advances in myeloma therapy using mAbs. This approach has been seen with the use of monoclonal antibodies (mAbs) to target antigens expressed on the surface of MM cells. The mechanism of action of this class of targeted therapy involves antibody and cell-mediated cytoxicity, leading to apoptosis of neoplastic plasma cells [72]. CD38 is a multifunctional cell surface glycoprotein that serves as a receptor for the transduction of activation/proliferation signals, expressed in > 80% of cases of MM, making it an ideal target [72]. Daratumamab, a fully humanized IgG kappa mAb targeting CD38 was initially approved after at least 1 line of therapy and has been recently published in the first-line setting in transplant-eligible patients in combination with VMP. In the phase III ALCYONE study, investigators randomly assigned 706 patients age 40–91 who were ineligible for ASCT to receive daratumumab plus VMP or VMP alone [11••]. Frailty was not assessed and patients had to have an ECOG performance status of no more than 2 and creatinine clearance of at least 40 mL/min. Results showed a 71.6 versus 50.2% PFS ($P < 0.001$) as well as significantly improved overall response rates with the mAb combination, leading to regulatory approval of this regimen. Of note, AEs were greater in the daratumumab combination, with the rate of grade 3 or 4 infections being 23.1 versus 14.7% with VMP alone. In addition, recent data presented at the 60th annual meeting of the American Society of Hematology from the phase III MAIA study of 737 transplant-ineligible patients age 45–90, two thirds of which had ECOG scores ≥ 1, also showed a benefit of upfront mAb therapy. In this study, newly diagnosed MM patients were randomized to daratumumab plus RD versus RD alone, with results again favoring the mAb combination, with a 30 month PFS of 71 versus 56% with RD alone ($P < 0.0001$) [73]. Rates of grade 3/4 pneumonia, neutropenia, and leukopenia were greater in the mAb combination. Though these studies did not use GA to stratify patients, the use of frailty as a stratification criterion is likely to evolve as more and more older patients are enrolled into clinical trials reflecting the true patient population with the disease.

Supportive Care

Monitoring for toxicity and providing supportive care is crucial to preventing disease-specific complications and to decreasing morbidity in elderly MM patients [16]. Myeloma-related skeletal complications in the elderly can be severe and debilitating, with up to 90% of patients having detectable bone lesions at presentation [74, 75•]. Calcium and vitamin D supplementation are recommended to maintain calcium homeostasis [76]. A short course of local radiation can be beneficial for pain control of symptomatic lytic lesions, particularly in patients unable to tolerate chemotherapy [77]. Bisphosphonates have been shown to reduce the risk of fractures, decrease morbidity, and prolong PFS synergistically with ant-myeloma agents [78, 79]. The current standard of care includes the use of bisphosphonates, such as zoledronic acid or pamidronate intravenously every 4 weeks with initial therapy, which should be continued in all patients with active disease [76]. In patients who achieve a VGPR or CR, bisphosphonate treatment may be discontinued after 2 years [80]. In the randomized CALGB 70604 trial evaluating 1800 patients with both solid and hematologic malignancies (278 of whom had MM), less frequent dosing of zoledronic acid every 3 months was noninferior to monthly dosing in terms of preventing skeletal related events leading some centers to favor the 3-month dosing [81•]. Renal impairment is a common side effect of MM and can be present in up to 40% of newly diagnosed patients [82]. Denosumab, a RANKL inhibitor, is another option approved for prevention of skeletal-related events in MM. In 2018, a randomized phase III study of 1718 newly diagnosed MM patients compared the use of denosumab in patients with newly diagnosed multiple

myeloma; denosumab was noninferior to zoledronic acid for time to skeletal-related events [75•]. All patients should have a dental evaluation prior to starting bone-modifying agents, especially given the greater incidence of dental issues in the elderly population [83]. The risk of bisphosphonate-induced osteonecrosis of the jaw with any of these bone-modifying agents may be reduced by prophylactic dental care [75•].

In addition to bone supportive medications, prophylaxis against both deep vein thrombosis and infection are important elements of specific regimens, particularly in elderly patients who may be more immunocompromised [84]. Patient receiving IMiDs should be on either low-dose aspirin or full-dose anticoagulation if they have a history of thrombosis, since this class of anti-myeloma drugs increases the risk of thrombosis. Antiviral prophylaxis for herpes zoster is required for patients receiving PIs. Additional antimicrobial prophylaxis and immunization against opportunistic infections can be considered during induction treatment, and especially following ASCT [85, 86].

An Approach to Tailor Treatment for Elderly MM Patients

The choice of frontline treatment of elderly MM patients with frailty and/or comorbidities must be individualized. These patients are generally not candidates for rigorous treatment plans comparable to their younger counterparts. Of the multiple considerations involved in choosing a management plan (Fig. 1), we believe the most important factors are the degree of frailty, aggressiveness of the MM presentation, and QOL. As mentioned above, there are several frailty indices that can be used to stratify patients [47, 49, 54]. In terms of disease aggressiveness, in addition to high-risk cytogenetics, factors warranting urgent treatment include management of acute spinal fractures or cord compromise, acute renal failure, symptomatic hypercalcemia or anemia, or plasma cell leukemia. In Fig. 2, we suggest an approach to select regimens based on the degree of frailty and the severity of disease presentation, although this is approach is not validated and should be individualized according to each patient's unique presentation. Of note, it is not unreasonable to consider only supportive care or hospice for frail patients who present aggressively. Data from randomized studies suggest that early integration of palliative care can improve outcomes, yet these resources are often underutilized in hematologic malignancies [87, 88]. QOL is a complex principle, influenced by the balance between disease-related symptoms, treatment-related toxicity, and treatment response [89]. In a study that assessed QOL across 1600 cancer survivors, survivors of MM were among those with the lowest QOL scores [90], highlighting the importance of frequently reassessing QOL. A more conservative approach should therefore be adopted in frail patients in which a less intensive therapy may be used, after which dose escalation may be considered if the treatment is tolerated and/or there is a lack of response [59].

Conclusions

Elderly MM patients are a heterogeneous group, with inherent challenges in management associated with the physiologic consequences of aging, preexisting comorbidities, and variable tolerability to treatment. Older MM patients remain at a greater risk for early mortality and experience poorer survival when presenting with treatment-limiting comorbidities. Incorporating GA can help support therapeutic decisions and guide goals of care conversations. Although predictive markers are needed to help choose a therapeutic regimen, attention to frailty can potentially reduce toxicity, improve survival, and increase QOL. It remains to be determined how to apply serial assessments of frailty at the time of disease relapse. Given the growing population of elderly MM patients, prospective clinical trials that incorporate frailty scores and continue to enroll patients over 65 are needed to improve the management of older MM patients.

Compliance with Ethical Standards

Conflict of Interest Crystal Antoine-Pepeljugoski declares that she has no conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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