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Management of Multiple Myeloma in Older Adults: Gaining Ground with Geriatric Assessment

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Abstract

Multiple myeloma increases in incidence with age. With the aging of the population, the number of cases of multiple myeloma diagnosed in older adults each year will nearly double in the next 20 years. The novel therapeutic agents have significantly improved survival in older adults, but their outcomes remain poorer than in younger patients. Older adults may be more vulnerable to toxicity of therapy, resulting in decreased dose intensity and contributing to poorer outcomes. Data are beginning to emerge to aid in identifying which individuals are at greater risk for toxicity of therapy; comorbidities, functional limitations and age over 80 are among the factors associated with greater risk. Geriatric assessment holds promise in the care of older adults with multiple myeloma, both to allow modification of treatment to prevent toxicity, and to identify vulnerabilities that may require intervention. Emerging treatments with low toxicity and attention to individualizing therapy based on geriatric assessment may aid in further improving outcomes in older adults with multiple myeloma.

Keywords

multiple myeloma; cancer; elderly; aging; treatment; geriatric assessment

Introduction

The incidence of multiple myeloma is increasing; with the aging of the population, there is projected to be a 90% increase in the number of cases of multiple myeloma diagnosed annually in older adults by 2034.¹ Advances in treatment, particularly the introduction of novel therapeutic agents, have significantly improved overall survival in older adults with multiple myeloma over the past 2 decades.² However, improved efficacy of therapeutic approaches must be balanced with the risk of toxicity of therapy. Older adults may be particularly vulnerable to toxicity of therapy; grade III/IV toxicities of therapy are associated with poorer survival among older adults on clinical trials.³ Adapting therapy to minimize toxicity may allow similar dose intensity and outcomes with lower toxicity, compared to

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more dose-dense strategies.⁴ However, older adults remain at greater risk for early mortality and experience poorer survival than their younger counterparts^{2,5}, highlighting the need for further research to optimize therapy in older adults with multiple myeloma.

Initial Evaluation

The initial, disease-focused evaluation of multiple myeloma for older adults with suspected multiple myeloma is the same as in younger individuals.⁶ This includes a history and physical examination, laboratory evaluation (Table 1a), imaging, bone marrow biopsy and aspirate with conventional cytogenetics and fluorescence *in situ* hybridization for recurring chromosomal translocations and deletions/duplications seen in multiple myeloma. In addition to the “CRAB” diagnostic criteria of hypercalcemia, renal insufficiency, anemia and bone lesions, recently updated indications for treatment of multiple myeloma now include 60% plasma cells on bone marrow biopsy or aspirate, a ratio of involved to uninvolved serum free light chains ≥ 100 and more than 1 focal lesions on MRI (Table 1b).⁷

Establishing a diagnosis of multiple myeloma is not always straightforward in older adults. Comorbidities and intercurrent illnesses may confound the evaluation. Anemia may be attributable to a number of other causes, such as nutritional deficiencies, acute blood loss, anemia of inflammation due to other medical conditions or even myelodysplasia, rather than evidence of end-organ damage caused by a malignant clonal proliferation of plasma cells. Attribution of anemia to multiple myeloma may require examination of historical laboratory values and exclusion of other etiologies, such as iron deficiency. Similarly, renal insufficiency may be related to comorbidities, such as hypertension or diabetes, rather than multiple myeloma; examining historical laboratory values for temporal trends in renal function and excluding recent exposure to nephrotoxins may aid in establishing whether renal insufficiency is related to a new diagnosis of multiple myeloma.

Following establishment of the diagnosis of multiple myeloma requiring therapy, staging should be determined. The International Staging System was developed as a simple prognostic tool, based on serum albumin and beta-2-microglobulin.⁸ Subsequently, some authors have called into question its utility in stratifying prognosis in older adults with multiple myeloma.⁹ More recently, the Revised-International Staging System has been developed, which also incorporates serum lactate dehydrogenase levels and high-risk cytogenetic abnormalities (Table 2).¹⁰ Of the more than 4000 patients included, one-third was over the age of 65. On multivariate analysis, the R-ISS remained prognostic, independent of age, suggesting that the R-ISS will have utility across the age spectrum in risk-stratifying patients.

Finally, the initial disease-focused evaluation should include assessment of chromosomal abnormalities. Genetic risk stratification helps direct treatment decisions, and retains prognostic significance in the older patient. Shorter progression free survival (PFS) and overall survival (OS) are seen with t(4;14) and del17p in both older and younger patients, though the incidence of t(4;14) decreases with age.¹¹ More investigation is needed to evaluate potential differences in myeloma genetics with aging.

Geriatric Assessment

Emerging data suggest that geriatric assessment may also aid in prognostication and therapeutic decision-making. In a recent study of over 800 older adult with multiple myeloma who participated in one of three clinical trials, participants completed a brief geriatric assessment, including functional status with activities of daily living (ADLs) and instrumental activities of daily living (IADLs), and comorbidities. The investigators then developed a scoring system to categorize participants as fit, intermediate-fit or frail (Figure 1). Patients who were categorized as frail were more likely to experience grade 3–4 nonhematologic toxicity of therapy, early discontinuation of treatment and shorter progression-free survival. The frailty score was also prognostic, with the 3-year overall survival of 57% in frail patients [hazard ratio (HR) 3.6, 95% confidence intervals (CI) 2.4–5.4], 76% in intermediate-fit patients [HR 1.6, 95% CI 1.0–2.6] and 84% in fit patients.¹² Other investigators have demonstrated that the burden of comorbidities is associated with poorer survival.^{13,14}

The detection of certain vulnerabilities, deficits or comorbidities may inform therapeutic decision-making in older adults with multiple myeloma. For example, patients with underlying diabetes may be vulnerable to worsening of glycemic control with the high-dose corticosteroids employed in most multiple myeloma regimens. Diabetes, both pre-existing and steroid-induced, is associated with poorer survival in multiple myeloma.^{15,16} Corticosteroid doses may be reduced or a low dose of intermediate-acting insulin may be utilized on the day of corticosteroid administration to reduce hyperglycemia.

Peripheral neuropathy is particularly problematic in older adults as chemotherapy-induced peripheral neuropathy is associated with a greater risk for functional impairment and falls.¹⁷ In patients with pre-existing peripheral neuropathy, strategies to reduce the risk of worsening neuropathy, such as preferentially utilizing non-neurotoxic agents, or administering bortezomib subcutaneously^{18,19} and weekly^{4,20}, should be considered. Subcutaneous administration of bortezomib is noninferior to intravenous bortezomib with regard to efficacy outcomes, and causes significantly less peripheral neuropathy.¹⁸ Similarly, administration of bortezomib once weekly is associated with similar dose intensity but lower rates of peripheral neuropathy than twice-weekly administration.²⁰

Renal dysfunction must be factored in to therapeutic decision-making, particularly dose selection in older individuals. Clinicians must be cognizant that renal function declines with age, and that a serum creatinine level within the reference range may fail to reflect the presence of renal insufficiency. The creatinine clearance should be estimated on all older adults with newly diagnosed multiple myeloma either through 24-hour urine collection for creatinine clearance or through an estimating equation such as the Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equations.²¹

Cognitive impairment requires special consideration for several reasons. Cognition may be assessed using screening instruments such tools as the Mini Mental Status Exam, the Montreal Cognitive Assessment or the Blessed Orientation-Memory-Concentration Test.^{22,23} The clinician should assess whether the patient has decision-making capacity²⁴

and whether a surrogate decision-maker has been identified.²³ In addition, older adults with underlying cognitive impairment may be more vulnerable to delirium²⁵, whether when exposed to medications that are potentially inappropriate in older adults²⁶ or during acute illnesses. Notably, corticosteroids are included in the American Geriatrics Society Beers Criteria as potentially inappropriate medications (PIM) in older adults due to potential exacerbation of delirium,²⁶ yet are a pivotal component of most multiple myeloma regimens. Another consideration in weighing therapeutic options is that older adults with cognitive impairment may have greater difficulty adhering to a complex regimen of oral medications unless they have adequate caregiver support to assist with self-administration of medications.²⁷

Finally, assessment of the patient's emotional and psychosocial health and social support are important in the comprehensive care of an older adult with multiple myeloma. High-dose corticosteroids may exacerbate anxiety and insomnia.²⁸ Financial burden of therapy is another important consideration; some treatments may present a significant burden²⁹, and the cost and burden of informal caregiving must be considered as well.³⁰ Almost half of partners of people living with multiple myeloma report significant anxiety, and one-third report unmet tangible, emotional and information needs.^{31–33} Consultation with a psychosocial professional and a social worker can be particularly helpful in these situations.²³

Initial therapy

After determining that an older adult has organ dysfunction related to myeloma, or other myeloma defining events (Table 1b), the most appropriate treatment must be chosen based on patient- and disease-related factors (described above in the sections on Initial Evaluation and Geriatric Assessment).

Most regimens for the older or transplant-ineligible patient have been built on the foundation of melphalan and prednisone (MP). Randomized phase 3 studies have established that adding thalidomide (MPT), lenalidomide (MPR), or bortezomib (VMP) to MP can improve outcomes for the older myeloma patient (Table 3). However, the standard 2- and 3-drug regimens used in younger patients also may be used for older patients. To improve tolerability, upfront dose reductions have been suggested based on age.³⁴ Because age alone is insufficient to predict treatment risk, the European Myeloma Network has adapted these suggestions to take both age and fitness into account (Table 4).³⁵

Adding a third drug to MP improves overall response (OR) in the older patient, but the benefit from adding a third agent can be lost due to increased toxicity. Two of six randomized trials comparing MPT to MP failed to show OS benefit despite improved OR.^{36–42} Two meta-analyses of these studies have since favored MPT over MP for PFS and OS^{43,44}, but strategies to prevent and treat hematologic, thromboembolic, and other toxicities must be employed.

Prospective randomized studies support using prolonged therapy with lenalidomide in the older myeloma patient. MM-015, which compared MPR with lenalidomide maintenance

(MPR-R) to fixed-duration therapy with MPR or MP, resulted in longer PFS with MPR-R compared to MPR (31 *versus* 14 months, HR 0.49, $p<.0001$), without differences in OS at a median follow-up of 3 years.⁴⁵ Health-related quality of life (HRQoL) studies favored MPR-R, possibly due to improved OR and delayed time to progression.⁴⁶ The FIRST study compared continuous treatment with lenalidomide and dexamethasone (Rd) until progression to treatment with Rd or MPT for 18 months. Continuous Rd resulted in longer PFS compared to fixed-duration Rd (25.5 *versus* 20.7 months, HR for progression or death 0.7, $p=.001$); OS data are still maturing.⁴⁷ HRQoL measures favored continuous Rd, and supported that better disease control correlates with improved HRQoL.⁴⁸ A meta-analysis of transplant eligible and ineligible patients (median age 68 years, range 61–74) treated on frontline randomized trials has also shown superior PFS and OS with continuous therapy using either lenalidomide or bortezomib with thalidomide (VT).⁴⁹

Bortezomib-based therapy has been explored in 2-, 3-, and 4-drug combinations in the older patient. VISTA showed superior OR, PFS, and OS with bortezomib with MP (VMP) compared to MP.⁵⁰ Concurrent HRQoL studies favored MP early in treatment, with similar HRQoL scores between MP and VMP at the end of treatment.⁵¹ UPFRONT compared bortezomib and dexamethasone (Vd), bortezomib, thalidomide, and dexamethasone (VTD), and VMP, showing no significant difference in OR, PFS, or OS between any arm. VTD was associated with more adverse events and worse HRQoL.⁵² Four-drug therapy with MPT + bortezomib (VMPT) followed by VT maintenance (VMPT-VT) *versus* VMP resulted in higher OR (89% *versus* 81%, $p=.01$), but greater grade 3/4 non-hematologic toxicities in the 4-drug arm (46% *versus* 33%, $p=.003$).⁴ Other combinations, such as a modified combination of weekly bortezomib, reduced-dose lenalidomide and dexamethasone (“RVD lite”), are being explored, with encouraging toxicity profiles.⁵³ Bortezomib-based regimens improve outcomes in older patients. Without a clearly superior regimen, treatment choice may be based on patient- and disease-related factors rather than expected response.

In the fit older patient, consolidation of initial remission with high-dose melphalan and autologous hematopoietic stem cell transplant (ASCT) may be appropriate, though there are no randomized studies examining standard high-dose melphalan (200mg/m²) in patients over 65 years.⁵⁴ Retrospective cohort studies have shown similar transplant-related mortality and OS in patients 65 years and older, supporting that ASCT may be feasible and effective in some patients.^{55–57} In contrast, IFM99-06 randomized patients between 65 and 75 years to initial treatment with melphalan and prednisone (MP), *versus* MP with thalidomide (MPT), *versus* ASCT with intermediate-dose melphalan (100mg/m²), and showed similar overall response (OR) but improved median OS with MPT *versus* ASCT (51.6 *versus* 38.3 months, HR 0.69, CI 0.49–0.96, $p=.027$). Death in the first 3 months of treatment was higher with ASCT compared to MPT, 9% *versus* 2%, respectively.³⁹

In very frail patients, treatment with a single agent and/or best supportive care may be reasonable. However, since treatment toxicity can be mitigated by upfront dose-reduction and/or less intensive treatment schedules, and complications averted by close follow-up and supportive care, treatment is an option for almost all myeloma patients, regardless of age or comorbidity.

Supportive care

All myeloma patients benefit from supportive care concurrent with myeloma-directed treatment. Areas of particular concern include bone health, prevention of infection, prevention of venous thrombosis, and pain management.

Bisphosphonates reduce the risk of fracture^{58,59}, and may prolong PFS and OS in myeloma patients⁶⁰. IMWG guidelines support the use of zoledronic acid or pamidronate intravenously every 3–4 weeks with initial therapy. Treatment may be discontinued after 1–2 years in patients reaching VGPR or CR, and should be continued in patients with active disease or resumed at relapse if bisphosphonates had been discontinued after good response to initial therapy.⁶¹ Less frequent bisphosphonate dosing may also be effective, though the myeloma-specific relevance is not clear: a randomized trial of over 1800 patients with multiple myeloma or bone metastases from breast or prostate cancer demonstrated that zoledronic acid administered every 3 months is noninferior to monthly zoledronic acid in preventing skeletal related events, with similar rates of adverse events.⁶² Bisphosphonate dosing should be monitored and adjusted for pre-existing and bisphosphonate-related renal dysfunction. Risk of bisphosphonate-induced osteonecrosis of the jaw may be reduced by using lower doses of pamidronate (30mg instead of 90mg) and prophylactic dental care.^{63,64} Calcium and vitamin D supplementation are recommended to maintain calcium homeostasis.⁶¹

Infection prophylaxis can reduce treatment morbidity. Antiviral medication is necessary to reduce the risk of varicella zoster reactivation with proteasome inhibitor-based therapy; retrospective studies have shown that doses of acyclovir as low as 200mg–400mg daily may be effective.^{65–67} Conversely, there is no clear role for initial empiric antibacterial prophylaxis. A U.S. community-based prospective study in patients starting myeloma therapy (median age 64 years, range 32–89), using either trimethoprim-sulfamethoxazole, ciprofloxacin or placebo, showed no reduction in serious bacterial infection during the first two months of treatment.⁶⁸ Antibacterial prophylaxis in the older myeloma patient is not routinely recommended, as it will increase the number of medications needed, and the potential for side effects and interactions, without proven benefit.

Prophylaxis against venous thrombosis is mandatory for any patient receiving an immunomodulatory agent in combination with a corticosteroid. Patients with myeloma requiring treatment should be assessed for risk factors for thrombosis,⁶⁹ which can include disease-related factors such as new diagnosis of myeloma or hyperviscosity, patient-related factors such as comorbidities (*e.g.* prior history of thrombosis or thrombophilia, obesity, diabetes, *etc.*), and external factors such as recent surgery and certain medications. In low-risk patients (none or one risk factor), daily aspirin is sufficient thrombosis prophylaxis. In higher risk patients (two or more risk factors), anticoagulation with low molecular weight heparin or full-dose warfarin is recommended.^{69,70} Daily low-dose warfarin is less effective in older myeloma patients and is not recommended.⁷¹ In an older adult with absolute contraindications to anticoagulation, avoiding immunomodulatory agent based therapy should be considered, so that thrombosis prophylaxis is not needed.

Pain is common at diagnosis of myeloma, and may result from complications of the disease, comorbidity, and later, treatment. Pain can impact the older patient in many ways, including causing depression and functional impairment. Managing pain in the older patient requires careful balance of treatment efficacy with side effects, and approaches to treatment may include pharmacotherapy, radiation therapy, surgery, kyphoplasty, physical therapy, and cognitive or behavioral therapy.^{72,73}

Conclusions

Clinical trials have established a variety of effective treatment options for the older myeloma patient, resulting in improved response, survival, and health-related quality of life in this population. Because the effects of aging are individual, a thorough initial assessment of the patient, including personal goals, comorbidity, functional status, psychosocial health, and social support, should happen at the same time as the initial myeloma assessment. All of this information needs to be considered when choosing treatment for the older individual. With attention to upfront dose-reduction when needed and supportive care, most myeloma therapies, including those studied in younger myeloma patients, also can be effective and well-tolerated options for the older adult. Opportunities to continue improving outcomes for the older myeloma patient include studies to better understand potential differences in the biology of myeloma with aging, and studies to more accurately and effectively assess geriatric risk and individualize treatment based on that assessment. Newer myeloma therapies in development such as monoclonal antibodies have little toxicity, and present an exciting opportunity to design highly effective, well-tolerated, targeted treatments for the older myeloma patient.

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ADL, activities of daily living; IADLs, instrumental activities of daily living

Figure 1.
International Myeloma Working Group Frailty Model¹²

Table 1

Table 1a. Laboratory evaluation of suspected multiple myeloma
Complete blood count
Comprehensive metabolic profile
Serum protein electrophoresis with immunofixation
Quantitative immunoglobulin levels (IgG, IgA, IgM)
Beta-2-microglobulin
Lactate dehydrogenase
Serum free light chain assay
24 hour urine collection for urine protein electrophoresis, urine immunofixation
Consider assessment of 25 hydroxy vitamin D levels

Table 1b. Revised IMWG diagnostic criteria for multiple myeloma
<p>Definition of multiple myeloma</p> <p>Clonal bone marrow plasma cells ≥10% or biopsy-proven plasmacytoma</p> <p>Plus ≥1 myeloma-defining event(s):</p> <ul style="list-style-type: none"> Any end-organ damage due to the plasma cell disorder <ul style="list-style-type: none"> (C)alcium – serum calcium >1mg/dL upper limit normal or >11mg/dL (>2.75mmol/L) (R)enal – creatinine clearance <40mL/min or serum creatinine >2mg/dL <177μmol/L (A)nemia – hemoglobin <2g/dL lower limit normal or <10mg/dL (B)one lesions – one or more osteolytic lesions on bone radiograph, CT, or PET/CT Any biomarker of malignancy (≥80% probability of end-organ damage within 2 years) <ul style="list-style-type: none"> Clonal bone marrow plasma cells ≥60% Involved (minimum ≥10mg/dL) to uninvolved serum free light chain ratio ≥100 >1 focal lesion (≥5mm in size) on MRI
<p>Definition of smoldering multiple myeloma</p> <p>Both criteria must be met</p> <ul style="list-style-type: none"> Serum monoclonal protein (IgG or IgA) ≥3g/L or urine monoclonal protein ≥500mg/24hours and/or clonal bone marrow plasma cells 10–60% Absence of myeloma-defining events or amyloidosis

Adapted from Rajkumar et al Lancet Oncol 2014

Table 2

International Staging System⁸ and Revised International Staging System¹⁰

ISS Stage	Albumin (g/dL)		Beta-2-microglobulin (mg/L)			
I	3.5	AND	<3.5			
II			Not I or III			
III						
R-ISS	ISS Stage		Condition	High-risk chromosomal abnormalities*	Lactate dehydrogenase	
I	I		AND	None	Normal	
II				Not R-ISS I or III		
III						
			AND	Present OR	Elevated	

* High risk chromosomal abnormalities include del(17p), t(4;14), or t(14;16) by fluorescence in situ hybridization

Table 3

Overview of Discussed Randomized Clinical Trials for Initial Treatment of Older Adults

3a. Response and Toxicity Considerations					
Clinical Trial (Trial Acronym)		Response (%)		OS (%)	Considerations
		PR	CR		
MPT vs MP (IFM01/01) ⁴⁰	MPT	62 *	7 *	44 * months	Thrombosis prophylaxis Myelosuppression Neuropathy
	MP	31	1	29.1 months	
MPR-R vs MPR vs MP (MM015) ⁴⁵	MPR-R	77 *	15	70 at 3 years	Thrombosis prophylaxis Myelosuppression Secondary malignancy
	MPR	68 *	5	62 at 3 years	
	MP	50	5	66 at 3 years	
Continuous Rd vs Rd vs MPT (FIRST) ⁴⁷	Cont. Rd	75 *	15	59 at 4 years	Thrombosis prophylaxis Myelosuppression Neuropathy
	Rd	73 *	14	56 at 4 years	
	MPT	62	9	51 at 4 years	
	VMP	71 *	35 *	56.4 * months	Myelosuppression Neuropathy Zoster prophylaxis
VMP vs MP (VISTA) ⁵⁰	MP	30	4	43 months	
	VMPT-VT	87	38	61 * at 5 years	Thrombosis prophylaxis Myelosuppression Neuropathy Zoster prophylaxis
	VMP	81	24	51 at 5 years	
VD vs VTD vs VMP (UPFRONT) ⁵²	VD	73	30	74 at 2 years, estimated	Thrombosis prophylaxis Myelosuppression Neuropathy Zoster prophylaxis
	VTD	80	40	74 at 2 years, estimated	
	VMP	69	33	78 at 2 years, estimated	
MPT vs MP vs Reduced-intensity ASCT (IFM99-06) ³⁹	MPT	81 *	15 *	51.6 * months	Thrombosis prophylaxis Myelosuppression Neuropathy
	MP	40	2	33.2 months	
	ASCT	72	17	38.3 months	

Table 3b. Trial Schedules and Doses

Trial	Starting Dose and Schedule			Cycle Days	Number of Cycles	Maintenance
MPT vs MP (IFM01/01)	MPT	M 0.2mg/kg days 1–4 P 2mg/kg days 1–4 T 100mg/day			12	No

Table 3b. Trial Schedules and Doses

Table 3b. Trial Schedules and Doses						
Trial	Starting Dose and Schedule			Cycle Days	Number of Cycles	Maintenance
MPR-R vs MPR vs MP (MM015)	MP	as in MPT				
	MPR-R	M 0.18mg/kg days 1–4 P 2mg/kg days 1–4 R 10mg days 1–21		28	9	R 10mg days 1–21 until progression
	MPR	as in MPR-R				No
	MP	as in MPR-R				No
Continuous Ld vs Ld vs MPT (FIRST) ^a	Cont. Ld	L 25mg days 1–21 d 40mg weekly		28	until progression	Ld until progression
	Ld	as in continuous Ld		28	18	No
	MPT	M 0.25mg/kg days 1–4 P 2mg/kg days 1–4 T 200mg/day		42	12	No
	VMP	V 1.3mg/m ² days 1, 4, 8, 11, 22, 25, 29, 32 cycles 1–4, days 1, 8, 15, 22 cycles 5–9 M 9mg/m ² days 1–4 P 60mg/m ² days 1–4		42	9	No
VMP/VT vs VMP	MP	as in VMP				
	VMP/VT	V 1.3mg/m ² days 1, 8, 15, 22 M 9mg/m ² days 1–4 P 60mg/m ² days 1–4 T 50mg daily		35	9	V 1.3mg/m ² every 14 days with T 50mg daily for 2 years or until progression/relapse
	VMP	as in VMPT				No
	VD	V 1.3mg/m ² days 1, 4, 8, 11 D 20mg days of/after V		21	8	V 1.6mg/m ² days 1, 8, 15, 22 every 5 weeks for 25 weeks
VD vs VTD vs VMP (UPFRONT)	VTD	V 1.3mg/m ² days 1, 4, 8, 11 T 100mg/day D 20mg days of/after V				
	VMP	V 1.3mg/m ² days 1, 4, 8, 11 M 9mg/m ² days 1–4 (every other cycle) P 60mg/m ² days 1–4 (every other cycle)				
	MPT	M 0.2mg/kg days 1–4 P 2mg/kg days 1–4 T 100mg/day to 400mg/day (highest tolerable dose)		42	12	No
	MP	as in MPT				
MPT vs MP vs Reduced-intensity ASCT (IFM99-06)	ASCT	2 ASCT with melphalan 100mg/m ² , 2 months apart				

* denotes p<.05

Abbreviations: D/d – dexamethasone, M – melphalan, P – prednisone, R/L – lenalidomide, T – thalidomide, V- bortezomib, ASCT – autologous hematopoietic stem cell transplant

Upfront dose adjustments recommended for age > 75 years and renal dysfunction

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Table 4**Suggested Dose Adjustments for Age and Fitness**

Risk Factors <ul style="list-style-type: none"> • Over 75 years of age • Needs help with activities of daily living • Organ dysfunction: renal, cardiac, pulmonary, hepatic Base initial dosing on risk factors Reduce dose by 1 dose level for grade 3/4 non-hematologic toxicity			
Drug	Dose Level 0 No risk factors	Dose Level -1 1 risk factor	Dose Level -2
Dexamethasone	40mg weekly	20mg weekly	10mg weekly
Prednisone	60mg/m ² d1–4/28–42 or 50mg every other day	30mg/m ² d1–4/28–42 or 25mg every other day	15mg/m ² d1–4/28–42 or 12.5mg every other day
Thalidomide	100mg daily	50mg daily	50mg every other day
Lenalidomide	25mg days 1–21/28	15mg days 1–21/28	10mg days 1–21/28
Bortezomib	1.3mg/m ² days 1, 4, 8, 11/21	1.3mg/m ² days 1, 8, 15, 22/35	1.0mg/m ² days 1, 8, 15, 22/35
Cyclophosphamide	100mg daily or 300mg/m ² d1, 8, 15/28	50mg daily or 150mg/m ² d1, 8, 15/28	50mg every other day or 75mg/m ² d1, 8, 15/28
Melphalan	0.25mg/kg or 9mg/m ² days 1–4/28–42	0.18mg/kg or 7.5mg/m ² days 1–4/28–42	0.13mg/kg or 5mg/m ² days 1–4/28–42

Adapted from Palumbo NEJM 2011³⁴, Palumbo Blood 2011³⁵, Palumbo Blood 2015