

## REVIEW

# International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation

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**In 2005, the first guidelines were published on the management of patients with multiple myeloma (MM). An expert panel reviewed the currently available literature as the basis for a set of revised and updated consensus guidelines for the diagnosis and management of patients with MM who are not eligible for autologous stem cell transplantation. Here we present recommendations on the diagnosis, treatment of newly diagnosed non-transplant-eligible patients and the management of complications occurring during induction therapy among these patients. These guidelines will aid the physician in daily clinical practice and will ensure optimal care for patients with MM.**

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## Introduction

In 2005, the first guidelines for the diagnosis and management of multiple myeloma (MM) were published by the Guidelines

Working Group of the UK Myeloma Forum (UKMF) on behalf of the British Committee for Standards in Haematology (BCSH) and by the Nordic Myeloma Study Group (NMSG).<sup>1</sup> Here an expert panel presents the revised and updated guidelines based upon a review of current available literature. These guidelines include new developments in disease classification and staging, as well as incorporating new therapeutic agents such as thalidomide, bortezomib and lenalidomide. The following are sections of the guidelines: (1) methodology, (2) epidemiology, (3) facilities, (4) diagnosis, (5) monitoring and start of therapy, (6) staging and prognostic factors, (7) response criteria, (8) treatment strategy (dose and age), (9) front-line therapy, phase II grade A recommendation level Ia evidence, (10) front-line therapy, phase II, grade B recommendations, level IIa evidence, (11) reduced-intensity transplant, (12) maintenance, (13) relapse III, phase III, grade A recommendation, level Ia evidence, (14) relapse II, phase II, grade B recommendations, level IIa evidence, (15) treatment strategy, (16) palliative care and (17) complications.

## Methodology

### Expert panel

The 2008 Update Committee of the International Myeloma Working Group (IMWG) consisted of a panel of experts in

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clinical medicine, clinical research, health services and related disciplines (biostatistics, medical decision-making, patient–physician communication), and a patient representative. The committee members are listed in Appendix A1. The panel reviewed the evidence relating to each clinical question and made writing assignments for each of the respective sections. Additional work on the guideline was completed through teleconferences and electronic mail. Each panel member participated in the preparation of the draft guideline, which was then disseminated for review by the entire panel.

### Literature and analysis

The electronic databases, MEDLINE, preMEDLINE and the Cochrane Collaboration Library, were searched from December 2004 to December 2008. Congress abstracts from the American Society of Hematology (ASH) annual meetings were also searched from 2006 to 2008. Articles/abstracts were included in this systematic review if they met the following criteria: (1) evidence-based practice guidelines addressing diagnosis and management of myeloma, or (2) randomized controlled trials (RCTs) or meta-analyses that (a) compared standard chemotherapy versus experimental new drugs in newly diagnosed and relapsed-refractory patients with MM, (b) reported overall survival (OS) or disease-free survival as a main outcome, and (c) were published in peer-reviewed journals or reported in a conference abstract. Articles published in a language other than English were excluded. Detailed chemotherapy protocols and dosages were not included as they are beyond the scope of this document.

### Recommendations

Questions regarding diagnosis, staging, front-line therapy and salvage therapy will be addressed by summarizing the available data followed by the recommendations of the panel. The levels of evidence and grades of recommendation are summarized in Table 1.

### Epidemiology

Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. It was estimated that MM would account for 19 920 new cancer cases in the United States in 2008, including

11 190 cases in men and 8730 cases in women, and 10 690 deaths.<sup>2</sup> The median age of myeloma patients at diagnosis is 69 years for men and 72 years for women.<sup>3</sup>

### Facilities

A consultant haematologist or oncologist should lead the care of patients with MM. However, owing to the existence of a range of complications that are likely to occur during the course of the disease (for example, bone disease, renal failure, haematological toxicity, deep vein thrombosis (DVT), infections and peripheral neuropathy), input from other professionals who specialize in these areas is required to provide effective and high-quality care to the patient (Table 2). It is important to maintain good communication between the general practitioner, the haematology team and other teams involved in caring for the patient throughout the course of the disease. In addition, the ability to give appropriate clinical care is related to the number of patients seen by a physician on a monthly basis.

### Recommendation

It is recommended to develop a specific clinical unit devoted to treatment of MM, and establish clear policies and protocols for access to specific therapies and supportive services. A minimum

**Table 2** Required expertise and services for management of patients with MM

Diagnostic services	Diagnostic haematology and haematopathology Clinical biochemistry and immunology Diagnostic radiology
Specialist services	Renal services, including rapid access to haemodialysis Clinical oncology/radiotherapy Orthopaedic surgery Neurosurgery Accredited bone marrow/stem cell transplant centre
Support services	Haematology/oncology nurse specialists Palliative care physicians/nurses Pharmacy with expertise and facilities for dispensing cytotoxic drugs Physiotherapy/rehabilitation Administration support for case registration, audit and clinical trials Patient information including information available social services and financial advise Patient support group

**Table 1** Levels of evidence and grades of recommendation

Evidence level	Source of evidence	Recommendation grade	Basis for recommendation
Ia	Meta-analysis of randomized controlled trials	A	At least one randomized controlled trial of good quality and consistency in addressing specific recommendation
Ib	At least one randomized controlled trial	B	Well-conducted studies but no randomized controlled trials on the topic of the recommendation
IIa	At least one well-designed, non-randomized study, including phase II trials and case-control studies		
IIb	At least one other type of well-designed, quasi-experimental study, that is, studies without planned intervention, including observational studies		
III	Well-designed, non-experimental description studies. Meta-analyses of randomized controlled trials or phase II studies which are published only 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		

of two newly diagnosed patients per month should receive induction therapy to ensure appropriate skill and experience of the health personnel.

## Diagnosis

There is no change from the original guidelines, as no relevant additional data have been published. The aim is to identify patients with active or symptomatic MM who require systemic therapy, and to exclude patients with monoclonal gammopathy of undetermined significance (MGUS), smouldering or indolent myeloma, and solitary plasmacytoma (Table 3).<sup>4</sup> It remains important to demonstrate the presence of 'myeloma-related organ dysfunction' or CRAB features (C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions), which may require biopsy and/or other specialized testing.

## Recommendation

The recommended tests for the diagnosis of myeloma and related organ dysfunctions are listed below. Most of these tests are well established and widely accepted.

1. History and Physical Examination
2. Routine Testing

- Complete blood count with differential and peripheral blood smear review
  - Chemistry panel including calcium and creatinine
  - Serum protein electrophoresis, immunofixation
  - Nephelometric quantitation of immunoglobulins
  - Routine urinalysis, 24 h urine collection for proteinuria, electrophoresis and immunofixation
  - Quantification of both urine M-component level and albuminuria
3. Bone Marrow Testing: Obtain an aspirate plus trephine biopsy with testing for cytogenetics, fluorescent *in situ* hybridization (FISH) and immunophenotyping.
  4. Imaging
    - Bone survey including spine, pelvis, skull, humeri and femurs.
    - Magnetic resonance imaging of the axial skeleton is very informative if available/feasible, but is not mandatory.
    - Whole-body fluorodeoxyglucose/positron emission tomography imaging is also not mandatory, but can be used to confirm MGUS (positron emission tomography negative) or exclude unsuspected and/or extramedullary myeloma (positron emission tomography positive), infection and/or an associated second malignancy. Positron emission tomography imaging was recently approved by CMS/Medicare (United States) for use in myeloma.

**Table 3** Diagnostic criteria

Diagnosis	Diagnostic criteria: all three required
Symptomatic multiple myeloma <sup>a</sup>	Monoclonal plasma cells in the bone marrow $\geq 10\%$ and/or presence of a biopsy-proven plasmacytoma Monoclonal protein present in the serum and/or urine <sup>b</sup> Myeloma-related organ dysfunction ( $\geq 1$ ) <sup>c</sup> [C] Calcium elevation in the blood (serum calcium $> 10.5$ mg/l or upper limit of normal) [R] Renal insufficiency (serum creatinine $> 2$ mg per 100 ml) [A] Anaemia (haemoglobin $< 10$ g per 100 ml or 2 g $<$ normal) [B] Lytic bone lesions or osteoporosis <sup>d</sup>
Monoclonal gammopathy of undetermined significance (MGUS)	Serum monoclonal protein low <sup>e</sup> Monoclonal bone marrow plasma cells $< 10\%$ No evidence of end-organ damage attributable to the clonal plasma cell disorder: Normal serum calcium, haemoglobin level and serum creatinine No bone lesions on full skeletal X-ray survey and/or other imaging if performed No clinical or laboratory features of amyloidosis or light chain deposition disease
Smouldering or indolent myeloma <sup>f</sup>	Monoclonal protein present in the serum 3 g per 100 ml or higher or Monoclonal plasma cells 10% or greater present in the bone marrow and/or a tissue biopsy No evidence of end-organ damage attributable to the clonal plasma cell disorder: Normal serum calcium, haemoglobin level and serum creatinine No bone lesions on full skeletal X-ray survey and/or other imaging if performed No clinical or laboratory features of amyloidosis or light chain deposition disease
Solitary plasmacytoma of bone	Biopsy-proven plasmacytoma of bone in a single site only. X-rays and magnetic resonance imaging and/or FDG PET imaging (if performed) must be negative outside the primary site. The primary lesion may be associated with a low serum and/or urine M-component The bone marrow contains no monoclonal plasma cells No other myeloma-related organ dysfunction

Adapted with permission from Kyle and Rajkumar.<sup>73</sup>

<sup>a</sup>These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smouldering or indolent myeloma.

<sup>b</sup>If no monoclonal protein is detected (non-secretory disease), then  $\geq 30\%$  monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

<sup>c</sup>A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classifications myeloma if proven to be myeloma related.

<sup>d</sup>If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then  $\geq 30\%$  plasma cells are required in the bone marrow.

<sup>e</sup>Low is defined as serum M protein  $< 3.0$  g per 100 ml.

<sup>f</sup>These criteria identify Stage IA myeloma by Durie/Salmon stage.

- The recent IMWG imaging guidelines provide a full summary of current overall recommendations.<sup>5</sup>

#### 5. Ancillary Testing

- $\beta_2$ -Microglobulin, C-reactive protein and lactate dehydrogenase
- Measurement of free light chains in serum is very important if conventional M-component quantitation is negative or equivocal, that is, in patients with non-secretory or oligosecretory myeloma, as well as in light chain myeloma. The recommendations for use of free light chain testing have recently been published.<sup>6</sup>

#### Monitoring and start of therapy

There is no change from earlier guidelines.<sup>1</sup> Systemic anti-myeloma therapy is indicated for initial treatment of symptomatic myeloma with myeloma-related organ dysfunction. However, no benefit from the early intervention has been shown for the treatment of asymptomatic myeloma,<sup>7,8</sup> although it should be noted that there are several ongoing studies evaluating new agents in the context of asymptomatic MM, and participation in these trials is encouraged.

#### Recommendation

Monitoring of MM during treatment should be according to the clinical conditions; for patients in remission, follow-up should be every 2 months. The criteria for retreatment are the same as those used at diagnosis with the exception that retreatment should be administered in patients without organ damage if the M-protein has doubled within less than 2 months.

#### Staging and prognostic factors

On the basis of the results of the clinical and laboratory evaluation discussed earlier, patients are initially classified as either having asymptomatic (smouldering) disease or symptomatic (active) disease. Those with symptomatic myeloma are then further categorized according to disease stage, based on the International Staging System (ISS). The ISS developed by the IMWG uses serum  $\beta_2$ -microglobulin and serum albumin to provide a reproducible three-stage classification system that defines three risk groups with median survival of 62 months (serum  $\beta_2$ -microglobulin  $<3.5$  mg/l and serum albumin  $>3.5$  g/l), 44 months (serum  $\beta_2$ -microglobulin  $>3.5$  mg/l and serum albumin  $<3.5$  g/l or serum  $\beta_2$ -microglobulin 3.5–5.5 mg/l) and 29 months (serum  $\beta_2$ -microglobulin  $>5.5$  mg/l).<sup>9</sup> Further factors, such as serum free light chain ratio or the bone resorption marker ICTP, incorporated into the ISS may improve the risk stratification.<sup>10,11</sup>

Cytogenetics and FISH can be used to detect chromosomal abnormalities. In MM patients, any chromosomal abnormality is associated with poorer outcomes compared with normal karyotype. Among FISH-based abnormalities, patients with isolated del 13 do not have a less favourable outcome, although del 13 associated with 17p deletion or t(4:14) are associated with poorer outcomes. By FISH, t(4:14) or t(14:16) is associated with poorer outcome; t(11:14) does not have negative outcome; hypodiploidy is associated with more favourable outcome.<sup>12,13</sup>

#### Recommendation

Cytogenetics and/or FISH should be performed in all newly diagnosed MM patients as well as subsequently at the time of relapse, as patients may develop new chromosomal abnormalities at the time of progression. Although treatment regimens, which include bortezomib and/or lenalidomide, may overcome poor prognosis, no specific alternate therapy is routinely recommended for patients with abnormal chromosomes. Risk stratification on the basis of cytogenetics or FISH warrants confirmation from further studies with large numbers of patients.

#### Response criteria

The response to therapy is a key determinant of myeloma treatment. Table 4 lists two different sets of response criteria, one developed by the European Group for Bone and Marrow Transplant (EBMT)<sup>14</sup> and the other developed by the IMWG.<sup>15</sup> The IMWG criteria were developed in 2006 and have been commonly used by a larger number of physicians and have substituted for the EBMT criteria. Serum free light chain assays are useful for monitoring patients with non-secretory myeloma,<sup>16,17</sup> and have recently been introduced in the definition of stringent complete response in the IMWG criteria.

#### Recommendation

The IMWG criteria have been validated and we recommend assessing response according to these criteria.

#### Overall treatment strategy related to age

Patients over 65 years of age are generally not considered to be candidates for transplantation outside the United States. However, as biological age may differ from chronological age in elderly patients, it is important to take biological age into account when determining if a patient is a candidate for transplantation. In addition to the age limit, patients with serious heart, lung, renal or liver dysfunction should not be considered for transplantation. With these limitations, it is generally accepted to use 65 years as the age limit for melphalan 200 mg/m<sup>2</sup> followed by autologous stem cell transplantation (ASCT). For patients 65–75 years of age, full-dose conventional therapy is suggested. For patients over 75 years of age (or younger with significant co-morbidities), the dosages of any therapy should be reduced and a more gentle approach considered.

#### Recommendation

Patients younger than 65 years should be considered candidates for induction therapy followed by ASCT. Patients aged 65–70 or younger with significant co-morbidities may be considered for reduced-dose intensity autologous transplantation. In patients 65–75 years of age full-dose conventional therapy should be considered. In patients older than 75 years or younger with co-morbidities, the dosages of therapy should be reduced accordingly.<sup>18</sup>

#### Front-line therapy, phase III, grade A recommendation, level Ia evidence

Phase III studies in newly diagnosed patients are summarized in Table 5. Thalidomide in combination with dexamethasone (TD)

**Table 4** Response criteria

Response	EBMT criteria	IMWG criteria
sCR	NA	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow <sup>a</sup> by immunohistochemistry or immunofluorescence <sup>b</sup>
CR	No M-protein detected in serum or urine by immunofixation for a minimum of 6 weeks and fewer than 5% plasma cells in the bone marrow; No increase in size or number of lytic bone lesions; Disappearance of soft tissue plasmacytomas	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow <sup>a</sup>
VGPR	NA	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	> 50% reduction in serum M-protein level and/or $\geq 90\%$ reduction in urine free light chain excretion or reduction to <200 mg/24 h for 6 weeks <sup>c</sup>	$\geq 50\%$ reduction of serum M-protein and reduction in 24 h urinary M-protein by $\geq 90\%$ or to <200 mg/24 h If the serum and urine M-protein are unmeasurable, <sup>d</sup> a $\geq 50\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, $\geq 50\%$ reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geq 30\%$ In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size of soft tissue plasmacytomas is also required
MR	25–49% reduction in serum M-protein level and/or 50–89% reduction in urine for light chain excretion, which still exceeds 200 mg/24 h for $\geq 6$ weeks <sup>c</sup>	NA
No change/stable disease Plateau	Not meeting the criteria of either minimal response or progressive disease No evidence of continuing myeloma-related organ or tissue damage <25% change M-protein levels and light chain excretion for 3 months	Not meeting criteria for CR, VGPR, PR or progressive disease NA
Progressive disease <sup>d</sup>	Myeloma-related organ or tissue damage continuing despite therapy or its reappearance in plateau phase > 25% increase in serum M-protein level (> 5 g/l) and/or > 25% increase in urine M-protein level (> 200 mg/24 h) and/or > 25% increase in bone marrow plasma cells (at least 10% in absolute terms) <sup>e</sup>	Increase of $\geq 25\%$ from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be $\geq 0.5$ g per 100 ml) <sup>f</sup> Urine M-component and/or (the absolute increase must be $\geq 200$ mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg per 100 ml Bone marrow plasma cell percentage; the absolute percentage must be $\geq 10\%$ <sup>g</sup> Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium > 11.5 mg per 100 ml or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Reappearance of disease in patients previously in CR, including detection of paraprotein by immunofixation	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). <sup>f</sup> It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcaemia (> 11.5 mg per 100 ml) (2.65 mmol/l) 4. Decrease in haemoglobin of $\geq 2$ g per 100 ml (1.25 mmol/l) 5. Rise in serum creatinine by 2 mg per 100 ml or more (177 $\mu$ mol/l or more)

**Table 4** (Continued)

Response	EBMT criteria	IMWG criteria
Relapse from CR <sup>d</sup> (To be used only if the end point studied is DFS) <sup>h</sup>	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of $\geq 5\%$ plasma cells in the bone marrow <sup>g</sup> Appearance of any other sign of progression (that is, new plasmacytoma, lytic bone lesion or hypercalcaemia)	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of $\geq 5\%$ plasma cells in the bone marrow <sup>g</sup> Appearance of any other sign of progression (that is, new plasmacytoma, lytic bone lesion or hypercalcaemia)

Adapted from Durie *et al.*<sup>15</sup> and Kyle and Rajkumar.<sup>73</sup>

Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a  $> 90\%$  decrease in the difference between involved and uninvolved free light chain (FLC) levels.

<sup>a</sup>Confirmation with repeat bone marrow biopsy not needed.

<sup>b</sup>Presence/absence of clonal cells is based upon the  $\kappa/\lambda$  ratio. An abnormal  $\kappa/\lambda$  ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting the presence of an abnormal clone is  $\kappa/\lambda$  of  $> 4:1$  or  $< 1:2$ .

<sup>c</sup>For patients with non-secretory myeloma only, reduction of plasma cells in the bone marrow by  $> 50\%$  of initial number (partial response) or 25–49% of initial number (minimal response) is required.

<sup>d</sup>All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

<sup>e</sup>In non-secretory myeloma, bone marrow plasma cells should increase by  $> 25\%$  and at least 10% in absolute terms; MRI examination may be helpful in selected patients.

<sup>f</sup>For progressive disease, serum M-component increases of  $\geq 1$  g per 100 ml are sufficient to define relapse if starting M-component is  $\geq 5$  g per 100 ml.

<sup>g</sup>Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

<sup>h</sup>For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

**Table 5** Phase III studies in newly diagnosed MM

Regimen	N	ORR (CR), %	Median PFS, months	Median TTP, months	Median survival, months
TD vs D (Rajkumar <i>et al.</i> <sup>20</sup> )	470	63 (7.7) vs 46 (2.6)	14.9 vs 6.5	22.6 vs 6.5	
TD vs MP (Ludwig <i>et al.</i> <sup>18</sup> )	289	68 (2) vs 50 (2)	16.7 vs 20.7	21.2 vs 29.1	41.5 vs 49.4
RD vs D (Zonder <i>et al.</i> <sup>21</sup> )	198	79.4 (22) vs 26.2 (4) <sup>a</sup>	77 vs 55% @ 1 year		93 vs 91% @ 1 year
RD vs Rd (Rajkumar <i>et al.</i> <sup>20</sup> )	445	82 (52) vs 70 (42) <sup>b</sup>			87 vs 75% @ 2 years
MPT vs MP (Palumbo <i>et al.</i> <sup>24,25</sup> )	255	76 (15.5) vs 47.6 (2.4)	21.8 vs 14.5		45.0 vs 47.6
MPT vs MP (Facon <i>et al.</i> <sup>26</sup> )	321	76 (13) vs 35 (2)	27.5 vs 17.8		51.6 vs 33.2
MPT vs MP (Hulin <i>et al.</i> <sup>27</sup> )	232	62 (7) vs 31 (1)	24.1 vs 19		45.3 vs 27.6
MPT vs MP (Gulbrandsen <i>et al.</i> <sup>23</sup> )	357	42 (6) vs 28 (3)	16 vs 14	20 vs 18	29 vs 33
VMP vs MP (San Miguel <i>et al.</i> <sup>29</sup> )	682	71(30) vs 35(4)		24 vs 17	83 vs 78% @ 16 months
VMP vs VPT (Mateos <i>et al.</i> <sup>30</sup> )	246	78 (18) vs 78 (23)			
VMPT vs VMP (Palumbo <i>et al.</i> <sup>31</sup> )	393	55 (31) vs 42 (16) <sup>c</sup>	83.9 vs 75.7% @ 2 years		89.5 vs 88.7% @ 3 years
MPT vs MP (Wijermans <i>et al.</i> <sup>28</sup> )	344	66 (2) vs 47% (2)	14 vs 10		37 vs 30

Abbreviations: CR, complete remission; MM, multiple myeloma; MP, melphalan and prednisone; MPT, MP plus thalidomide; ORR, overall response rate (at least partial remission); PFS, progression-free survival; RD, lenalidomide and high-dose dexamethasone; Rd, lenalidomide and low-dose dexamethasone; TD, thalidomide and high-dose dexamethasone; TTP, time to progression; VGPR, very good partial response; VMP, MP plus bortezomib; VMPT, VMP plus thalidomide; VPT, bortezomib, prednisone, thalidomide.

<sup>a</sup>Percentages reported for ORR include minor response.

<sup>b</sup>Percentages reported for CR include VGPR.

<sup>c</sup>Percentages reported for ORR are at least VGPR.

showed clear benefit in overall response rate (ORR) compared with high-dose dexamethasone alone or melphalan–prednisone (MP).<sup>18,19</sup> In addition, TD resulted in a benefit in time to progression compared with high-dose dexamethasone, whereas compared with MP there was no significant difference.<sup>18</sup> The incidence of grade 3 or 4 adverse events was higher with TD, and OS was inferior compared with MP.

Lenalidomide plus dexamethasone (RD) resulted in a higher complete response (CR) rate and 1-year progression-free survival (PFS) compared with high-dose dexamethasone alone, and the combination of lenalidomide plus low-dose dexamethasone

(Rd) showed further benefit in terms of OS compared with RD.<sup>20–22</sup> In addition, the reduction of the dexamethasone dose in the Rd regimen also resulted in a reduction of adverse events compared with RD.<sup>20</sup>

Five randomized studies have compared the combination of thalidomide and MP (MPT) to MP in elderly patients with newly diagnosed MM. These studies consistently reported that MPT resulted in higher ORR (42–76 vs 28–48%), higher at least very good partial response (VGPR)/near-CR (nCR) (15–47 vs 6–8%),<sup>23</sup> and longer PFS (13–27.5 vs 10–19 months).<sup>23–28</sup> However, only two studies demonstrated improved OS with MPT (45.3–51.6 vs

27.7–32.2 months)<sup>26–27</sup> and two studies reported similar OS with MPT (33–47.6 months) and MP (29–45 months).<sup>23,25</sup> The data strongly support the use of MPT as the standard of care for elderly myeloma patients. In all studies the MPT regimen was associated with a significantly higher incidence of grade 3 or 4 non-haematological adverse events, including neurological adverse events, infections, cardiac toxicity and thromboembolism. Therefore, antithrombotic prophylaxis is recommended when using MPT. The dosage of thalidomide needs to be modified based on the tolerance in the elderly to minimize toxicity. In patients > 75 years of age, the recommended dose is 100 mg per day.

The bortezomib plus MP (VMP) regimen resulted in significant improvement in ORR, time to progression and OS compared with MP.<sup>29</sup> The incidence of peripheral neuropathy, gastrointestinal complications and herpes zoster infection was higher with VMP. When comparing the VMP regimen with the bortezomib, thalidomide and prednisone (VTP) regimen, there were no significant differences in ORR, but VMP had less non-haematologic adverse events than VTP.<sup>30</sup> The thalidomide plus VMP (VMPT) regimen did result in higher VGPR and CR rates than the VMP regimen, although longer follow-up is needed to assess their effects on PFS and OS.<sup>31</sup> The incidence of the most common adverse events (neutropenia, thrombocytopenia, peripheral neuropathy and infections) was similar between the thalidomide plus VMP and VMP regimens. When weekly infusions of bortezomib were used in the thalidomide plus VMP schema, the incidence of grade 3–4 peripheral neuropathy was reduced in comparison with the standard biweekly infusion without influencing outcome.<sup>30,31</sup>

### Recommendation

In five randomized studies, MPT has shown consistent improvement in PFS (and/or time to progression) but inconsistent OS advantage. MPT is considered a standard of care for patients > 65 years. In one randomized trial, VMP showed both PFS and OS improvement. VMP is another standard of care for elderly patients. In the VMP regimen, weekly infusion of bortezomib significantly reduces the incidence of PN and should be considered in patients with pre-existing PN.

Although TD was superior to dexamethasone in the older patient population, as defined by improved PFS, it is associated with inferior OS compared with MP, and is not recommended as standard therapy in the elderly patient population ineligible for high-dose therapy and ASCT. Higher doses of thalidomide are especially difficult in elderly and frail patients.<sup>18</sup> The combination of RD demonstrated improvement on PFS compared with dexamethasone alone, but Rd was superior to RD, and was better tolerated. Thus, Rd can be considered a standard of care, especially in patients who wish to postpone ASCT.

## Front-line therapy, phase II, grade B recommendation, level IIa evidence

The combination of melphalan, prednisone and lenalidomide (MPR) at the maximum tolerated dose (0.18 mg/kg melphalan, 2 mg/kg prednisone and 10 mg lenalidomide) achieved an ORR of 81%, at least VGPR of 47.6%, median time to progression and PFS of 28.5 months, and 2-year OS of 90.5%.<sup>32</sup> Myelosuppression, including grade 3 or 4 neutropenia in 52.4% of patients, was the main adverse event. Grade 3 or 4 non-haematological adverse effects were less frequent and included febrile neutropenia (9.5%), skin rash (9.5%) and thromboembolism (4.8%). Similar results were obtained from another phase I/II study, which reported an ORR of 69%, at least VGPR rate of 31%, median PFS of 16.7 months and median OS of 23 months following MPR treatment.<sup>33</sup> This combination is currently being validated in a randomized phase III trial comparing MPR with and accepted standard MPT.

### Recommendation

Although showing interesting results, the MPR regimen needs validation in a randomized study, before it can be recommended in clinical practice for the induction of elderly patients with newly diagnosed MM.

## Reduced intensity autologous transplant

Results of reduced intensity transplantation studies are summarized in Table 6. Patients over 65 years of age are not generally considered to be eligible for melphalan 200 mg/m<sup>2</sup> followed by ASCT. Two randomized studies compared intermediate dose melphalan (100 mg/m<sup>2</sup>) and reduced intensity ASCT with MP. In patients aged 65–70 years, ASCT was superior to MP.<sup>34</sup> However, in patients aged 65–75 years, response rates were superior with ASCT, but there was no difference in PFS or OS compared with MP.<sup>26</sup>

The efficacy of bortezomib, pegylated liposomal doxorubicin and dexamethasone (PAD) induction therapy before reduced intensity ASCT, followed by consolidation with lenalidomide and prednisone, and maintenance with lenalidomide alone, was evaluated in patients aged 65–75 years. Preliminary data from this study reported that the ORR was 94% following PAD and 100% following consolidation with lenalidomide and prednisone; at least VGPR rate was 59% (13% CR) following PAD and 88% following consolidation with lenalidomide and prednisone.<sup>35</sup> These data indicate that this is a highly effective regimen in elderly patients.

**Table 6** Reduced intensity transplant studies in newly diagnosed MM

Regimen	N	ORR (CR), %	Median PFS, months	Median TTP, months	Median survival, months
MEL 100+ASCT vs MP (Palumbo <i>et al.</i> <sup>34</sup> )	194	67 (25) vs 49 (8) <sup>a</sup>	28 vs 16.4 <sup>b</sup>		58 vs 37.2
MEL 100+ASCT vs MP (Facon <i>et al.</i> <sup>26</sup> )	322	65 (18) vs 35 (2)	19.4 vs 17.8		38.3 vs 33.2
PAD+tandem MEL 100 ASCT+RP (Palumbo <i>et al.</i> <sup>35</sup> )	102	100 (53)	92% at 1 year	97% at 1 year	92% at 1 year

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete remission; MEL, melphalan; MM, multiple myeloma; MP, melphalan and prednisone; nCR, near-CR; ORR, overall response rate (at least partial remission); PAD, bortezomib, pegylated liposomal doxorubicin and dexamethasone; PFS, progression-free survival; RP, lenalidomide and prednisone; TTP, time to progression.

<sup>a</sup>Percentages reported for CR include nCR.

<sup>b</sup>Event-free survival.

### Recommendation

Intermediate-dose melphalan followed by ASCT can be used in patients aged 65–70 years or younger with pre-existing comorbidities, where full-dose ASCT appears too toxic. The use of bortezomib-based approaches for induction before ASCT is suggested. Consolidation with lenalidomide, although quite appealing, needs further validation in randomized trials.

### Maintenance

Maintenance therapy has the potential to provide new treatment options for patients with MM. However, although maintenance therapy with thalidomide following ASCT was shown to be superior to tandem ASCT in terms of PFS and OS at 3 years in patients younger than 60 years,<sup>36</sup> there is currently no evidence regarding the efficacy of maintenance therapy in elderly patients. Future studies are needed to assess the role maintenance therapy with novel agents, such as bortezomib, thalidomide and lenalidomide.<sup>37</sup>

### Recommendation

There is insufficient evidence regarding the use of maintenance therapy in elderly patients.

### Therapy at relapse, phase III data, grade A recommendation, level Ia evidence

Phase III studies in relapsed or refractory MM are summarized in Table 7. For patients with relapsed and/or refractory MM, bortezomib monotherapy is superior to high-dose dexamethasone,<sup>38,39</sup> bortezomib in combination with pegylated liposomal doxorubicin is superior to bortezomib monotherapy<sup>40</sup> and lenalidomide plus dexamethasone is superior to high-dose dexamethasone.<sup>41,42</sup>

### Recommendation

- Bortezomib with or without dexamethasone or in combination with liposomal doxorubicin is recommended in relapsed/refractory patients
- Lenalidomide in combination with dexamethasone is recommended in relapsed/refractory patients

### Therapy at relapse, phase II data, grade B recommendation, level IIa evidence

Phase II studies in relapsed or refractory MM are summarized in Table 8.

**Table 7** Phase III clinical studies in relapsed and/or refractory patients

Regimen	N	ORR (CR), %	Median response duration, months	Median TTP, months	Median survival, months
V vs D (Richardson <i>et al.</i> <sup>38</sup> )	669	38 (6) <sup>a</sup> vs 18 (0.6)	8.0 <sup>a</sup> vs 5.6	6.2 <sup>a</sup> vs 3.5	80 <sup>a</sup> vs 66% at 1 year
V vs V+PLD (Orlowski <i>et al.</i> <sup>40</sup> )	646	41 (2) vs 44 (4)	7.0 vs 10.2	6.5 vs 9.3	65 vs 76% at 15 months
RD vs D (Dimopoulos <i>et al.</i> <sup>41</sup> )	351	60 (16) vs 24 (3)		11.3 vs 4.7	Not reached vs 20.6
RD vs D (Weber <i>et al.</i> <sup>42</sup> )	353	61 (14) vs 20 (0.6)		11.1 vs 4.7	29.6 vs 20.2

Abbreviations: CR, complete remission; D, dexamethasone; ORR, overall response rate (at least partial remission); RD, lenalidomide and dexamethasone; TTP, time to progression; V+PLD, bortezomib plus pegylated liposomal doxorubicin; V, bortezomib; VD, bortezomib and dexamethasone.

<sup>a</sup>Extended median follow-up of 22 months of the bortezomib arm reported an ORR of 43%, CR of 9%, median response duration of 7.8 months, median TTP of 6.2 months and median survival of 29.8 months (Richardson *et al.*<sup>39</sup>).

### Thalidomide–dexamethasone combination

Several phase II studies have reported that thalidomide–dexamethasone (TD) is effective in patients with relapsed or refractory MM.<sup>19,34,43</sup> Retrospective studies have reported significant improvement in OS with TD salvage therapy compared with chemotherapy (patients with 1 earlier therapy) and second ASCT.<sup>34</sup> TD is associated with less neurotoxicity, somnolence and constipation than thalidomide alone, but the risk of DVT is higher.

### Bortezomib–dexamethasone combination

The ORR was 51%, including 11% CR. Dexamethasone was added in 208 patients (33%), of whom 70 (34%) showed improved response.<sup>44</sup>

### Thalidomide combinations with chemotherapy

Thalidomide–dexamethasone has been incorporated in several chemotherapy regimens, with responses of 75–76% in combination with doxorubicin<sup>45,46</sup> and 57–79% in combination with cyclophosphamide.<sup>47–50</sup> Of note, the combination of thalidomide with dexamethasone and doxorubicin can increase the risk of DVT to 25%.<sup>46</sup> The use of an intermittent schedule for thalidomide administration resulted in a low cumulative incidence of DVT and peripheral neuropathy.<sup>48</sup>

### Lenalidomide combinations with chemotherapy

Lenalidomide has also been evaluated in combination with conventional chemotherapy. Lenalidomide (maximum tolerated dose of 10 mg) in combination with doxorubicin, vincristine and dexamethasone achieved an ORR of 75% (29% CR/nCR) and a median PFS of 12 months.<sup>51</sup> Lenalidomide (maximum tolerated dose of 25 mg) in combination with doxorubicin and dexamethasone (RAD) achieved an at least VGPR rate of 74% (21% CR) in the appropriate dose level (5 + G).<sup>52</sup> Lenalidomide in combination with cyclophosphamide and dexamethasone (RCD) achieved an ORR of 65% (5% CR) in 21 heavily pretreated patients.<sup>53</sup>

### Bortezomib combinations with chemotherapy

Bortezomib in combination with cyclophosphamide has been tested in several phase I/II trials, with ORR of 75–89%.<sup>54–56</sup> Bortezomib in combination with doxorubicin and low-dose dexamethasone has been reported; 67% of patients achieved at least PR 25% with at least VGPR.<sup>57</sup>

### Combinations of novel agents

Bortezomib, thalidomide and dexamethasone (VTD) in heavily pretreated refractory patients (92% had earlier ASCT;



**Table 8** Phase II studies in relapsed or refractory MM

Regimen	N	ORR (CR), %	Median PFS, months	Median TTP, months	Median survival, months
TD (Dimopoulos <i>et al.</i> <sup>19</sup> )	44	55 (0)	10 <sup>a</sup>	4.2	12.6
TD (Palumbo <i>et al.</i> <sup>43</sup> )	77	41 <sup>b</sup> (3)		12	Not reached
TD vs chemotherapy (Palumbo <i>et al.</i> <sup>34</sup> )	120	46 vs 42	17 vs 9		19 vs 19
TD+doxorubicin (Offidani <i>et al.</i> <sup>45</sup> )	50	76 (26)	22	17 <sup>c</sup>	79% at 1 year
DVd-T (Hussein <i>et al.</i> <sup>46</sup> )	49	75 (20)	15.5		39.9
CTD (Kyriakou <i>et al.</i> <sup>47</sup> )	52	79 (17)	34% at 2 years <sup>c</sup>	Not reached	73% at 2 years
CTD (Dimopoulos <i>et al.</i> <sup>48</sup> )	53	60 (5)		8.2	17.5
CTD (Garcia-Sanz <i>et al.</i> <sup>49</sup> )	71	57 (2)	57% at 2 years		66% at 2 years
CTD (Kropff <i>et al.</i> <sup>50</sup> )	60	72 (4)	11 <sup>c</sup>		19
DVd-R (Baz <i>et al.</i> <sup>51</sup> )	62	75 (15)	12		Not reached
CVD vs VD (Davies <i>et al.</i> <sup>54</sup> )	36	75 (31) vs 47 (5)	7 vs 5		
CVD (Kropff <i>et al.</i> <sup>55</sup> )	54	82 (16)	12 <sup>c</sup>		22
CVP (Reece <i>et al.</i> <sup>56</sup> )	37	89 (53) <sup>d</sup>		15	24.3
VTD (Pineda-Roman <i>et al.</i> <sup>58</sup> )	85	63 (22) <sup>e</sup>	6% at 4 years <sup>c</sup>		23% at 4 years
VMPT (Palumbo <i>et al.</i> <sup>74</sup> )	30	67 (17)	61% @at 1 year		84% at 1 year
VMDT (Terpos <i>et al.</i> <sup>61</sup> )	62	66 (13)		9.3	
VTD vs MyVTD (Ciolli <i>et al.</i> <sup>62</sup> )	70	81 vs 59	15 vs 8	19 vs 11	
RVD (Richardson <i>et al.</i> <sup>60</sup> )	64	67 (24) <sup>e</sup>	21 <sup>f</sup>	Not reached	Not reached
RCD (Morgan <i>et al.</i> <sup>53</sup> )	21	65 (5)		5.7	

Abbreviations: CR, complete remission; CTD, TD plus cyclophosphamide; CVD, VD plus cyclophosphamide; CVP, cyclophosphamide, bortezomib, and prednisone; DVd-R, DVd and lenalidomide; DVd-T, pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone and thalidomide; MM, multiple myeloma; MyVTD, VTD plus myocet; nCR, near-CR; ORR, overall response rate (at least partial remission); PFS, progression-free survival; RCD, lenalidomide, cyclophosphamide and dexamethasone; RVD, VD plus lenalidomide; TD, thalidomide and dexamethasone; TTP, time to progression; VD, bortezomib and dexamethasone; VMDT, bortezomib, melphalan, dexamethasone and thalidomide; VMPT, bortezomib, melphalan, prednisone and thalidomide; VTD, TD plus bortezomib.

<sup>a</sup>Median TTP for responders not reached, expected to exceed 10 months.

<sup>b</sup>>50% decline in myeloma protein.

<sup>c</sup>Event-free survival

<sup>d</sup>Patients treated at dose levels 5 and 6 (bortezomib: 1.3 mg/m<sup>2</sup> days 1, 4, 8, 11 (level 5) and 1.5 mg/m<sup>2</sup> days 1, 8, 15 (level 6); cyclophosphamide: 300 mg/m<sup>2</sup> per week; prednisone: 100 mg every 2 days).

<sup>e</sup>Percentage for CR includes nCR.

<sup>f</sup>Duration of response.

74% had earlier thalidomide) resulted in an ORR of 63% (22% nCR).<sup>58</sup>

In a phase I study, the combination of lenalidomide and bortezomib achieved an ORR of 39% (6% CR/nCR). There was no significant peripheral neuropathy and only one DVT episode.<sup>59</sup> In a phase II study that evaluated lenalidomide, bortezomib and dexamethasone in patients with relapsed/refractory MM and 1–3 earlier lines of therapy, the ORR was 67% (24% CR/nCR).<sup>60</sup>

Four drug combinations, of bortezomib, melphalan, prednisone/dexamethasone and thalidomide either daily (thalidomide plus VMP)<sup>61</sup> or intermittently (VMDT), resulted in an ORR of 66–67%, including at least VGPR in 40–43%. Addition of other agents, such as doxorubicin or liposomal doxorubicin, to the backbone of bortezomib/thalidomide also resulted in significant responses.<sup>62</sup>

### Recommendation

Both TD and VD remain convenient regimens for relapsing or refractory patients. Other approaches, including combinations with chemotherapy or novel agents, should be considered when established salvage regimens have been already used. The alternative combinations should be used to increase the therapeutic options when standard salvage regimens have been used.

### Overall treatment strategies for relapsing patients

In managing the patients with relapsed or refractory MM several key points should guide the choice of treatment:

- (1) For patients who relapse following a durable response (that is, longer than the median PFS for the previous therapy), the same treatment should be repeated.
- (2) For patients who relapse following a short response (that is, shorter than the median PFS for the previous therapy), the patient should be sequentially introduced to new regimens.
- (3) Drugs that were used before the rechallenge remain secondary options if there was no clinical evidence of progression under that drug.
- (4) The choice of drug depends on pre-existing co-morbidities.

Primary salvage therapy includes bortezomib and dexamethasone, bortezomib and doxorubicin, or lenalidomide and dexamethasone and is currently recommended for patients with relapsed or refractory MM. Combinations with chemotherapy, such as doxorubicin or cyclophosphamide, or melphalan, or immunomodulatory drugs, are alternative, less tested options for these patients. The choice of combination depends on earlier exposure to a particular drug and concomitant co-morbidities, which might contraindicate the delivery of a specific compound.

Lenalidomide- or bortezomib-based regimens are also recommended for patients who relapse after thalidomide-based treatment.<sup>63,64</sup> Patients with residual neuropathy following thalidomide- or bortezomib-based therapy may not tolerate either agent. For these patients, lenalidomide-based therapy is recommended.

In patients with renal impairment close follow-up of the renal function is needed. Bortezomib-based combinations are preferred as they are associated with improvement in renal function. Lenalidomide is also an option with dose adjustment.

Combinations including doxorubicin or cyclophosphamide may increase haematological toxicity and be contraindicated in patients with pre-existing cytopenia.

Cytogenetic abnormalities, such as del 13 or t(4;14) or del 17, are considered negative prognostic factors. Preliminary data indicate that bortezomib may cancel the negative impact of these cytogenetic abnormalities,<sup>30</sup> lenalidomide the negative effect of del13 and t(4;14),<sup>32</sup> and thalidomide the negative impact of del 13.<sup>26</sup>

### Palliative care

The aim of palliative care is to relieve disabling symptoms rather than obtain control of disease activity. This will require good communication with the patient to ensure that the wishes of the patient are addressed. Palliative care may include planning for terminal care (for example, hospice, home care and so on), management of bone pain, psychological support and management of other complications (for example, hypercalcaemia, renal failure, infections and so on).

### Recommendation

The primary aim at this stage is to alleviate symptoms. Good supportive care and continuity of care are important. Good communication between the patient, palliative care team and the doctor are essential to ensure that the desires and concerns of the patient are addressed.

### Complications

#### Bone disease

Skeletal complications,<sup>1,65</sup> such as vertebral compression or collapse from osteoporosis, and pain arising from these complications are common. The pain requires an active approach that

includes systemic analgesia, local measures and chemotherapy. The use of analgesics in myeloma is summarized in Table 9.

Local radiotherapy is effective for pain relief of bone disease. Studies have reported pain relief in 91–97% of patients, including complete relief in 21–26%, with fractionated radiotherapy.<sup>66,67</sup>

Vertebroplasty involves percutaneous injection of polymethylacrylate or equivalent material into the vertebral body.<sup>68</sup> The procedure provides local pain relief and bone strengthening, but does not restore vertebral height. However, a recent randomized Phase III trial of balloon kyphoplasty (a procedure in which balloon expansion of the area of vertebral damage is used before the polymethylacrylate injection) showed marked reduction in back disability and pain at 1-month after procedure.<sup>69</sup> Balloon kyphoplasty also improves vertebral height.<sup>68</sup>

Bone pain, hypercalcaemia and pathological fractures are important causes of morbidity and mortality in patients with myeloma. Long-term bisphosphonate treatment is increasingly being used to try to prevent these problems. Available options include intravenous pamidronate, intravenous zoledronic acid as well as oral clodronate in some countries (for example the United Kingdom). Osteonecrosis of the jaw is an uncommon but potentially serious complication of intravenous bisphosphonates.

**Recommendation.** The use of prescribed analgesics should follow established principles of the World Health Organization.<sup>70</sup> Consider use of balloon kyphoplasty, if appropriate,<sup>68,69</sup> as an alternate for pain relief. Use of non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to the potential for gastric irritation and adverse effects on renal function. For difficult problems, the support and expertise from in-hospital pain clinics should be requested. The use of 'alternative' medical procedures may be beneficial to some patients (for example, relaxation techniques, aromatherapy and hypnosis).

**Table 9** Analgesia in multiple myeloma;

Class	Examples	Comments
Simple non-opioid analgesics	Paracetamol: 1 g 4–6 hourly Useful in mild-to-moderate pain	Oral as tablets or liquid; suppositories available
Non-steroidal anti-inflammatory drugs		Should be avoided or used only with caution
Weak opioids	Provide effective analgesia for moderate pain, for example, Codeine 8 mg/paracetamol 500 mg as co-codamol tablets; usual dosage is two tablets 6 hourly Codeine 30–60 mg or dihydrocodeine 30–60 mg up to 4 hourly	Confusion, drowsiness may be associated with initial usage in some Weak (and strong) opioids Cause constipation which usually requires simple laxatives Caution required in renal impairment
Strong (natural) opioids	Provide effective analgesia for moderate to severe pain Morphine; as liquid or tablets commencing at 5–10 mg orally and given 4 hourly is the treatment of choice in severe pain Patients can be 'converted' to slow release preparations when daily requirements are established, breakthrough pain can be treated with additional doses of 5–10 mg morphine in short acting formulation as required Diamorphine is preferred for parenteral usage, it is highly soluble and is most suitable for use in a syringe driver for continuous administration or as a 4 hourly injection	Confusion, drowsiness, constipation—same principles as for weaker opioids
Synthetic opioids	Provide effective analgesia for moderate to severe pain Oxycodone, which may be given orally Fentanyl given as slow release transdermal patches may be a valuable alternative to slow release morphine for moderate-to-severe chronic pain	

The use of radiotherapy should be limited whenever possible as the long-term use of radiation can ultimately affect haematopoietic reserve and bone healing. When using local radiotherapy, the recommended dose for control of bone pain in myeloma is an 8-Gy single fraction.

The bisphosphonates are recommended. All patients should receive a comprehensive dental examination and appropriate preventive dentistry before bisphosphonate therapy. It is generally recommended to continue bisphosphonate therapy for 2 years; however, 1 year is sufficient for patients in CR/nCR. Bisphosphonates should be resumed if the patient experiences a relapse with new onset of skeletal-related events.

### Renal failure

Renal impairment is common in myeloma. Factors involved in the pathogenesis of renal failure in MM include, the capacity of the light chain component of the immunoglobulin to cause proximal tubular damage, dehydration, hypercalcaemia, hyperuricaemia, infection and use of nephrotoxic drugs. Use of NSAIDs, including over-the-counter drugs, is a frequent precipitating factor.

**Recommendation.** Maintain a high fluid intake (at least 3 l/day), avoid potentially nephrotoxic drugs (for example, aminoglycosides and NSAIDs), correction of hypercalcaemia and treatment of infection. Clear communication is needed between the nephrologist and the myeloma team to optimize the outcome. Agents such as thalidomide and bortezomib require no dose modification in the context of renal dysfunction. Lenalidomide can be used, but should be dose modified and haematological function watched closely in the early cycles.

### Haematological toxicity

A common symptom of myeloma is myelosuppression. Supportive care and dose modifications might be needed to manage the myelosuppression.

**Neutropenia.** The greatest concern with neutropenia is the occurrence of infections. The use of granulocyte-colony stimulating factor is effective and well-tolerated method to decrease or prevent the occurrence or lower the severity of neutropenia.

**Recommendation.** Treatment should be withheld for grade 4 neutropenia lasting at least 7 days despite granulocyte-colony stimulating factor administration. When the adverse event resolves to grade 2, treatment can be reintroduced with dose reduction at the start of the next cycle. Prophylaxis with granulocyte-colony stimulating factor is also recommended for the prevention of febrile neutropenia in patients at high risk based on age, medical history, disease characteristics and myelotoxicity of the chemotherapy regimen.

**Anaemia.** Erythropoiesis-stimulating agents (ESAs; epoetin and darbepoetin) can be used to treat chemotherapy-associated anaemia, and iron supplements may improve the effectiveness of ESAs. However, using ESAs to maintain haemoglobin above 12 g per 100 ml in cancer patients may create serious health risks. For patients at high risk for developing blood clots (earlier blood clot, recent major surgery, long periods of bed rest or limited activity and certain types of chemotherapy and hormone therapy), it is important to weigh the risks and benefits of these

drugs. Thalidomide and lenalidomide in combination with ESAs appears to increase the risk of thrombosis.<sup>71</sup>

**Recommendation.** Erythropoiesis-stimulating agent treatment is generally recommended when the haemoglobin level is below 9 g per 100 ml; however, treatment may begin earlier (haemoglobin 10–12 g per 100 ml) for patients with heart disease or those who have difficulties performing regular daily activities. The ESA dose should be adjusted to maintain a high enough haemoglobin level to avoid blood transfusion, but below 12 g per 100 ml.

**DVT.** The choice of thromboprophylaxis depends on the risk of venous thromboembolism associated with a given regimen.<sup>71</sup> The following risk factors should be taken into account when determining the form of thromboprophylaxis: individual risk factors (age, obesity, history of venous thromboembolism, central venous catheter, co-morbidities, surgical procedures and inherited thrombophilia), myeloma-related risk factors (diagnosis and hyperviscosity) and therapy-related risks (high-dose dexamethasone, doxorubicin or multiagent chemotherapies).

**Recommendation.** Aspirin is only recommended for patients with no risk factors or one individual/myeloma-related risk factor. Low-molecular-weight heparin or full-dose warfarin is recommended for patients with at least two individual/myeloma-related risk factors.

**Infections.** Infections<sup>1</sup> are common in MM and the risk increases during the course of the disease. Strategies to prevent and manage infection depend on the clinical situation.

**Recommendation.** For all MM patients, fever should be treated promptly with broad-spectrum antibiotics. Intravenous antibiotics are required for severe systemic infection. For patients starting on chemotherapy, prophylactic trimethoprim-sulphamethoxazole is recommended for the first 2 months or during steroid administration periods. Acyclovir prophylaxis is recommended for all patients receiving bortezomib-based therapy, and may be useful during the induction period in order to reduce the risk of VZV reactivation.

**Peripheral neuropathy.** Peripheral neuropathy<sup>72</sup> is an adverse event that is frequently reported with bortezomib and thalidomide therapy. As there are currently no pharmacological medications known to relieve neuropathic symptoms, dose and treatment schedule modifications are the mainstays for treating peripheral neuropathy.

**Recommendation.** For bortezomib, a dose reduction to 1.0 mg/m<sup>2</sup> is recommended for grade 1 with pain or grade 2 peripheral neuropathy; dose interruption until peripheral neuropathy resolves with re-initiation at 0.7 mg/m<sup>2</sup> per week is recommended for grade 2 with pain or grade 3 peripheral neuropathy, and treatment discontinuation is recommended for grade 4 peripheral neuropathy. As alternative, the biweekly bortezomib infusion can be reduced to weekly infusion when grade 1 with pain peripheral neuropathy occurs. If grade 2 or higher are present, interruption is suggested until grade 1 is reached followed by restart on a weekly basis.

## Conflict of interest

The authors declare no conflict of interest.

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## Appendix A-1

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