

International Myeloma Working Group Consensus Statement for the Management, Treatment, and Supportive Care of Patients With Myeloma Not Eligible for Standard Autologous Stem-Cell Transplantation

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A B S T R A C T

Purpose

To provide an update on recent advances in the management of patients with multiple myeloma who are not eligible for autologous stem-cell transplantation.

Methods

A comprehensive review of the literature on diagnostic criteria is provided, and treatment options and management of adverse events are summarized.

Results

Patients with symptomatic disease and organ damage (ie, hypercalcemia, renal failure, anemia, or bone lesions) require immediate treatment. The International Staging System and chromosomal abnormalities identify high- and standard-risk patients. Proteasome inhibitors, immunomodulatory drugs, corticosteroids, and alkylating agents are the most active agents. The presence of concomitant diseases, frailty, or disability should be assessed and, if present, treated with reduced-dose approaches. Bone disease, renal damage, hematologic toxicities, infections, thromboembolism, and peripheral neuropathy are the most frequent disabling events requiring prompt and active supportive care.

Conclusion

These recommendations will help clinicians ensure the most appropriate care for patients with myeloma in everyday clinical practice.

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INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm that affects primarily elderly patients.^{1,2} During the past decade, considerable progress has been made in the management of MM, prompting the International Myeloma Working Group (IMWG) to develop these updated guidelines.³⁻⁶

ble A1, online only).⁷ Some of the treatment regimens recommended for consideration are not approved by the regulatory authorities for these indications and hence should not be considered as standard care but rather as reasonable treatment options. In the recommendations, approved regimens are highlighted in bold font.

METHODS

In 2012, an Update Committee of the IMWG performed a review of key literature, including searches of the Cochrane library, Medline, the Internet, and major meeting reports. Expert consensus was used to propose additional recommendations when published data were insufficient. The Grades of Recommendation, Assessment, Development, and Evaluation system were used to grade recommendations (Appendix Ta-

RECOMMENDATIONS

Diagnosis

The diagnostic process aims to distinguish between monoclonal gammopathy of undetermined significance, asymptomatic (smoldering) MM, symptomatic MM, solitary plasmacytoma, and other plasma cell diseases based on the IMWG criteria (Table 1). Symptomatic MM is defined as the presence of $\geq 10\%$ clonal bone marrow plasma

Table 1. Diagnostic Criteria for Plasma Cell Diseases

Diagnosis	Diagnostic Criteria
MGUS	All three criteria must be met: Serum monoclonal protein (IgG or IgA) < 3 g/100 mL Clonal bone marrow plasma cells < 10% Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Smoldering (asymptomatic) MM	Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥ 3 g/100 mL and/or clonal bone marrow plasma cells ≥ 10% Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
MM (symptomatic)	All three criteria must be met: Clonal bone marrow plasma cells ≥ 10%* Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory MM) Evidence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder, specifically: Hypercalcemia: serum calcium ≥ 11.5 mg/100 mL Renal insufficiency: serum creatinine > 1.73 mmol/L Anemia: normochromic, normocytic with hemoglobin value > 2 g/100 mL below lower limit of normal or hemoglobin value < 10 g/100 mL Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures
Solitary plasmacytoma	All four criteria must be met: Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI of spine and pelvis (except for primary solitary lesion) Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Other plasma-cell diseases	Waldenstrom's macroglobulinemia Systemic AL amyloidosis Monoclonal Ig deposition disease POEMS syndrome

Adapted from Kyle Leukemia 2009.
Abbreviations: AL, amyloid light chain; CRAB, hypercalcemia, renal failure, anemia, or bone lesions; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MRI, magnetic resonance imaging; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes.
*Monoclonal plasma cells usually account for ≥ 10% of all nucleated cells, but they may range from < 5% to almost 100% (International Myeloma Working Group: Br J Haematol 121:749-757, 2003).

cells and organ damage (hypercalcemia, renal failure, anemia, or bone lesions [CRAB]).⁸ In addition, the presence of ≥ 60% bone marrow involvement or rapidly climbing paraprotein, regardless of CRAB, are considered by some authors as MM-related symptoms.⁹

The diagnostic work-up should include three subsequent levels of investigation to confirm the diagnosis, assess the prognosis, and establish the appropriate treatment (Table 2). Serum free-light chain (FLC) assay is useful for diagnosis and monitoring of nonsecretory myeloma, when small amounts of monoclonal protein are secreted in the serum and/or urine, and in light chain–only myeloma.¹⁰⁻¹² Magnetic resonance imaging (MRI) and positron emission tomography integrated with computed tomography (PET/CT) may be useful in selected circumstances (eg, to detect soft tissue lesions arising from bone lesions, spinal cord compression, and asymptomatic lesions and to evaluate a painful area of the skeleton). MRI is indicated in nonsecretory myeloma for initial assessment and follow-up or to detect occult lesions in asymptomatic MM.^{13,14}

Recommendations:

- The IMWG criteria should be used to diagnose plasma cell disorders (Grade C/IV; Table 1).
- The recommended investigations of a suspected myeloma should incorporate the tests in Table 2 (grade C/IV).

Pretreatment Considerations: Definitions of Fit and Unfit Patients

The operative cutoff age of 65 years is no longer sufficient to identify elderly patients. Aging is associated with an increased fre-

quency of comorbidities, frailty, and disability, which have a negative effect on outcome.

Age, comorbidities, and geriatric assessment should be used to define patients' status (very fit, fit, and unfit). Unfit patients are characterized by older age, comorbidity, organ dysfunctions (cardiac, pulmonary, hepatic, GI, renal), and limits in mental/mobility functions. To assess comorbidity, the Charlson index can be used.¹⁵ To assess frailty and disability, Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) can be adopted.¹⁶ Fit patients should receive full-dose therapy, whereas unfit patients need reduced dose-intensity treatment.

Recommendation:

- The assessment of organ function, comorbidities (with the Charlson index), frailty, and disability (defined by ADL and IADL) should be considered to define patients' status (grade C/IV).

Staging and Prognostic Factors

The International Staging System (ISS) is used to assess the prognosis of patients with symptomatic MM (Appendix Table A2, online only).¹⁷ ISS stage III is associated with poor prognosis. Chromosomal abnormalities t(4;14), t(14;16), and t(14;20); chromosome 1 abnormalities; and del17p detected by fluorescent in situ hybridization (FISH) are associated with poor prognosis,¹⁸⁻²¹ whereas the isolated 13q deletion is not considered a high-risk feature. Hyperdiploidy, t(11;14), and t(6;14) are considered

Table 2. Diagnostic Work-Up for Patients With MM

Work-Up	Description	General Practice	Clinical Trial
First-level investigations to make diagnosis			
History and physical examination		Always	Always
Blood and urine	Complete blood count and differential; chemistry, including creatinine and calcium; serum protein electrophoresis and immunofixation, quantification of immunoglobulin; 24-hour urine collection for proteinuria, electrophoresis, and immunofixation	Always	Always
	Serum free light chains	For oligo and nonsecretory MM and light chain only	Always
Bone marrow	Aspirate and trephine biopsy with plasma cells phenotyping	Always	Always
Imaging	Skeletal survey	Always	Always
Second-level investigations to assess prognosis			
Blood	Albumin, β_2 -microglobulin, LDH	Always	Always
	Serum free light chains	Not indicated	Preferred
Cytogenetic	Metaphase karyotype	Preferred	Always
FISH	t(4;14), t(11;14), t(14;16), t(14;20), chromosome 13 deletion, 17p13 deletion, and chromosome 1 abnormalities	Preferred	Always
Third-level investigations required before starting therapy or enrollment onto clinical trials			
Performance status	Karnofsky performance status and WHO scale	Always	Always
Patient status	Assessment of comorbidity, frailty, and disability (cumulative illness rating scale or Charlson score; ADL and IADL score)	Preferred	Always
Organ function	Cardiac, pulmonary, hepatic, GI, and renal function	Always	Always
Infectious disease	Hepatitis B and C, HIV	Always	Always
Additional pretreatment investigations			
Imaging	MRI PET/CT	In selected circumstances	Preferred
Prognostic	GEP	Not indicated	Preferred

Abbreviations: ADL, Activities of Daily Living; FISH, fluorescent in situ hybridization; GEP, gene expression profiling; IADL, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MM, multiple myeloma; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

standard-risk features. The combination of FISH data with ISS stage improves risk assessment.²⁰ An abnormal κ/λ FLC ratio at diagnosis seems to predict poor prognosis.²² Gene expression profiling (GEP) is emerging as a predictive tool to further refine risk stratification.^{23,24} The prognostic role of PET/CT has been recently investigated in transplantation-eligible patients,²⁵ although a standardization of this procedure is needed to translate its use into clinical practice. The achievement of complete response (CR) after initial treatment is associated with improved progression-free (PFS) and overall survival (OS).^{26,27}

Recommendations:

- The ISS should always be used at diagnosis (grade C/IV).
- Chromosomal abnormalities should be detected to predict outcome (grade C/IV).
- New prognostic markers (FLC, GEP, and PET/CT) need additional evaluations (grade C/IV).

Indications for Treatment

For asymptomatic patients, close monitoring is suggested every 1 to 3 months. Clinical trials are currently evaluating the role of early therapy with novel agents in high-risk asymptomatic myeloma.²⁸ Conversely, patients with active and symptomatic MM, defined by the presence of CRAB symptoms, require immediate treatment.

Second-line treatment is indicated when there is either a clinical relapse (reoccurrence of CRAB symptoms) or a significant and quick paraprotein increase (doubled monoclonal protein within 2 months, with an increase in the absolute levels of monoclonal protein of ≥ 1 g/dL in serum or of ≥ 500 mg per 24 hours in urine confirmed by two consecutive measurements).²⁹ Whether to start treatment in case of biochemical relapse (25% increase in the paraprotein from the lowest response value without CRAB symptoms) is an open issue.

Recommendations:

- Asymptomatic patients should be carefully monitored every 1 to 3 months (grade C/IV).
- Initial therapy is indicated when CRAB symptoms occur (grade C/IV).
- Re-treatment is indicated in case of clinical relapse or if the paraprotein has doubled within 2 months (grade C/IV).

Definition of Response to Therapy

The uniform response criteria were recently revised by the IMWG (Table 3).^{29,30} The definitions of immunophenotypic CR, molecular CR, and FLC response were introduced to refine the depth of response. MRI and PET/CT have not been incorporated into the response criteria assessment.²⁹

Table 3. Response Criteria

Response	Criteria
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed
sCR	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with > four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10 ⁻⁵)
VGPR	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h If serum and urine M protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥ 30% In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed
MR for relapsed refractory myeloma only	≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89% In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD	Increase of 25% from lowest response value in any of following: Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; Urine M component (absolute increase must be ≥ 200 mg/24 h) and/or; Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder Two consecutive assessments before new therapy are needed

NOTE. Data adapted.^{8,9,30a}
Abbreviations: CR, complete response; FLC, free light chain; M, monoclonal; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Recommendation:

- The updated IMWG criteria (Table 3) should be used to assess response every 30 to 60 days during treatment (grade C/IV).

Front-Line Therapy

Patients age 65 to 75 years are generally considered ineligible for autologous stem-cell transplantation (ASCT). Because biologic age can differ from chronologic age, this strict range may differ by approximately 5 years.

Different therapeutic approaches may be adopted according to age and patient status (Table 4). For patients age 65 to 70 years in excellent clinical condition (very fit), or younger patients with comorbidities, a reduced dose-intensity ASCT with melphalan 100 mg/m² (MEL100) can be safely adopted instead of full-dose melphalan 200 mg/m² (MEL200). For patients age 65 to 75 years in good clinical condition (fit), full-dose conventional chemotherapy is indicated, whereas for frail patients age > 75 years (unfit), or younger patients with comorbidities, reduced dose-intensity therapy is suggested.

The choice of treatment should take into account patient status (Fig 1), the risk/benefit ratio of each regimen (Table 5), and patient

quality of life. Patients with newly diagnosed myeloma should be referred to specialized units to receive appropriate care (Appendix, online only).

Reduced-Intensity Autologous Transplantation

In patients age 65 to 70 years, MEL100 followed by ASCT was superior to standard melphalan-prednisone (MP), improving both event-free survival (28 v 16.4 months) and OS (58 v 37.2 months),⁵⁵ but in patients age 65 to 75 years, MEL100 was inferior to MP-thalidomide (MPT; PFS, 19.4 v 27.5 months).³¹ In patients age 65 to 75 years, bortezomib-based induction, tandem MEL100, lenalidomide-prednisone consolidation, and lenalidomide maintenance led to a median PFS of approximately 4 years.⁵⁶ In selected very fit patients, ASCT remains feasible well beyond the age limit of 65 years. As recommended for patients age < 65 years, bortezomib-based induction and lenalidomide maintenance should be considered for patients undergoing ASCT.⁵⁷

Recommendation:

- Very fit patients age 65 to 75 years, unsuitable for MEL200, may benefit from MEL100 (grade B/IIa).

Table 4. Selected Therapeutic Schemas

Regimen	Schedule	CR (%)	PFS/EFS/ITP	OS
Induction regimens				
MPT	Melphalan: 4 mg/m ² given orally on days 1-7 every 4 weeks for six cycles ³¹ or 0.25 mg/kg on days 1-4 every 6 weeks for 12 cycles ³² ; prednisone: 40 mg/m ² given orally on days 1-7 every 4 weeks for six cycles ³¹ or 2 mg/kg on days 1-4 every 6 weeks for 12 cycles ³² ; thalidomide: 100 mg/day given orally continuously until progression or intolerance ³¹ or 200 mg/day continuously for 12 cycles of 6 weeks ³²	13-16	Median, 20.3 months ³³	Median, 39.3 months ³³
CTDa	Cyclophosphamide: 500 mg/wk for six to nine cycles every 3 weeks; thalidomide: 100 mg/day increased to 200 mg/day for six to nine cycles every 3 weeks; dexamethasone: 20 mg on days 1-4 and 15-18 for six to nine cycles every 3 weeks ³⁴	13	Median, 13 months	Median, 33 months
VMP	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles; melphalan: 9 mg/m ² given orally on days 1-4 every 6 weeks for nine cycles; prednisone: 60 mg/m ² given orally on days 1-4 every 6 weeks for nine cycles ³⁵ ; as alternative, bortezomib: 1.3 mg/m ² on days 1, 8, 15, and 22 every 6 weeks for nine cycles ³⁶	24-30	Median, 22-27 months	At 2 years, 85% to 87%
VMPT	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles; melphalan: 9 mg/m ² given orally on days 1-4 every 6 weeks for nine cycles; prednisone: 60 mg/m ² given orally on days 1-4 every 6 weeks for nine cycles; thalidomide: 50 mg/day given orally continuously for nine cycles ³⁶	38	Median, 33 months	At 3 years, 86% ³⁷
VTP	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycle one), every 6 weeks, and 1.3 mg/m ² on days 1, 8, 15, and 22 every 5 weeks (cycles two to six); thalidomide: 100 mg/day given orally for six cycles; prednisone: 60 mg/m ² given orally on days 1-4 every 6 weeks for six cycles ³⁸	28	Median, 31 months*	At 3 years, 70%*
VCD	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, and 11 every 4 weeks for four to 12 cycles; cyclophosphamide: 300 mg/m ² given orally on days 1, 8, 15, and 22 every 4 weeks for four to 12 cycles; dexamethasone: 40 mg/day given orally on days 1-4, 9-12, and 17-20 every 4 weeks for four to 12 cycles ³⁹ ; as alternative, bortezomib: 1.5 mg/m ² given as bolus intravenous infusion on days 1, 8, 15, and 22 ⁴⁰	39†	—	—
VRd	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks for eight cycles; lenalidomide: 25 mg given orally on days 1-14 every 3 weeks for eight cycles; dexamethasone: 20 mg given orally on days 1, 2, 4, 5, 8, 9, 11, and 12 every 3 weeks for eight cycles ⁴¹	37	At 18 months, 75%‡	At 18 months, 97%‡
Rd	Lenalidomide: 25 mg given orally on days 1-21 every 4 weeks for four cycles§; dexamethasone: 40 mg given orally on days 1, 8, 15, and 22 every 4 weeks for four cycles ⁴²	4	Median, 25 months	At 2 years, 87%
MPR	Melphalan: 0.18 mg/kg given orally on days 1-4 every 4 weeks for nine cycles; prednisone: 2 mg/kg given orally on days 1-4 every 4 weeks for nine cycles; lenalidomide: 10 mg given orally on days 1-21 every 4 weeks for nine cycles ⁴³	3	Median, 14 months	Not reached

(continued on following page)

Table 4. Selected Therapeutic Schemas (continued)

Regimen	Schedule	CR (%)	PFS/EFS/ITP	OS
Maintenance regimens				
T	Thalidomide: 50 mg given orally, increased to 100 mg if tolerated after 4 weeks, until progression ⁴⁴	—	Median, 11 months	Median, 38 months
R	Lenalidomide: 10 mg given orally on days 1-21 every 4 weeks until progression ⁴³	—	Median, 26 months	—
VT	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion every 2 weeks for 2 years or until progression; thalidomide: 50 mg given orally for 2 years or until progression ^{36,37}	45	Median, 27 months	Median, not reached
Salvage regimens				
V	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks for eight cycles and on days 1, 8, 15, and 22 every 5 weeks for following three cycles ⁴⁵	6	Median, 6 months	At 1 year, 80%
V-Peg	Bortezomib: 1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks; peg: 30 mg/m ² on day 4 of each cycle for eight cycles or until progression ⁴⁶	4	Median, 9 months	At 15 months, 76%
RD	Lenalidomide: 25 mg given orally on days 1-21; D: 40 mg on days 1-4, 9-12, and 17-20 every 4 weeks for four cycles and on days 1-4 for following cycles until progression ⁴⁷	14	Median, 11 months	Median, 29.6 months
Carfilzomib	Carfilzomib: 20 mg/m ² given as 2-10 minute intravenous infusion on days 1, 2, 8, 9, 15, and 16 every 4 weeks (cycle one) and 27 mg/m ² on days 1, 2, 8, 9, 15, and 16 every 4 weeks for up to 12 cycles ⁴⁸	0.4	Median, 3.7 months	Median, 15.6 months

Abbreviations: CR, complete response; CTDa, cyclophosphamide-thalidomide-dexamethasone; D, dexamethasone; EFS, event-free survival; FISH, fluorescent in situ hybridization; MPR, melphalan-prednisone-lenalidomide; MPT, melphalan-prednisone-thalidomide; OS, overall survival; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide plus low-dose dexamethasone; RD, lenalidomide plus high-dose dexamethasone; TTP, time to progression; V, bortezomib; V-Peg, bortezomib plus pegylated liposomal doxorubicin; VCD, bortezomib, cyclophosphamide, and dexamethasone; VGPR, very good partial response; VMp, bortezomib-melphalan-thalidomide; VMPT, bortezomib-melphalan-prednisone-thalidomide; VTP, bortezomib-thalidomide-prednisone.

*For both patients enrolled in VTP or VMp arms; study detected no significant difference between two treatment arms (VMP v VTP).

#With or without transplantation.

||Patients with adverse interphase FISH receiving thalidomide showed no significant PFS benefit and worse OS (*P* = .009).

§After four cycles, patients could discontinue therapy to pursue stem-cell transplantation or continue treatment until disease progression.

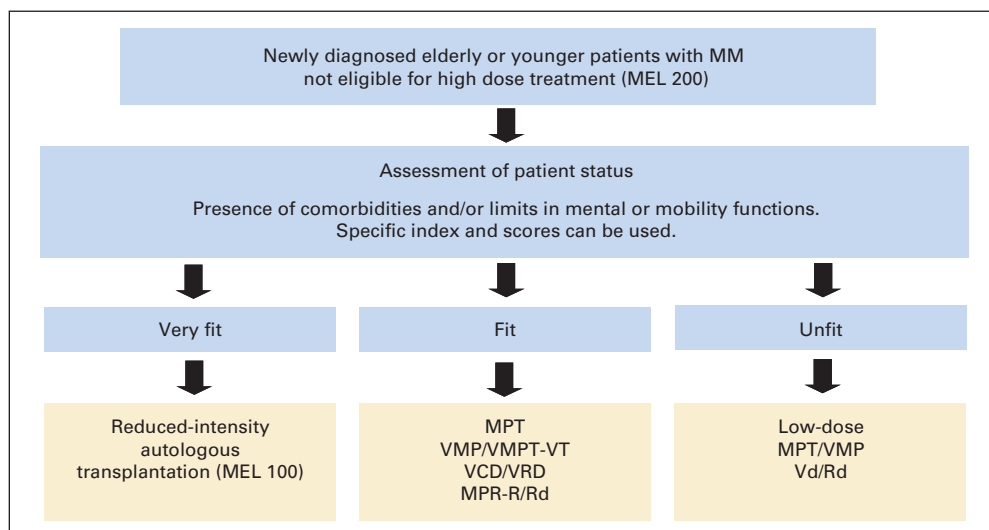


Fig 1. Treatment algorithm for elderly patients with multiple myeloma (MM). MEL 100, melphalan 100 mg/m²; MEL 200, melphalan 200 mg/m²; MPR-R, melphalan-prednisone-lenalidomide followed by lenalidomide; MPT, melphalan-prednisone-thalidomide; Rd, lenalidomide plus low-dose dexamethasone; Vd, bortezomib-dexamethasone; VCD, bortezomib-cyclophosphamide-dexamethasone; VMP, bortezomib-melphalan-prednisone; VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide; VRD, bortezomib-lenalidomide-dexamethasone.

Thalidomide-Based Regimens

Thalidomide combined with dexamethasone (TD) was superior to high-dose dexamethasone for partial response (63% v 41%)⁵⁸ and time to progression (TTP; 22.6 v 6.5 months)⁵⁹ but was more toxic. Similarly, TD was superior to MP for responses, but PFS was similar, and OS was shorter.⁶⁰

Six randomized studies compared MPT with standard MP. Despite differences in doses and schedules among the trials, better responses and PFS were reported with MPT.^{31,32,49-53} The effect on OS varied across the studies, and only two trials showed a significant survival benefit.^{31,52} In a meta-analysis of data from 1,682 patients, MPT improved PFS by 5.4 months and OS by 6.6 months.³³ Severe adverse events (AEs), especially nonhematologic, were higher with MPT and negatively affected the prognosis.⁵³ Thalidomide-related AEs included cytopenia, thrombosis, fatigue, and peripheral neuropathy.

Cyclophosphamide-thalidomide-dexamethasone improved responses compared with MP, with similar survival outcomes and higher incidence of AEs.³⁴ Thalidomide doses > 100 mg per day are poorly tolerated and not appropriate for elderly patients. MPT has the advantage of oral administration and reduced hematologic toxicity, but it is associated with an increased risk of peripheral neuropathy, deep-vein thrombosis, and cardiac events. The use of this combination is supported by different phase III trials.

Bortezomib-Based Regimens

In a large phase III trial, the addition of bortezomib to standard MP (VMP) significantly increased CR from 4% to 30%, TTP by approximately 7 months, and OS by 13 months.^{35,61} Bortezomib-related AEs included primarily neutropenia, thrombocytopenia, and peripheral neuropathy.⁶² When the twice-per-week bortezomib

Table 5. Grade 3 to 4 AEs

Regimen	Neutropenia (%)	Thrombocytopenia (%)	VTE (%)	Peripheral Neuropathy (%)*	Infection (%)	Fatigue (%)	GI (%)	SPM (%)
Induction								
MPT ^{31,32,49-53}	16-48	3-14	3-12	6-23	4-28	3-8	5-11	NA
CTD ³⁴	NA	NA	16	7	13	NA	4	NA
VMP ³⁵	40	37	1	22	10	8	17	6
VMP weekly ^{54†}	33	19	3	8	11	4	6	NA
VMPT ³⁶	38	22	5	15	13	6	6	NA
VTP ³⁸	22	12	2	9	1	NA	2	NA
VRd ⁴¹	9	6	5	6	5	3	2	NA
Rd ⁴²	20	5	12	2	9	9	NA	NA
MPR ⁴³	66	40	5	0	13	2	5	2
Salvage								
V ⁴⁵	14	30	0	8	13	6	19	NA
V-Peg ⁴⁶	29	23	1	4	3	6	14	NA
RD ⁴⁷	41	15	15	2	22	6	10	NA

Abbreviations: AE, adverse event; CTD, cyclophosphamide-thalidomide-dexamethasone; MPR, melphalan-prednisone-lenalidomide; NA, not available; Rd, lenalidomide plus low-dose dexamethasone; RD, lenalidomide plus high-dose dexamethasone; SPM, second primary malignancy; V, bortezomib; V-Peg, bortezomib plus pegylated liposomal doxorubicin; VMP, bortezomib-melphalan-thalidomide; VMPT, bortezomib-melphalan-prednisone-thalidomide; VTE, venous thromboembolism; VTP, bortezomib-thalidomide-prednisone.

*Sensory neuropathy/motor neuropathy/neuralgia.

†Weekly infusion of bortezomib.

schedule was decreased to once per week, the rate of grade 3 to 4 peripheral neuropathy was significantly reduced from 28% to 8%, without affecting efficacy.^{38,54} Recently, subcutaneous bortezomib proved to be as effective as intravenous administration, with a reduced risk of peripheral neuropathy.⁶³

The four-drug combination of bortezomib, melphalan, prednisone, and thalidomide followed by continuous bortezomib-thalidomide (VMPT-VT) demonstrated better responses and a PFS prolongation of 8 months compared with VMP, but the efficacy advantage was mainly reported in fit patients 65 to 75 years of age.^{36,37} Bortezomib-thalidomide-prednisone (VTP) as induction, followed by VT or bortezomib-prednisone, was not superior to VMP and was associated with more serious AEs and discontinuations.³⁸

Promising results were obtained when cyclophosphamide (VCD)^{39,40} or lenalidomide (VRD)⁴¹ were combined with bortezomib-dexamethasone (VD), producing high-quality responses. Bortezomib, either intravenously or subcutaneously, induces high and rapid responses. Bortezomib does not increase the risk of thromboembolism and may be used in patients with renal failure, but peripheral neuropathy and thrombocytopenia are the main dose-limiting toxicities. The benefits of VMP and VMPT-VT are supported by phase III trials; alternatively, VCD or VRD can be adopted.

Lenalidomide-Based Regimens

The combination lenalidomide plus low-dose dexamethasone (Rd) was better tolerated than lenalidomide plus high-dose dexamethasone (RD), with a significant survival benefit (2-year OS, 87% v 75%). The most common grade ≥ 3 AEs were thrombosis, infections, and fatigue and were more frequent with RD.⁴²

Melphalan-prednisone-lenalidomide followed by lenalidomide (MPR-R) significantly prolonged median PFS by 17 months in comparison with fixed-duration melphalan-prednisone-lenalidomide (MPR) and by 18 months compared with MP. However, this advantage was not confirmed in patients age > 75 years. During induction, the most frequent AEs were hematologic. The incidence rates per 100 patient-years of hematologic second primary malignancies (SPMs) were 1.92, 1.30, and 0.40 in the MPR-R, MPR, and MP groups, respectively, whereas solid SPMs were heterogeneous and balanced across arms.⁴³

Lenalidomide has the advantage of the oral administration and the lack of neurologic toxicity, although myelosuppression is common, and the prevention of venous thromboembolism is recommended. MPR-R is supported by a phase III trial, whereas the evaluation of Rd compared with melphalan-based regimens is ongoing.

Recommendations:

- Fit patients should receive full-dose therapy. **MPT, VMP, Rd, VMPT-VT, and MPR-R** are reasonable therapeutic options (grade A/Ib).
- **MPT** may be preferred for its oral administration and lower cost (grade C/IV).
- **VMP** and VMPT-VT or VCD and VRD may be preferred in patients who need rapid, profound cytoreduction. Once-per-week subcutaneous bortezomib should be considered because of the lower incidence of AEs (grade C/IV).
- Rd or MPR-R may be preferred when oral administration and the lack of peripheral neuropathy are major considerations (grade C/IV).

Treatment Options for Unfit Patients

Unfit patients are more susceptible to AEs with subsequent treatment discontinuations that significantly affect dose-intensity and efficacy. In these patients, lower dose-intense therapies are suggested. The three-drug combination MPT has consistently showed a PFS improvement that was less pronounced in patients age > 75 years, whereas VMP was superior to MP in patients age > 75 years.^{35,52,61} In a randomized study, the outcome was similar between VD, VMP, and VT-dexamethasone, but the discontinuation rate was lower with VD.⁶⁴ The combination Rd was equally effective in younger and elderly patients. Therefore, two-drug combinations such as corticosteroid plus lenalidomide, thalidomide, or bortezomib should be considered safe treatment options for unfit patients.⁶⁴⁻⁶⁷

Low-dose dexamethasone is mandatory because of the higher toxicity and mortality rates associated with high-dose dexamethasone.⁴² Lower doses of dexamethasone (10-20 mg/wk) are better tolerated. Thalidomide at 50 mg per day and lenalidomide at 15 mg per day are the preferred doses in this setting.^{52,68} Subcutaneous once-per-week bortezomib 1 mg/m² is highly suggested in unfit patients.^{38,54,63} Because the risk of AEs is higher at the beginning of treatment, therapy may be started at lower doses and subsequently increased after 2 to 4 months if tolerated or if the disease is not adequately controlled.

Recommendation:

- Unfit patients should receive reduced-dose **MPT or VMP** or two-drug combinations with bortezomib or lenalidomide and low-dose dexamethasone (ie, Vd or Rd; grade C/IV).

Maintenance Therapy

Maintenance treatment has consistently prolonged PFS but has inconsistently improved survival.^{44,69} In a recent meta-analysis, continuous thalidomide improved PFS, with a late OS benefit.⁴⁴ In another meta-analysis, lenalidomide reduced the risk of progression by 65% in both young and elderly patients.⁷⁰

In the MRC Myeloma IX trial, the longest PFS was reported in patients treated with thalidomide both at induction and after induction; the shortest PFS was seen in the group treated with MP without thalidomide.⁴⁴ Continuous thalidomide showed no PFS benefit and worse OS in patients with adverse FISH.

In a prespecified landmark analysis of the MM015 trial, continuous lenalidomide significantly extended PFS from the start of lenalidomide (26 months) as compared with placebo (7 months), regardless of age.⁴³ Similarly, VT prolonged median PFS by approximately 14 months.³⁷ Continuous therapy with VT or bortezomib-prednisone led to a median PFS of 30 months versus 24 months, respectively.⁷¹

Drug-related toxicity associated with continuous thalidomide therapy may limit its long-term administration. Lenalidomide is well tolerated, although it is also associated with a higher risk of SPMs. Continuous treatment with bortezomib has the inconvenience of injection administration and a slight increased risk of peripheral neuropathy.

In the future, the impact of maintenance on response and outcome after progression needs to be clarified. Similarly, the optimal duration of maintenance should be defined (for a fixed duration of 2 years or until progression/intolerance).

Recommendations:

- The routine use of maintenance in transplantation-ineligible patients is not yet validated.

- Thalidomide is an option for standard-risk patients, although its long-term use is limited by the risk of peripheral neuropathy (grade A/Ib).
- Lenalidomide is well tolerated but associated with a higher risk of SPMs (grade A/Ib).
- Bortezomib can be an effective alternative, with lower risk of peripheral neuropathy than thalidomide (grade B/IIa).

Therapy for Relapsed Disease

When treating patients with relapsed myeloma, duration of response to previous therapy is a fundamental factor to consider. Repeating the same treatment is a valuable option for patients with a durable response lasting more than 20 to 24 months after induction at diagnosis and more than 9 to 12 months after therapy at relapse. In the case of short-term remission duration or progression during initial therapy, an alternative regimen is suggested.

Standard treatments include bortezomib or lenalidomide combined with dexamethasone or bortezomib-pegylated liposomal doxorubicin.^{45-47,72,73} Rd is highly suggested because it is better tolerated compared with RD.

Re-treatment with bortezomib is a feasible option.⁷⁴ Re-exposure to immunomodulatory drugs such as lenalidomide after previous thalidomide seems feasible; however, efficacy and survival may be lower.^{75,76}

In case of stable disease without CRAB symptoms, the treatment strategy should not be changed. The asymptomatic status, rather than a response improvement, is the most relevant factor to consider during salvage treatment.⁷⁷ In case of biochemical relapse, especially during maintenance therapy, increasing the dose of the current drug and subsequently adding another agent is a sensible strategy.

In a recent survey, poor outcome was reported once patients became refractory to both bortezomib and immunomodulatory drugs.⁷⁸ Ongoing trials are exploring novel agents, such as new proteasome inhibitors (carfilzomib combined with lenalidomide-dexamethasone), anti-CS1 monoclonal antibody (elotuzumab plus lenalidomide-dexamethasone or VD), histone-deacetylase inhibitors (panobinostat and vorinostat), and bendamustine. The US Food and Drug Administration recently approved carfilzomib for progressive MM after at least two prior therapies, including bortezomib and immunomodulatory agents, and pomalidomide in patients relapsed/refractory to lenalidomide.^{48,79} Thalidomide is preferred for its limited hematologic toxicity; bortezomib is preferred in case of renal failure or previous deep-vein thrombosis; lenalidomide is suggested in case of concomitant peripheral neuropathy. Palliative care is essential when cure is no longer possible (Appendix, online only).

Recommendations:

- Repeating the same treatment should be considered after long-lasting remission (20-24 months); an alternative regimen is suggested for patients with shorter remission duration (9 to 12 months; grade C/IV).
- **VD or bortezomib-pegylated liposomal doxorubicin and lenalidomide-dexamethasone** are the treatments of choice (grade A/Ib).

Bone Disease

Bone disease is a highly disabling event that can cause pain, pathologic fractures, spinal cord compression, and hypercalcemia.⁸⁰ Pain requires pharmacologic analgesia, together with chemotherapy,

bisphosphonates, and local interventions.⁸¹ Radiotherapy may be useful to prevent further osteolysis at the fracture site; percutaneous vertebroplasty and balloon kyphoplasty are suggested in case of painful spinal fractures.

Oral clodronic acid, intravenous pamidronic acid, and zoledronic acid are the available bisphosphonate treatments.⁸²⁻⁸⁴ Zoledronic acid significantly reduced skeletal-related events (SREs) and improved OS compared with sodium clodronate.^{85,86} Zoledronic acid was as effective as pamidronate in preventing SREs.^{87,88} No difference was observed between monthly pamidronate at 30 or 90 mg.⁸⁹ Renal impairment and osteonecrosis of the jaw are infrequent but serious complications of intravenous bisphosphonates.

Recommendations:

- Analgesics should be used to treat uncontrolled pain. Low-dose radiation therapy (8 Gy, single fraction) of limited involved fields should be used in case of pain not responding to therapy. Vertebroplasty and kyphoplasty should be considered for painful vertebral collapse (grade C/IV).
- Amino-containing bisphosphonates are recommended for the prevention and management of SREs, independently of bone disease status at baseline. Renal function should be carefully monitored, drug doses should be reduced, and dental evaluation should be performed before starting therapy (grade A/Ib). There is insufficient evidence to recommend bisphosphonates in asymptomatic MM.

Renal Failure

Renal failure occurs because of FLC-related damage of proximal tubules, along with hypercalcemia, hyperuricaemia, dehydration, infections, and nephrotoxic drugs. The immediate start of an effective MM treatment is the mainstay to recover renal function. High-dose dexamethasone is a rapid intervention to assure a fall in light chain load.⁹⁰ Bortezomib can be administered safely, without dose adjustments, and should be preferred in the event of dialysis.⁹¹⁻⁹⁵ Limited data are present on the role of thalidomide in this setting.^{96,97} Lenalidomide is active,^{98,99} but dose reductions are mandatory depending on the creatinine clearance values.^{100,101} Doxorubicin and cyclophosphamide do not require dose adjustments. Adjusted doses of bisphosphonates are indicated to correct hypercalcemia. Additional studies of the new large-pore hemodialysis membranes to physically remove light chains are awaited.

Recommendations:

- High-dose dexamethasone (40 mg per day for 4 days) should be started promptly, along with high fluid intake (≥ 3 L per day of saline solution; grade C/IV).
- In case of acute renal failure or for patients requiring dialysis, bortezomib can be safely used without dose modifications (grade C/IV).
- In case of chronic renal impairment, thalidomide and lenalidomide can be administered. Appropriate lenalidomide dose reductions are mandatory: 10 mg per day when creatinine clearance is 30 to 50 mL/min; 15 mg every other day when creatinine clearance is < 30 mL/min; 5 mg per day after dialysis when patient requires dialysis (grade C/IV).

Hematologic Toxicity

Myelosuppression is primarily induced by chemotherapy, but patient characteristics, disease stage, type of current and previous

treatments, and neutrophil count $< 1,000$ cells/mL at baseline are additional risk factors of severe neutropenia. Granulocyte colony-stimulating factor (G-CSF) should be used to permit patients to stay on treatment longer.^{102,103} Anemia can be managed in the short term with transfusions. Erythropoiesis-stimulating agents are indicated during chemotherapy, particularly with renal impairment, when the hemoglobin concentration is < 10 g/dL, and there is no improvement despite response to therapy.¹⁰⁴⁻¹⁰⁶ Thrombocytopenia is common with bortezomib, lenalidomide, and alkylating agents, whereas it rarely occurs with thalidomide.¹⁰³

Recommendations:

- G-CSF is recommended to prevent febrile neutropenia in patients at high risk based on age, medical history, disease characteristics, and the expected myelotoxicity of chemotherapy.
- When grade 3 to 4 neutropenia occurs during chemotherapy, G-CSF should be added. If neutrophil count restores to $> 1,000$ cells/mL, therapy can be resumed without dose modifications. If neutrophil count remains $< 1,000$ cells/mL, treatment should be delayed until neutrophils recovery and resumed at reduced doses (grade C/IV).
- Patients with hemoglobin < 10 g/dL during chemotherapy should receive erythropoietin, which should be stopped if an increase of hemoglobin ≥ 1 g/dL after 4 weeks of treatment is not obtained (grade A/Ib). Iron supplementation is recommended if transferrin saturation is inadequate.
- If grade 4 thrombocytopenia occurs, treatment should be withheld; it can be resumed when the event resolves to grade 2 (grade C/IV).

Thromboembolism

Myeloma has a high risk of venous thromboembolism (VTE).¹⁰⁷ Patient-related risk factors include advanced age, history of VTE or inherited thrombophilia, obesity, comorbidities, central venous catheter in situ, immobility, and surgery. Myeloma-related factors include the diagnosis of myeloma itself, disease burden, and hyperviscosity. Treatment-related factors include the use of thalidomide or lenalidomide, particularly when combined with high-dose steroids or doxorubicin or multiagent chemotherapy, and the concomitant use of erythropoietin.¹⁰⁸⁻¹¹⁰

The role of low-molecular weight heparin (LMWH) in preventing VTE is well recognized; aspirin (ASA) should be used in selected circumstances, and fixed low-dose warfarin has generally been shown to be ineffective.^{111,112} The American College of Chest Physicians guidelines recommend LMWH or low-dose unfractionated heparin in outpatients with tumors and risk factors for VTE, including thalidomide and lenalidomide therapy.¹¹³

Recommendations:

- Patients with MM should receive appropriate thromboprophylaxis based on risk factors for the first 4 to 6 months of treatment, until disease control is achieved or as long as the risk of thromboembolism remains high (grade C/IV).
- During thalidomide or lenalidomide treatment, ASA should be administered to low-risk patients (with \leq one risk factor). High-risk patients (with \geq two risk factors) should receive prophylactic LMWH or dose-adjusted therapeutic warfarin for 4 to 6 months followed by ASA (grade B/IIa)
- The dose of LMWH should be adjusted according to renal function (grade C/IV).

- For patients who develop VTE, treatment should be temporarily interrupted, and they should receive anticoagulation therapy. When stable anticoagulation is achieved, chemotherapy can be restarted (grade C/IV).

Infections

MM can cause impairment of immune function, with consequent increased risk of infections, particularly during active disease, or treatment with high-dose dexamethasone, myelotoxic agents, or multidrug combinations.^{114,115} Herpes zoster is a possible complication related to bortezomib administration.³⁵

Recommendations:

- For unfit patients with comorbidities and for patients with an increased infection rate, oral antibiotic prophylaxis should be considered for the first 3 months of therapy. Trimethoprim-sulfamethoxazole prophylaxis should be considered at least during the first 2 to 3 months of chemotherapy or steroid administration (grade C/IV)
- Antiviral prophylaxis, such as acyclovir or valacyclovir, is recommended against zoster reactivation during bortezomib treatment and for 30 to 60 days after its discontinuation (grade C/IV).
- Patients with MM should be treated promptly with broad-spectrum antibiotics in case of fever or suspected infections (grade C/IV).

Peripheral Neuropathy

Peripheral neuropathy can be caused by the disease itself or by thalidomide and bortezomib therapy. Because treatment-emergent peripheral neuropathy is related to the duration of drug exposure and is cumulative,^{116,117} early reduction or temporary discontinuation of the drug should be adopted.^{118,119} Subcutaneous and weekly bortezomib infusions significantly reduced peripheral neuropathy, without considerably affecting outcome.¹¹⁶ Neuropathic pain is often poorly responsive to standard analgesia, but gabapentin and opioid drugs may improve symptoms.¹²⁰⁻¹²²

Recommendations:

- Close monitoring of patients receiving bortezomib and thalidomide is highly recommended. Patients should be informed about the risk of peripheral neuropathy and instructed to promptly seek medical advice when symptoms emerge. When grade 1 peripheral neuropathy with pain or grade ≥ 2 occur, treatment should be interrupted until resolution of symptoms and reinitiated at lower doses (grade C/IV).
- Prompt thalidomide dose reductions (from 100 to 50 mg per day) are essential to avoid irreversible damage (grade C/IV).
- Once-per-week bortezomib at a dose of 1.3 mg/m² should be reduced to 1.0 mg/m² and subsequently to 0.7 mg/m² per week (grade C/IV).

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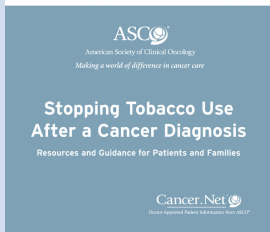
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Quitting Smoking for People With Cancer



ASCO offers a companion piece to the Tobacco Cessation Guide that physicians can give to their patients who smoke. This booklet reinforces the message that quitting smoking is beneficial, no matter what the diagnosis. It also offers information on the health benefits of quitting smoking, how patients can talk to the doctor about their tobacco use, various methods patients can use to quit smoking, and a list of resources, including help lines and mobile apps, that patients can use to stop smoking. The booklets can be ordered as a set of 10 provider guides/115 patient booklets or as a set of 125 patient booklets through the ASCO University Bookstore (www.cancer.net/estore). ASCO members receive a 20% discount.



American Society of Clinical Oncology

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Facilities and Services

To provide high-quality care, it is strongly advisable that patients with myeloma are diagnosed and treated in clinical hematology units, with specific expertise in the management of multiple myeloma (MM). The hematology team should coordinate and share the care of patients, assuring a good communication flow between the general practitioner and other specialists involved in the management of complications. Accurate information should be provided to patients and their caregivers so they are able to make sensible decisions.

Recommendation:

- The general practitioner should refer patients to specialized units with MM experts to offer the most appropriate care (grade C/IV).

Palliative Care

Palliative care aims to optimize the comfort, function, and social support of patients and their families, when cure is no longer achievable (WHO definition of palliative care is available at <http://www.who.int/cancer/palliative/definition/en/>). In the absence of effective antimyeloma treatments, counseling for patients and families provided by a palliative specialist is suggested. To relieve the disabling myeloma-related symptoms, low doses of cyclophosphamide, corticosteroids, or thalidomide may be used. Treatment of pain should start with nonopioid analgesic agents, but weak or stronger opioid analgesics should be introduced when previous agents are ineffective (WHO Expert Committee: World Health Organ Tech Rep Ser 804:1-75, 1990).

Recommendation:

- Terminal care should include a multidisciplinary approach aimed at alleviating symptoms and addressing patient desires (grade C/IV).

Management of Patients With MM Not Eligible for Transplantation

Table A1. Levels of Evidence and Grade of Recommendations

Level of Evidence	Source of Evidence	Grade of Recommendation	Rationale for Recommendation
Ia	Meta-analyses of randomized controlled trials	A	At least one randomized controlled trial of good quality and consistency addressing specific recommendation
Ib	At least one randomized controlled trial		
IIa	At least one well-designed, nonrandomized study, including phase II trials and case-control trials	B	Well-conducted studies but no randomized controlled trials on topic of recommendation
IIb	At least one other type of well-designed, quasi-experimental study (ie, studies without planned intervention, including observational studies)		
III	Well-designed, nonexperimental descriptive studies; meta-analyses or randomized controlled trials or phase II studies only published in abstract form	C	Expert committee reports and/or clinical experience of respected authorities
IV	Expert committee reports or opinions and/or clinical experience of respected authorities		

Table A2. International Staging System

Stage	Description
I	Serum β_2 -microglobulin < 3.5 mg/L and serum albumin \geq 3.5 g/dL
II	Serum β_2 -microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL or serum β_2 -microglobulin 3.5 to < 5.5 mg/L
III	Serum β_2 -microglobulin \geq 5.5 mg/L