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REVIEW ARTICLE

Multiple Myeloma in the Older Adult: Better Prospects, More Challenges

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ABSTRACT

Purpose
Multiple myeloma (MM) is disproportionately diagnosed in older adults; with the aging of the population, the number of older adults diagnosed with MM will increase by nearly 80% in the next two decades. Duration of survival has improved dramatically over the last 20 years, but the improvements in older adults have not been as great as those in younger adults with MM.

Methods
In this article, we address treatment approaches in older adults who are eligible for and those ineligible for high-dose therapy with autologous stem-cell transplantation as well as supportive care considerations and the potential role for geriatric assessment in facilitating decision making for older adults with MM.

Results
The evidence from recent studies demonstrates that combinations of novel and conventional antimyeloma agents result in improved response rates and, in some cases, improved progression-free and overall survival. However, some older adults are particularly vulnerable to toxicities of therapy and discontinuation of therapy and, consequently, they have poorer survival. In addition, older adults may prioritize other outcomes of therapy, such as quality of life, over more conventional end points such as disease response and duration of survival. Geriatric assessment can facilitate risk-stratification of older adults at greater risk for adverse events from therapy and aid in personalizing therapy for vulnerable or frail older adults.

Conclusion
Survival in older adults with MM is improving with novel therapeutics, but efficacy must be balanced with risk of toxicity of therapy and maintenance of quality of life. Novel instruments such as geriatric assessment tools may facilitate these aims.

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INTRODUCTION

Multiple myeloma (MM), an incurable malignancy of plasma cells, is a disease of older adults; the median age at diagnosis is older than age 70 years.[1] The increasing incidence of MM with age, combined with the aging population, yields the already evident increase in the number of older adults with MM in oncology clinics and an anticipated 77% increase by 2030 in the number of adults older than age 65 years diagnosed with MM each year.[2,3]

New therapeutic agents and improving supportive care have lengthened survival in MM.[4-6] However, most studies suggest that improvements in older adults with MM have been small compared with those in younger individuals.[6,7] Although the 5-year relative survival for patients younger than age 65 years improved by more than 17% between 1998 and 2002 and between 2003 and 2007, it improved by only 3.3% in patients age 75 years and older.[8] Further, two thirds of patients who die within the first year of diagnosis are older than age 70 years.[9] Data on patients diagnosed as recently as 2010 show that older adults are beginning to close the gap with younger patients and, interestingly, suggest that older adults may be surpassing younger patients in gains in survival.[5] However, most data available to date have shown the opposite.[6-8] Hence, age-related disparities are an important impetus for examining the challenges of caring for older adults with MM and focusing on factors contributing to poorer outcomes in older adults.

The complexity of caring for older adults with MM arises in part from the heterogeneity of aging (Fig 1). Older adults with MM are particularly vulnerable to adverse events (AEs) associated with multidrug combinations, which can lead to dose reductions or cessation of therapy altogether. Clearly, treatment discontinuation is associated with poorer outcomes.[10] Proactive estimation of an

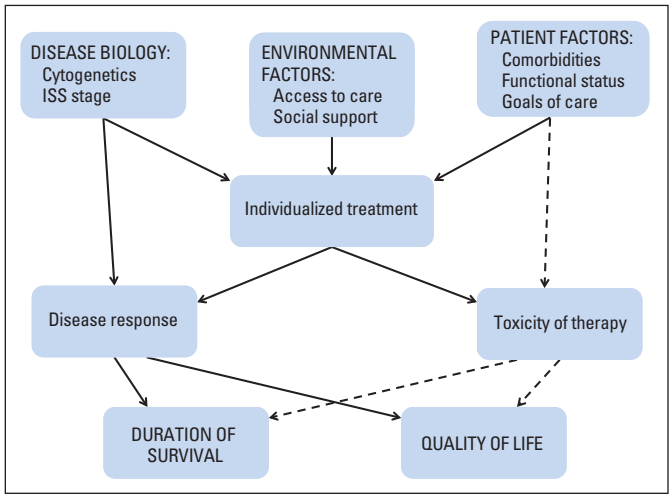

Fig 1. Conceptual model of relationships among factors influencing outcomes in older adults with multiple myeloma. Solid arrows indicate positive relationships and/or influences; dashed arrows indicate negative relationships and/or influences. Disease biology, environmental factors, and patient factors all influence treatment decisions. Disease response is influenced by both the biology of disease and the intensity of therapy, which in turn influence duration and quality of survival. Patient factors, such as comorbidities and poor functional status, as well as more intense therapy, increase the risk of toxicity. Toxicity results in both shorter survival and poorer quality of survival. ISS, International Staging System.

older adult's capacity to tolerate intensive treatment requires paying attention to factors beyond chronologic age. Although it is associated with chronologic age, physiologic aging is better described by constructs emphasized in geriatrics, including comorbidities, functional status and/or dependence, frailty, and cognitive impairment.[11] In addition, the goals of care for older adults may differ from those in younger adults; older adults facing serious illness are more likely to prioritize symptom control, maintenance of independence, and preservation of cognitive function over prolonged survival.[12,13] Therefore, integrating geriatric principles, understanding of the risk of toxicity of therapy, selecting therapy based on that anticipated risk, aggressively managing toxicity, and incorporating the individual's treatment goals will be critical to striking a balance between increasing longevity and reducing outcome disparities while maintaining quality of life in older adults with MM.

In this article, we provide an overview of available data pertaining to the treatment of older adults with MM; highlight the importance of integrating novel concepts, including geriatric assessment and the idea that improving overall survival (OS) may not be the primary goal of therapy for all patients; and discuss some of the challenges in improving outcomes in this complex population. The growing numbers of older adults with MM are increasing the importance of research dedicated to MM in older adults and of practical strategies for managing MM in these patients.

THERAPY FOR TRANSPLANTATION-INELIGIBLE PATIENTS

MM treatment algorithms immediately diverge on the basis of the assessment of the individual's eligibility for high-dose chemotherapy with hematopoietic autologous stem-cell transplantation (ASCT). ASCT is not a viable option for many patients with MM because of advanced chronologic age, comorbidities, poor performance status, or patient preference. Consequently, non-ASCT–based treatment approaches have a vital role in the framework of MM therapy, particularly for older patients.

The alkylator plus corticosteroid therapeutic backbone for MM arose in the 1960s with melphalan and prednisone (MP). Decades of research investigating more aggressive, non-ASCT conventional chemotherapy regimens resulted in slight improvements in objective response rates (ie, reduction in measured monoclonal proteins) but no difference in more meaningful outcomes such as survival.[14] The addition of novel agents to MP has provided several therapeutic options for ASCT-ineligible patients with MM. For non-ASCT candidates, thalidomide was added to MP (MPT) and explored in several randomized trials. Both bortezomib and lenalidomide have been examined in combinations that either build on or eschew MP. A full discussion of all randomized trials is not possible here, but salient details from some of the largest trials are provided in Table 1.

Thalidomide

Meta-analyses of the several randomized trials of MP versus MPT are instructive in making sense of the large and sometimes conflicting mass of data. It is clear that toxicity, particularly nonhematologic toxicity, is doubled with the addition of thalidomide to MP (eg, 39% with MPT *v* 17% with MP; hazard ratio [HR], 2.8; 95% CI, 2.2 to 3.5).[22] Response rates and depth of response are enhanced with thalidomide (overall response rate of 59% for MPT *v* 37% for MP; $P < .001$).[23] Progression-free survival (PFS) is consistently improved with MPT by about 6 months in most studies (Table 1) as well as in meta-analyses.[23,24] Median OS appears to be prolonged by several months, although that finding is less definitive (Table 1); in two meta-analyses, one demonstrated significant improvement in OS with MPT (HR, 0.83; 95% CI, 0.73 to 0.94; $P = .004$) and, in the other, the benefit was not statistically significant (HR, 0.80; 95% CI, 0.63 to 1.02; $P = .07$).[23,24] Thus, it can be stated that thalidomide improves responses, delays relapse, and may prolong survival but clearly increases toxicity. Striking a balance between efficacy and toxicity is critical in clinical decision making for older adults with MM.

Lenalidomide

Lenalidomide was developed as a more potent, less toxic analog of thalidomide. Working off the MP backbone, one study examining MP versus melphalan, lenalidomide, and prednisone (MPR) with lenalidomide maintenance (MPR-R) or without showed that the addition of lenalidomide to MP during induction and maintenance prolongs PFS, with a toxicity profile that compares favorably with MPT. OS has not been improved to date, but follow-up is immature (Table 1).[18]

To test the concept of omitting melphalan, the Eastern Cooperative Oncology Group studied lenalidomide with either low- or high-dose dexamethasone (40 mg once per week [Rd] or 40 mg for 4 days on, 4 days off [RD], respectively) in newly diagnosed MM and demonstrated high response rates, with a median PFS of 25.3 months in patients given low-dose dexamethasone and an 87% 2-year OS. Response rates were superior in patients given lenalidomide and high-dose dexamethasone (RD); however, this improvement in response rates came at the expense of increased toxicity, which directly resulted in poorer PFS and OS (Table 1).[19] This established two paradigms in myeloma: first, lenalidomide and dexamethasone is a standard regimen for initial treatment, and second, low-dose (once per week)

Table 1. Initial Therapy in Older Adults With MM: Randomized Trials of MP With or Without the Addition of Novel Agents

Trial Name	Reference	Regimen	Median PFS (months)	Median OS (months)	Toxicity Rate (%)	
					Any Grade 3 to 4	Nonheme Grade 3 to 4
Italian Group for Hematological Malignancies of the Adult (GIMEMA)	Palumbo et al[15]	MP	14.5	47.6	22	NR
		MPT	21.8	45	55	NR
Intergroupe Francophone du Myelome (IFM) 99-06	Facon et al[16]	MP	17.8	33.2	NR	16
		MPT	27.5	51.6	NR	42
Hemato-Oncologie voor Volwassenen Nederland (HOVON) 49	Wijermans et al[17]	MP	9	31	29	NR
		MPT	13	40	50	NR
Intergroupe Francophone du Myelome (IFM) 01-01	Hulin et al[20]	MP	18.5	29.1	NR	13*
		MPT	24.1	44	NR	42*
Eastern Cooperative Oncology Group (ECOG) E4A03	Rajkumar et al[19]	Rd	25.3	87 (at 2 years)	35	NR
		RD	19.1	75 (at 2 years)	52	NR
Multiple Myeloma 015 (MM015)	Palumbo et al[18]	MP	13†	66 (at 3 years)	NR	5*
		MPR	14†	62 (at 3 years)	NR	14*
		MPR-R	31†	70 (at 3 years)	NR	15*
Velcade As Initial Standard Therapy in Multiple Myeloma (VISTA) trial	San Miguel et al[21]	MP	16.6	43	80	NR
		MPV	24	56.4	91	NR

Abbreviations: MM, multiple myeloma; MP, melphalan and prednisone; MPR, melphalan, prednisone, and lenalidomide; MPR-R, melphalan, prednisone, and lenalidomide with lenalidomide maintenance; MPT, melphalan, prednisone, and thalidomide; MPV, melphalan, prednisone, and bortezomib; NR, not reported; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and low-dose dexamethasone; RD, lenalidomide and high-dose dexamethasone.
*Discontinuation rate because of toxicity, specifically during induction where applicable. Global (ie, "any" or "nonhematologic") toxicity incidence not reported.
†Statistically significant for MPR-R *v* MP and MPR-R *v* MPR only.

dexamethasone is a preferable alternative to higher doses of dexamethasone across many regimens. This study also highlighted the critical difficulties in using surrogate end points such as response rates to predict longer-term, more meaningful outcomes such as OS (see Outcomes Relevant to Older Adults).

Efforts continue to identify an optimal approach to maximize efficacy in non-ASCT patients, while maintaining a favorable toxicity profile. In the FIRST (Frontline Investigation of Lenalidomide + Dexamethasone Versus Standard Thalidomide) study, presented at the 2013 American Society of Hematology Annual Meeting, more than 1,600 older adults with newly diagnosed MM were randomly assigned to MPT for 12 cycles (approximately 17 months), Rd for the same duration, or Rd continuously. Continuous Rd improved PFS over MPT; all secondary end points supported the clinical benefit of Rd. OS data appeared to be improved with Rd, but prespecified statistical cutoffs were not met, and those data are maturing.[25]

Bortezomib

Bortezomib is another important option for initial therapy in older adults with MM. The VISTA (Velcade As Initial Standard Therapy in Multiple Myeloma) trial showed that adding intravenous bortezomib twice per week to MP is effective, with improvements in median OS (56.4 *v* 43 months for bortezomib, melphalan, and prednisone [VMP] *v* MP; $P < .001$), although the benefit came at the expense of substantial toxicity, primarily peripheral neuropathy.[21] Advances in therapy are forthcoming with the advent of other combination regimens that either substitute other conventional agents for melphalan (such as bortezomib, cyclophosphamide, and dexamethasone [VCD])[26] or that omit conventional chemotherapy entirely (such as bortezomib, thalidomide, and prednisone [VTP][27]; lenalidomide, bortezomib, and dexamethasone [RVD][28]; or carfilzomib, lenalidomide, and dexamethasone).[29] Except for VTP, these combination regimens have generally been studied in single-arm phase II studies in unselected populations (ie, not specifically older adults with MM), and they appear promising, but randomized trials are not yet available. In one of the few randomized trials of bortezomib combinations in older adults, VTP has been shown to be an effective alternative to VMP, although with different toxicity profiles.[27] In one other small study, VCD and RVD appeared similar in efficacy.[30] Overall, proteasome inhibition is an important option in MM treatment regimens, although the optimal way of incorporating it is still being elucidated.

HEMATOPOIETIC ASCT IN OLDER ADULTS

Randomized trials confirmed the role of ASCT in patients younger than age 65 years; however, adults older than age 65 years were categorically excluded from these pivotal studies.[31,32]Over the past two decades, ASCT has been increasingly used in older adults; from 1995 to 2005, the proportion of individuals older than age 70 years undergoing ASCT increased more than five-fold, from less than 1% to 5%.[33] The rising number of older adults undergoing ASCT merits examination of studies on the feasibility, toxicity, and efficacy of ASCT among older adults selected for this treatment strategy.

Mobilization and Engraftment

Peripheral blood stem-cell mobilization and collection are generally feasible among selected older adults with MM. The effect of advancing age on bone marrow reserve is evident from the fact that, in multiple studies, older adults with MM collect fewer total $CD34^+$ cells and may require more apheresis sessions. Ultimately, however, older patients with MM appear to be as likely to collect adequate stem cells to proceed with ASCT as younger patients.[34-37] This association between age and poorer mobilization is partially explained by other risk factors for poor mobilization associated with age, including type and length of

prior therapy, premobilization platelet count, and mobilization regimen.[37] The CXCR4 antagonist plerixafor appears to minimize age-related differences in stem-cell mobilization and collection.[38]

Any small differences in stem-cell collection between older and younger patients with MM do not result in meaningful differences in engraftment among patients proceeding to ASCT. There are no significant age-related differences in time to neutrophil engraftment.[39,40] Age-related differences in platelet recovery are minimal. In one study, this difference was evident only in the subgroup that had received suboptimal numbers of $CD34^+$ cells per kilogram, and in another, the difference was less than 1 day (14.5 days to platelet count $>$ 20,000 cells per microliter among younger *v* 15 days among older patients; $P = .049$).[37,39]

Toxicity and TRM

Early studies suggested greater treatment-related mortality (TRM) among older adults undergoing ASCT but included several different malignancies and conditioning regimens.[41] More recently, empirical dose reduction (eg, melphalan dose reduction from 200 to 140 mg/m^2) has been incorporated as standard of care for older adults in many transplantation programs, as have more rigorous patient selection and aggressive supportive care. With these modifications, contemporary studies that specifically examine patients with MM who are receiving high-dose melphalan have shown similar TRM rates in older and younger patients.[39,40,42,43] Nonetheless, certain toxicities are more common in older adults, including cardiac arrhythmias (8% *v* 0%; $P = .02$)[42] and GI toxicity (68% *v* 46% grade 3 to 4 diarrhea; $P = .06$; 45% *v* 23% grade 3 to 4 oral or GI toxicity; $P = .06$).[42,44] Otherwise, the incidence of other toxicities, including neutropenic fevers, other infectious complications, and admission to an intensive care unit, are similar in older and younger patients with MM who were selected for ASCT.[39,40,42,44]

Comorbidities may be a better predictor of morbidity associated with ASCT than age. Comorbidities are associated with greater toxicity and increased length of hospital stay.[45] That said, comorbidities alone have limitations in predicting toxicity. Other standardized and more robust assessment tools such as geriatric assessment (see Geriatric Assessment in Older Adults With MM) may allow more precise prediction of ASCT-associated morbidity and mortality than age alone.

Effectiveness

In the absence of randomized studies on the efficacy of ASCT in older adults with MM, cohort studies give insight into the potential benefit of high-dose therapy over conventional chemotherapy. Several cohort studies have compared the response rates, PFS, and OS with ASCT between older and younger patients (Tables 2 and 3). These studies are limited by small sample sizes, retrospective methodology, and different benchmarks for which age is categorized as "older"; patients categorized as older in some studies would have been included in the younger comparison group in other studies. Although

Table 2. Studies of the Efficacy and Effectiveness of ASCT in Older and Younger Adults With MM (published 2003-2013)

Reference	Study Design	Older Cohort		Younger Cohort		Melphalan Dose
		No. of Patients	Age Range (years)	No. of Patients	Age Range (years)	
Muta et al[42]	Retrospective cohort study	25	65-76	63	51-64	100-200 mg/m^2
El Cheikh et al[39]	Retrospective cohort study	82	65-77	104	60-65	100-200 mg/m^2
Kumar et al[40]	Matched pair analysis	33	70-75	60	37-64	140-200 mg/m^2
Gertz et al[48]	Retrospective cohort study	137	$>$ 65	541	$\leq$ 65	140-200 mg/m^2
Jantunen et al[44]	Retrospective cohort study	22	65-73	79	39-64	140-200 mg/m^2
Krejci et al[49]	Retrospective cohort study	30	66-69	103	31-60	140-200 mg/m^2
Terpos et al[50]	Retrospective cohort study	32	61-70	95	27-60	100-200 mg/m^2; 140 mg/m^2 $\pm$ TBI
Reece[51]	Registry	110	60-73	382	30-59	Several doses and regimens $\pm$ TBI
O'Shea et al[52]	Retrospective cohort study	60	61-72	151	26-60	100-200 mg/m^2; 140 mg/m^2 $\pm$ TBI
Lenhoff[46]	Population-based registry	120	60-64	294	$<$ 60	200 mg/m^2

CR Rate (%)			PFS					OS From Transplantation				
			Older Cohort		Younger Cohort			Older Cohort		Younger Cohort		
Older Cohort	Younger Cohort	*P*	Median (months)	Rate (%)	Median (months)	Rate (%)	*P*	Median (months)	Rate (%)	Median (months)	Rate (%)	*P*
12	24	.06	17.1		20.8		NS	40.8		72.5		.07
41 (CR or VGPR)	48 (CR or VGPR)	NS	27	22 (5-year)	45	37 (5-year)	$<$ .001		54 (5-year)		57 (5-year)	NS
42	28	NS	28.5 (TTP)		17.8 (TTP)		.07	Not reached				NS
40	30	NS	17 (TTP)		17 (TTP)		NS	44		44		NS
44	36	NR	23		21		NS	57		66		NS
NR	NR	—	NR		NR		—	25.7		71		.002
NR	NR	—	NR		NR		—	37.6		50.4		NS
33	34	NS		35 (3-year)		44 (3-year)	NS		58 (3-year)		55 (3-year)	NS
NR	NR	—	NR		NR		—	48.3		50.9		NS
37	36	NS	24 (EFS)		36 (EFS)		.005	48		67		.004

Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; EFS, event-free survival; MM, multiple myeloma; NR, not reported; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; TBI, total-body irradiation; TTP, time to progression; VGPR, very good partial response.

Table 3. Studies of the Efficacy and Effectiveness of HDT/ASCT and Non-ASCT Treatment in Older Adults With MM (published 2003-2013)

		HDT/ASCT		Non-ASCT			CR Rate (%)			Median PFS (months)			OS From Transplantation				
													HDT/ASCT		Non-ASCT		
Reference	Study Design	No. of Patients	Age Range (years)	No. of Patients	Age Range (years)	Treatment	HDT/ASCT	Non-ASCT	*P*	HDT/ASCT	Non-ASCT	*P*	Median (months)	Rate (%)	Median (months)	Rate (%)	*P*
Facon et al[16]	Randomized controlled trial	126	65-75	MPT, 125; MP, 196	65-75	ASCT: VAD × 2, chemomobilization; melphalan 100 mg/m^2, repeated 2 months later; MPT × 12 cycles; MP × 12 cycles	18	MPT, 13; MP, 2	< .001	19.4	MPT, 27.5; MP, 17.8	< .001	38.3		MPT, 51.6; MP, 33.2		.027 (MPT *v* MEL100)
Lenhoff[46]	Population-based registry	120	60-64	97	60-64	ASCT: VAD, then HDT/ASCT and IFN-α-2B maintenance; Non-ASCT: MP ± IFN-α-2B	37	NR	NR	24 (EFS)	NR	.02	48		28		.02*
Offidani et al[47]	Post hoc analysis of phase II trial	26	65-75	62	65-91	Non-ASCT: ThaDD × 6, then maintenance thalidomide; ASCT: ThaDD × 4, then HDT/ASCT	57	24	.032	32	29	NS		82 (3-year); 49 (5-year)		66 (3-year); 46 (5-year)	NS

Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; EFS, event-free survival; HDT, high-dose therapy; IFN-α-2B, interferon alfa-2B; MEL100, melphalan 100 mg/m^2; MM, multiple myeloma; MP, melphalan and prednisone; MPT, melphalan, prednisone, and thalidomide; NR, not reported; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; ThaDD, thalidomide, pegylated liposomal doxorubicin, and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; VGPR, very good partial response.

*Risk ratio, 0.65; 95% CI, 0.42 to 0.92.

most studies have found no difference, a few have suggested that older adults may have lower PFS and OS than younger patients after ASCT.

Other studies have compared older adults receiving non-ASCT therapy with those undergoing ASCT (Table 3), with conflicting results regarding the benefit of ASCT over conventional therapy in older adults. In the IFM (Intergroupe Francophone du Myelome) 99-06 trial, patients age 65 to 75 years with MM were randomly assigned to MP alone, MPT, or induction chemotherapy followed by two courses of intermediate-dose melphalan (100 mg/m^2) with ASCT.[16] In that study, the thalidomide-containing regimen produced superior PFS and OS compared with the intermediate-dose melphalan-ASCT strategy. Because that study used an intermediate dose of melphalan twice rather than the single dose of 140 mg/m^2 or 200 mg/m^2 generally used in ASCT, it did not definitively answer whether novel therapies supplant standard high-dose therapy with ASCT as it is most commonly used. In a Swedish registry study in which the older patient group consisted of patients age 60 to 64 years, ASCT was associated with better survival than conventional therapy.[46] However, this analysis may have been confounded by comorbidities or poorer functional status, which independently influence survival. Finally, in a post hoc analysis of a phase II study, the subgroups of patients older than age 65 years who underwent ASCT were compared with those who did not.[47] Eligibility for ASCT was based on age, performance status, and comorbidities, among other factors. Both groups received thalidomide-based induction; transplantation-eligible patients went on to receive ASCT, and those who were ineligible received two additional cycles of chemotherapy followed by thalidomide maintenance. Although the ASCT group had a higher response rate, PFS and OS were similar to that in the non-ASCT group. Thus, the effectiveness of ASCT in older patients in the era of novel agents remains an important area of investigation. But, in general, ASCT can be a feasible and efficacious component of therapy for selected older patients with MM.

Which older adults are eligible for ASCT remains poorly defined. Through October 2000, the Centers for Medicare and Medicaid Services restricted coverage for ASCT for MM to patients age 77 years or younger because of the absence of data in patients above that threshold; the age-based restriction was removed in November 2000. Chronologic age alone is an inadequate metric for identifying older adults who are candidates for ASCT. However, moving beyond a simple age threshold introduces the challenge of identifying specific criteria to select older adults who are candidates for ASCT. Unfortunately, such explicit formal criteria do not exist. Ultimately, comprehensive geriatric assessment (CGA) may provide a more objective method for patient selection, but currently, patient selection for ASCT remains rooted in clinical judgment, which incorporates multiple factors such as chronologic age, comorbidities, functional status, and psychosocial support, among other things.[53] Table 4 lists factors that have been incorporated into decision making regarding ASCT in older adults with MM.

Table 4. Factors to Consider in Clinical Decision Making About ASCT in Older Adults With MM

Factor
Performance status and/or functional status
Cardiac function
Liver function
Pulmonary function
Infectious disease
Psychosocial support
Patient goals and preferences

Abbreviations: ASCT, autologous stem-cell transplantation; MM, multiple myeloma.

BIOLOGY OF MM ACROSS THE AGE SPECTRUM

More intensive treatment, including ASCT, in younger patients almost certainly contributes to age-related disparities in outcomes. However, one must ask whether the poorer survival in older adults is related to intrinsic differences in the underlying MM biology, as in age-related differences seen in acute myelogenous leukemia or diffuse large B-cell lymphoma. Although treatment factors undoubtedly contribute, there are age-related differences in prognostic factors reflective of MM biology. In a study of more than 10,000 patients with MM, older patients (older than age 50 years) were more likely to present with International Staging System stage III MM, low albumin, high β_2-microglobulin, low hemoglobin, and increased creatinine.[54] There were no differences in the frequency of increased levels of serum lactate dehydrogenase, in the degree of bone marrow plasma cell infiltration, or in the frequency of cytogenetic abnormalities. However, in another study in which chromosomal abnormalities were detected by fluorescent in situ hybridization, differences in their prevalence were noted; deletion of chromosome 13 (q14 band) and translocation t(4;14) were less common with increasing age.[55] The prevalence of deletions of chromosome 17 (q13 band) was similar across the age spectrum. More sophisticated methods of exploring the biologic heterogeneity in MM, from gene expression profiling to next-generation sequencing, will undoubtedly aid in further exploring potential age-related differences in the biology of this disease.

CHALLENGES IN EXPANDING THE KNOWLEDGE BASE IN OLDER ADULTS WITH MYELOMA

Clinical Trial Exclusion

Older adults are commonly excluded from cancer clinical trials. Arbitrary age cutoffs are being removed from clinical trial design,[56] but more problematic are occult factors that exclude older patients from clinical trial enrollment, including concomitant comorbidities, abnormal laboratory tests, and physical disability.[57] Unfortunately, these factors are common in older patients; consequently, clinicians rely on evidence from randomized controlled investigations based on younger patients without concomitant comorbidity and disability to make treatment decisions. Thus, a barrier to best care for older adults with MM is the challenge in applying clinical trial results to the general population with MM, which is generally older and more vulnerable than a typical clinical trial population.

Outcomes Relevant to Older Adults

Patients with MM do not prioritize prolongation of life at the expense of other considerations as highly as physicians estimated they would.[58] Functional status and quality of life are also important outcomes, arguably for all patients with MM, but especially for older adults who may suffer more toxicity from therapy. Thus, traditional

disease-focused clinical trial outcomes may not be the most important outcomes to older adults with MM.

Although disease-focused end points such as response rates and PFS remain central to clinical trials, these can be problematic in studies of older adults. In a randomized trial of thalidomide and high-dose dexamethasone (TD) versus MP, the response rate was higher with TD, but OS was greater with MP because of the high rate of death as a result of toxicity in the TD arm.[59] Similarly, lenalidomide with high-dose dexamethasone yielded higher response rates but poorer OS than lenalidomide with low-dose dexamethasone because of greater toxicity.[19] Yet in another study in which higher response rates were achieved without incurring excessive toxicity, depth of response did correlate with PFS and OS.[60] Furthermore, in older adults treated with MPR-R, MPR, or MP, better response to therapy was associated with improvements in health-related quality of life (HRQOL).[61]

Thus, HRQOL is a complex phenomenon, influenced by the balance between toxicity of therapy and symptoms of disease, which may be ameliorated by disease response. Such conflicting studies highlight the challenges of using surrogate end points such as response rates as predictors of longer-term or more meaningful end points such as quality of life (QOL) or OS in older adults with MM. Thankfully, clinical trials in this population are beginning to examine how chemotherapy regimens influence HRQOL.

Geriatric Assessment in Older Adults With MM

CGA is a global evaluation of the health of older adults; it goes beyond a typical disease-focused evaluation and aims to identify unrecognized issues, to intervene, and to prevent future problems (see article in this issue of the *Journal of Clinical Oncology* regarding the practical implementation of CGA in oncology practice). Domains of the CGA include comorbidities, function (including dependence in daily activities and falls), cognition, polypharmacy and/or inappropriate medications, social support, and depression and/or psychological distress. CGA can predict chemotherapy toxicity and survival in patients with cancer,[62-64] but data on CGA specifically in patients with hematologic malignancies are lacking because the prior studies were either primarily or entirely dedicated to solid tumor.[65-67]

The available data are beginning to confirm the clinically intuitive hypothesis that geriatric syndromes are predictive and prognostic in MM. In a study of 1,500 older adults treated in clinical trials, renal insufficiency, as one comorbidity, predicted a greater risk of nonhematologic AEs; in turn, AEs and drug discontinuation were associated with a greater risk of death in the first 6 months after initiation of treatment.[10] Comorbidities are prognostic in patients with MM, independent of International Staging System stage.[68] That said, in older adults with cancer, comorbidities and performance status are, at best, only weakly correlated, and performance status alone grossly underestimates the level of disability in older adults.[69,70] Stratification of older adults based on comorbidities and disability appears to be highly prognostic; elders categorized as frail (based on age, comorbidity, and dependence in daily activities) had higher rates of nonhematologic AEs and discontinuation of therapy and were nearly three times as likely to die as elders categorized as fit (hazard ratio [HR], 2.9; $P < .001$).[71] Such studies provide early evidence that CGA will play a key role in

Table 5. Suggested Dose Modifications and Considerations in Treatment Selection in Older Adults With MM

Agent	Dosing Adjustments			Other Considerations
	Standard Dose	Reduced Dose	Further Reduction	
Bortezomib	1.3 mg/m^2 twice per week on days 1, 4, 8, and 15 every 4 weeks	1.3 mg/m^2 once per week	1.0 mg/m^2 once per week	Strongly consider subcutaneous administration Consider whether patient has pre-existing renal insufficiency Consider using if patient has prior history of venous thromboembolism Consider whether adherence to an oral regimen is problematic
Lenalidomide (in Rd regimen)	25 mg per day on days 1-21 every 28 days	15 mg per day on days 1-21 every 28 days	10 mg per day on days 1-21 every 28 days	Consider whether patient has pre-existing neuropathy Consider whether patient prefers an orally administered regimen
Thalidomide	100 mg per day	50 mg per day	50 mg every other day	Consider whether patient prefers an orally administered regimen
Melphalan	0.25 mg/kg or 9 mg/m^2 on days 1-4 every 4-6 weeks	0.18 mg/kg or 7.5 mg/m^2 on days 1-4 every 4-6 weeks	0.13 mg/kg or 5 mg/m^2 on days 1-4 every 4-6 weeks	Avoid as initial therapy in older adults who are eligible for ASCT
Cyclophosphamide	100 mg per day on days 1-21 every 28 days or 300 mg/m^2 on days 1, 8, and 15 every 28 days	50 mg per day on days 1-21 every 28 days or 150 mg/m^2 on days 1, 8, and 15 every 28 days	50 mg every other day on days 1-21 every 28 days or 75 mg/m^2 on days 1, 8, and 15 every 28 days	May be given intravenously if oral administration is not tolerated or adherence to oral medications is problematic
Dexamethasone	40 mg on day 1 once per week or consider 20 mg per day on days 1 and 2 each week	20 mg on day 1 once per week	10 mg on day 1 once per week	
Prednisone	60 mg/m^2 on days 1-4 or 50 mg every other day	30 mg/m^2 on days 1-4 or 25 mg every other day	15 mg/m^2 on days 1-4 or 12.5 mg every other day	

NOTE. Doses listed reflect suggested dose modifications for agents in corticosteroid-incorporating doublets. Starting doses in combination regimens may vary. Modified from Palumbo et al[73] and Wildes et al.[74]

Abbreviations: ASCT, autologous stem-cell transplantation; MM, multiple myeloma; Rd, lenalidomide and low-dose dexamethasone.

older adults with MM in the future, in both stratifying risks and guiding interventions.

SUPPORTIVE CARE IN OLDER ADULTS

Given the increased propensity of older patients to experience drug toxicity and the association of AEs and treatment discontinuation with death, careful attention to selection of therapeutic agents, dose, and supportive care are imperative to ensure optimal outcomes in older adults with MM. Attention to dosing and route of administration can also make a substantial difference in tolerance of therapy in vulnerable older adults. For example, administration of bortezomib subcutaneously once per week, rather than intravenously twice per week, dramatically improves tolerability and decreases rates of neuropathy without compromising effectiveness.[72] Table 5 presents a summary of empirical dose modifications proposed by the European Myeloma Network and considerations for individualized treatment selection.[73,74] The European Myeloma Network proposed that factors including age older than 75 years, patients requiring assistance in daily activities (eg, personal care or household tasks), and cardiac, pulmonary, hepatic, or renal dysfunction warrant consideration of dose modification.[73] It is important to note, however, that such general guidelines can be challenging to implement, given the wide array of chemotherapy combinations available in today's clinical practice. Doses must always be considered in light of the entire drug combination being used. A "start slow and low" dosing strategy is worth consideration, with escalation in subsequent cycles if the drug is tolerated without significant toxicity and if response is inadequate.

Routine supportive care may require particular attention in older adults. Bisphosphonates are a mainstay of therapy in myeloma for prevention of skeletal-related events, but they require dose modification for renal impairment. Serum creatinine measurement alone is an inadequate reflection of renal function in older adults, which should be estimated by the Cockcroft-Gault method or another formula, or by 24-hour urine collection.[75] Unfortunately, many of the equations for estimating glomerular filtration rate have not been well validated at the extremes of age.

Ironically, supportive care itself may create or exacerbate polypharmacy. Proteasome inhibitors necessitate antiviral prophylaxis for shingles, immunomodulatory agents require prophylaxis for venous thromboembolism, and corticosteroids may call for GI prophylaxis and, in some cases, additional agents for glycemic control in diabetic patients. Antibacterial and antifungal prophylaxis may be warranted in some situations as well. Antiemetics and antihistamines are commonly used drugs. Use of opioid analgesics for pain management may require the addition of scheduled laxatives to obviate constipation. Cytopenias may necessitate growth factors. Ultimately the older adult with MM may require numerous new medications. Thus, careful review of the patient's existing medications, education regarding the administration and indication for each medication, and attention to potential drug-drug interactions is essential.

In conclusion, MM is a disease that has seen great success in extending survival over the past two decades. Combination therapy, including novel agents, is associated with improved responses and survival, although often at the cost of increased toxicity. The approach to therapy in older adults with MM must be individualized, based not only on the patient's disease characteristics but also on the patient's overall health, which may be summarized by using CGA. Ultimately, CGA may help predict which patients with MM are at greater risk for toxicity of chemotherapy, as it has in solid tumors, and aid in helping patients and clinicians develop a personalized approach to therapy to optimize the chance for control of disease while minimizing risk of toxicity and helping the individual meet their goals for their MM treatment.

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