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### The Singapore Myeloma Study Group Consensus Guidelines for the management of patients with multiple myeloma

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**ABSTRACT**

Multiple myeloma (MM) is an incurable plasma cell neoplasm with an incidence of 100 patients per year in Singapore. Major advances have been made in the diagnosis, risk stratification and treatment of MM in the recent past. The reclassification of a subset of patients with smouldering MM, based on high-risk biomarkers, and the development of the revised international staging system are among the key new developments in diagnosis and staging. The use of novel agent-based treatment has resulted in significant improvements in the survival and quality of life of many patients with MM. Determining the optimal use of proteasome inhibitors, immunomodulators and, more recently, monoclonal antibodies is an area of ongoing investigation. In this guideline, we aim to provide an overview of the management of MM, incorporating the latest developments in diagnosis and treatment.

*Keywords: evidence-based, guideline, multiple myeloma, Singapore*

## **INTRODUCTION**

Approximately 100 people per year are diagnosed with multiple myeloma (MM) in Singapore. Recent therapeutic advances with novel agents have changed the disease landscape, and while once largely untreatable, MM patients now have a higher likelihood of entering remission with prolonged survival. These guidelines were developed by the Singapore Myeloma Study Group (SMSG) to provide evidence-based recommendations for the diagnosis and management of MM in the local setting. This guideline is not meant to be prescriptive and is intended to be used in conjunction with the physicians' clinical judgement.

The guideline is divided into five sections:

- I. Diagnosis, Staging and Risk Stratification
- II. Supportive Care
- III. Management of Transplant-Eligible Patients
- IV. Management of Transplant-Ineligible Patients
- V. Drug Toxicity and Dose Adjustments

## **METHODS**

The SMSG performed a review of the key literature until 31 December 2015. These included MEDLINE, Cochrane Library, and major meeting reports from the American Society of Hematology, American Society of Clinical Oncology, European Society of Hematology and the International Myeloma Workshop. Key recommendations from the International Myeloma Working Group (IMWG) and British Committee for Standards in Haematology have also been incorporated. These were summarised into a draft, which the SMSG revised and also proposed recommendations in situations where there was insufficient published data.

We suggest the IMWG guidelines as a reference for readers looking for more details on specific aspects on the management of MM.

## **I. DIAGNOSIS, STAGING AND RISK STRATIFICATION**

### **Background**

The diagnosis and staging of MM is a rapidly evolving field. The definition of MM in previous IMWG consensus statements has required the presence of organ damage, specifically hypercalcaemia, renal impairment, anaemia and bone lesions, commonly recognised by the acronym CRAB.<sup>(1)</sup> Monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) are defined by specific levels of monoclonal protein and clonal bone marrow plasma cells in the absence of organ involvement, and the majority of these patients progress to develop MM at varying rates.<sup>(1)</sup>

The traditional approach to management of these patients is to withhold treatment until the onset of organ involvement, given the absence of evidence that early treatment impacts outcome.<sup>(2)</sup> The treatment options for MM have improved significantly over the last ten years.<sup>(3)</sup> Recent data has shown that a subset of patients who lacked organ damage and were classified as SMM according to the previous IMWG criteria have active disease that may benefit from treatment.<sup>(4,5)</sup> The IMWG has updated their definition of MM to take these changes into account.<sup>(6)</sup> The following are the key changes made in the 2014 IMWG consensus on diagnosis of MM:

- The presence of  $\geq 10\%$  monoclonal plasma cells in the marrow is a requirement for the diagnosis of MM.
- The presence of a monoclonal protein in the serum or urine is not mandatory to make a diagnosis of MM.

- In the absence of CRAB features, the presence of at least one of three high-risk biomarkers (see below) is sufficient to establish a diagnosis of MM.

### **Diagnosis of symptomatic MM as defined by IMWG 2014**

According to the IMWG 2014 consensus, a diagnosis of MM can be made in the presence of monoclonal plasma cells in the bone marrow ( $\geq 10\%$ ), or biopsy proven bony or extramedullary plasmacytoma, and any one or more of the myeloma defining events.

1. End organ damage attributable to the underlying plasma cell proliferative disorder:

- Calcium elevation ( $> 2.75$  mmol/L or  $> 0.25$  mmol/L above the upper limit of normal)
- Renal dysfunction (creatinine clearance  $< 40$  mL/min or serum creatinine  $> 177$   $\mu$ mol/L)
- Anaemia (haemoglobin [Hb]  $< 10$  g/dL or  $> 2$  g/dL below lower limit of normal)
- Bone disease ( $\geq 1$  osteolytic lesions on skeletal radiography, computed tomography [CT] or magnetic resonance imaging [MRI])

2. Any one or more of the following features (biomarkers of high risk):

- Clonal bone marrow plasma cell percentage  $\geq 60\%$
- Involved/uninvolved serum free light chain (SFLC) ratio  $\geq 100$
- More than one focal lesion on magnetic resonance imaging studies

### **Recommendations**

#### ***1. Screening for monoclonal gammopathy***

Although the presence of a monoclonal protein is not mandatory for the diagnosis of MM, approximately 97% of patients with MM have a monoclonal protein.<sup>(6)</sup> The finding of a monoclonal protein is also a frequent cause of referrals from other medical specialists who screen patients for monoclonal gammopathies. Serum protein electrophoresis (SPEP) is often

used as a screening test for identification of a monoclonal protein. Serum immunofixation (IFE) is, however, mandatory to confirm monoclonality. SFLC is important in the diagnosis of patients with light chain MM who may have CRAB features but no evidence of a monoclonal heavy or light chain on SPEP and IFE. SLFC is also relevant for the prognostication of patients with MGUS and the identification of patients with ‘high-risk SMM’, who would now be classified as MM. Furthermore, SFLC plays an important role in the diagnosis of light chain amyloidosis.<sup>(7)</sup> We therefore recommend that SPEP, IFE and SFLC be used as screening tests for a monoclonal protein. When SPEP, IFE and SFLC are available, screening for a monoclonal protein in the urine adds limited diagnostic or prognostic information and we do not recommend its routine use.<sup>(7)</sup> We recommend using SPEP, IFE and SFLC in the format of a ‘screening panel’ for the convenience of clinical and laboratory staff. The finding of a monoclonal protein does not confirm the diagnosis of MM. The investigation and management of MGUS and other B-cell neoplasms associated with a monoclonal protein is beyond the scope of this guideline.

**Box 1. Recommended investigations – screening for monoclonal gammopathy:**

- 1.1 Serum protein electrophoresis
- 1.2 Serum immunofixation
- 1.3 Serum free light chain study

***2. Investigations for confirmation of diagnosis and risk stratification***

Bone marrow aspiration and trephine biopsy (BMAT) are mandatory for the diagnosis of MM. Immunohistochemical assessment of light chain restriction on the trephine specimen is recommended to confirm plasma cell clonality.<sup>(6)</sup> BMAT is especially important in the 3% of patients with non-secretory MM who present with CRAB features and no evidence of a

monoclonal protein on the screening investigations described above. A full blood count (FBC), serum creatinine and calcium levels are essential to confirm the presence of anaemia, renal impairment and hypercalcaemia. Quantification of the serum M protein by densitometry is recommended at diagnosis, as this provides a baseline for the assessment of treatment response.<sup>(8)</sup>

A whole body skeletal survey is recommended as the first-line investigation for lytic skeletal lesions. If the skeletal survey shows no lytic lesions, a whole body low-dose CT (WBLDCT) or MRI is recommended if the patient has no other CRAB features.<sup>(9)</sup> Whole body MRI or WBLDCT is also recommended if the skeletal survey is negative and the patient has symptoms that suggest bone lesions. An MRI spine is indicated if there is a clinical suspicion of spinal cord compression. Whole-body MRI is also recommended for all patients diagnosed with SMM, as the finding of a lesion on MRI will lead to the diagnosis being reclassified as MM. Positron emission tomography (PET) should be considered in the event that a definitive diagnosis of bone lesions is not possible based on skeletal survey (CT or MRI).<sup>(6)</sup> MRI and PET-CT are also important tools for distinguishing truly solitary bone plasmacytoma from MM by identifying additional occult bone lesions.

Risk stratification of MM during the last decade has been based on the international staging system (ISS; Table 1), together with genetic information obtained through bone marrow karyotyping and fluorescent *in situ* hybridisation, known as the combined genetics-ISS model.<sup>(10)</sup> The presence of t (4;14), 17p13 del, t (14;16), t (14;20), 1p and 1q abnormalities have been shown to carry an adverse prognosis. While t (4;14) and 17p13 del have been shown to be adverse across studies, the data for t (14;16) and chromosome 1q abnormalities have been more controversial.<sup>(10)</sup> The revised international staging system (R-ISS), which incorporates the prognostic power of the ISS, genetics and lactate

dehydrogenase, has recently been proposed by the IMWG (Table 2).<sup>(11)</sup> We recommend the use of the R-ISS in routine practice for staging and prognostication.

**Box 2. Recommended investigations – confirmation of diagnosis and risk stratification:**

- 2.1 Bone marrow aspirate and trephine
- 2.2 Serum M protein quantification
- 2.3 Full blood count, sodium, potassium, urea, creatinine and calcium corrected
- 2.4 Serum  $\beta 2$  microglobulin, albumin and lactate dehydrogenase
- 2.5 Fluorescent *in situ* hybridisation myeloma panel: FGFR3/MMSET, MAF-B, translocations, del 17p are the minimum requirements; the inclusion of probes to detect 1p and 1q abnormalities is also recommended
- 2.6 Karyotyping on bone marrow specimen
- 2.7 Flow cytometry not routinely recommended at diagnosis
- 2.8 Whole body skeletal survey
- 2.9 Whole body low-dose computed tomography or magnetic resonance imaging (MRI) if skeletal survey is negative with no other CRAB criteria (positron emission tomography can be considered in ambiguous cases)
- 2.10 MRI if skeletal survey is negative and patient has symptoms suggestive of a bone lesion, or if there is clinical suspicion of cord compression



### ***3. Pre-treatment evaluation***

The pre-treatment evaluation points 1–9 suggested below are recommended for all patients with newly diagnosed MM. The protocol for financial assessment and assistance (point 10) may vary between institutions.

1. Height, weight, body surface area to be recorded
2. Urine human chorionic gonadotropin test for females of child-bearing age
3. Liver function tests
4. Viral screen: hepatitis B surface antigen, anti-hepatitis B core total, anti-hepatitis C virus and HIV serology
5. Glucose 6 phosphate dehydrogenase quantification
6. Contraception (advise use during therapy and for two years after treatment)
7. Dental review (pre-bisphosphonate): patients who have undergone dental extraction should have a two-week rest period prior to commencement of bisphosphonate<sup>(12)</sup>
8. 25 hydroxy vitamin D level
9. Consent for chemotherapy and counselling about treatment regimen and side effects (acute and long term)
10. Financial assessment and referral to social worker for bortezomib and lenalidomide

### ***4. Conclusion***

Our knowledge of the biology of MM has increased rapidly over the last decade. Therefore, the diagnosis and prognostication of MM has evolved significantly, with a number of clinical and genetic parameters proving to be of prognostic use. It is noteworthy, however, that selected investigations (such as those used in the R-ISS) can provide accurate prognostication at a reasonable cost. There is little doubt that the diagnosis and risk-stratification of MM will

evolve further in the near future, allowing for more targeted and risk-adapted therapeutic approaches.<sup>(13)</sup>

## **II. SUPPORTIVE CARE**

### **Introduction**

Holistic care for patients with MM goes beyond offering patients the best available anti-myeloma treatment options. While MM is still incurable, novel therapies have vastly improved the response rates and options available to patients at relapses, hence improving survival.<sup>(12)</sup> Hence, patients with MM live longer and are more vulnerable to the cumulative toxicity of treatments. The symptom burden in this group of patients may not necessarily be improved with the introduction of more anti-myeloma treatment options. The role of supportive care to ensure that these patients remain minimally affected by the complications of disease and treatment should not be overlooked, for it plays an important role in ensuring that the quality of life of these patients is not compromised.

### **Complications related to multiple myeloma**

The incidence of MM-related organ and tissue involvement at initial presentation is summarised in Table 3.<sup>(14)</sup> We propose the following recommendations for the supportive management of patients with MM in conjunction with references made to published guidelines.<sup>(15,16)</sup> The measures suggested here may be undertaken to ameliorate the effects of MM-related complications, as well as to prevent further morbidities.

### **Hypercalcaemia**

Osteoclast-mediated bone destruction in MM may lead to hypercalcaemia. There is a broad spectrum of clinical manifestations ranging from polydipsia, polyuria, abdominal pain to

renal and even neurological deficits, including coma and obtundation.<sup>(17)</sup> When other causes of hypercalcaemia have been excluded, definitive treatment for MM should be undertaken without delay. Supportive therapy should also be commenced while awaiting response to the definitive therapy.

Hydration with intravenous normal saline is usually adequate for mild hypercalcaemia ( $\text{Ca}^{2+} = 2.6\text{--}2.9$  mmol/L). For moderate to severe hypercalcaemia ( $\text{Ca}^{2+} > 2.9$  mmol/L), bisphosphonates should be given in addition to hydration. In the treatment of malignancy-related hypercalcaemia, intravenous zoledronic acid 4 mg was found to be superior to intravenous pamidronate in resolving hypercalcaemia.<sup>(18)</sup> Close monitoring of fluid balance and expectant diuresis should also be considered.<sup>(15)</sup>

### **Renal complications**

Renal impairment in MM patients occurs as a result of light chain mediated damage of renal tubules, together with a combination of hypercalcaemia, infections and use of nephrotoxic agents.<sup>(19)</sup> In patients presenting with renal impairment, there is a pressing need to curtail further worsening of renal function and possibly reverse renal insults, in order to avoid the need for long-term renal replacement therapy.

To prevent further worsening of renal function, hydration should be optimised and nephrotoxic agents avoided. The largest impact on reversal of renal damage is with early institution of anti-myeloma treatment, which may reverse myeloma-related renal complications in up to 50% of patients.<sup>(20)</sup> This hinges upon attaining an accurate diagnosis and degree of light chain involvement as soon as possible. Bortezomib with high-dose dexamethasone has been found to effective in this setting.<sup>(20)</sup>

At the time of publication, there is insufficient evidence to support the role of plasma exchange or high cut-off dialysis in patients with suspected light chain cast nephropathy. A

meta-analysis of 147 patients with MM and renal failure suggested improved renal outcome in patients treated with chemotherapy and plasmapheresis rather than chemotherapy only.<sup>(21)</sup> Small cohort studies reported sustained renal recovery and dialysis independence in 75% of patients with renal impairment who were placed on high cut-off dialysis.<sup>(22)</sup> However, larger scale studies are required to provide conclusive guidelines on the use of plasmapheresis or high cut-off dialysis in MM patients with severe renal impairment.

### **Anaemia**

Anaemia is a frequent complication in MM and may significantly impair patients' quality of life.<sup>(23,24)</sup> After exclusion of haematinic deficiency or blood loss, patients with persistent Hb < 10 g/dL should receive treatment for anaemia attributable to myeloma. A therapeutic trial of an erythropoiesis-stimulating agent may be administered with the aim to increase Hb levels without exceeding 12 g/dL. Subcutaneous erythropoietin alfa 40,000 units or erythropoietin beta 30,000 units per week may be used at the start of the therapy.<sup>(15)</sup> Effective treatment of anaemia with erythropoietin effectively decreases transfusion requirements and improves quality of life.<sup>(23)</sup> Erythropoietin can be stopped if no response is observed after 6–8 weeks.

### **Management of bone disease and related complications**

MM bone disease often results in pain, pathologic fractures and spinal cord compression.<sup>(14)</sup> Long bone fractures require stabilisation and consideration of subsequent radiotherapy. Local radiotherapy with 8 Gy in a single fraction has been shown to be useful for pain relief.<sup>(25)</sup> An orthopaedic opinion should be sought to consider pre-emptive surgery for any large lytic lesion that may potentially cause instability.

If there is any clinical suspicion of spinal cord compression, urgent MRI of the spine should be performed and orthopaedic surgeons consulted regarding the need for immediate

surgical intervention. Dexamethasone 40 mg daily should be commenced in addition to spinal nursing. Adjunctive radiotherapy may be employed to control tumour growth and prevent irreversible neurological damage.<sup>(26)</sup>

All patients with symptomatic MM, regardless of the presence of bone lesions, should be treated with a bisphosphonate, the first choice being zoledronic acid. Beyond bone health, zoledronic acid has been shown to have anti-cancer activity in myeloma, with improvements in overall survival seen in patients on treatment.<sup>(27)</sup> Pamidronate is an option in patients with a creatinine clearance of < 30 mL/min. A dose of 30 mg monthly is suggested. The minimum duration of bisphosphonate therapy is two years, as long as a very good partial response (VGPR) or complete response (CR) is achieved. Bisphosphonates should be restarted at the time of relapse.<sup>(12)</sup>

Denosumab, a human monoclonal antibody against receptor activator of nuclear factor kappa-B ligand, has been demonstrated to reduce bone-related events in patients as effectively as zoledronic acid.<sup>(28)</sup> Bisphosphonate, but not denosumab, deposits in bone with a long half-life, which may make a difference in long-term efficacy as well as adverse effects.<sup>(29)</sup> Randomised trials comparing denosumab with zoledronic acid in MM are still in progress. Denosumab is, therefore, not recommended outside the context of a clinical trial at this point.

We recommend the measurement of 25 hydroxyl vitamin D levels in all patients at diagnosis. Vitamin D and calcium replacement is indicated in patients with vitamin D deficiency or in those on bisphosphonate treatment. It is contraindicated in patients with hypercalcaemia. The recommended daily dose for replacement is calcium 1,500 mg and vitamin D 1,000 IU.<sup>(30)</sup>

### **Infective complications**

The combination of disease-related hypogammaglobulinaemia and treatment-related immunosuppression increases susceptibility to and severity of infections in MM patients.<sup>(15)</sup> Antiviral prophylaxis using acyclovir is recommended for patients receiving proteasome inhibitor (PI) and anti-*Pneumocystis jiroveci* pneumonia prophylaxis is recommended for patients receiving high-dose steroids.<sup>(31,32)</sup> The routine use of antibacterial and antifungal prophylaxis in MM patients cannot be recommended at the time of publication.

Prophylactic intravenous immunoglobulin may also be considered for patients in plateau phase with hypogammaglobulinaemia and recurrent bacterial infections. We recommend intravenous immunoglobulin 0.4 g/kg monthly for six months in patients with more than two significant infective episodes per year.<sup>(33)</sup> Prophylactic antiviral therapy for hepatitis B carriers and management of neutropenic fever should be carried out according to institutional protocols.

### **Thrombotic complications**

Although patients with active malignancy are at a higher risk of thromboembolic complications, current guidelines do not advocate routine thromboprophylaxis for patients with malignancy.<sup>(34)</sup> The use of immunomodulators, such as thalidomide and lenalidomide, increases the risk of venous thromboembolism in patients with MM, especially when used in combination with steroids or chemotherapy.<sup>(35,36)</sup> A meta-analysis performed on the thromboembolic risks of thalidomide and lenalidomide in MM patients demonstrated that the highest risk occurs in patients with newly diagnosed MM receiving thalidomide and dexamethasone without thromboprophylaxis. The three-month venous thromboembolism risk is 12% in this group. In other MM patients treated with thalidomide or lenalidomide, the venous thromboembolism risk was 3%–5%.<sup>(37)</sup>

There are no randomised trials comparing the treatment outcome of MM patients on thalidomide or lenalidomide with and without thromboprophylaxis. Moreover, there is insufficient observation regarding the risk of major bleeding on thromboprophylaxis. There are also no head to head comparisons between the forms of anticoagulants (low-molecular-weight heparin vs. aspirin vs. target-specific oral anticoagulants). Some guidelines are based on extrapolations from other risk groups, and hence, there is no evidenced based guideline available on the use of thromboprophylaxis in patients with MM treated with thalidomide and lenalidomide. While the IMWG recommends risk assessment, this has not been validated. It has been suggested that the use of prophylaxis may confer decreased risk, but no clear benefit has been proven.

The SMSG proposes the following recommendation with reference to the risk assessment model suggested by the IMWG (Table 4).<sup>(35)</sup> Patients should receive thromboprophylaxis for the first six months of treatment, until disease control is achieved or for as long as the risk of thromboembolism remains high. In addition, the following are recommended:

- For all newly diagnosed MM patients treated with thalidomide or lenalidomide, consider aspirin prophylaxis
- For all MM patients treated with thalidomide or lenalidomide in combination with steroids or chemotherapy, consider aspirin prophylaxis
- For all MM patients on thalidomide or lenalidomide with two or more other risk factors, consider low-molecular-weight heparin at prophylactic dose

It is noteworthy that the incidence of venous thromboembolism in Asian MM patients on thalidomide and lenalidomide may be less than that of their western counterparts.<sup>(38,39)</sup> These recommendations should, therefore, be considered in this context, and the risk and benefit of anticoagulation assessed on a case by case basis.

## **Conclusion**

Care of the patient with MM requires attention to factors beyond disease status. Attention to disease and treatment-related complications, as well as collaboration among primary care physicians, other specialists and haematologists would ensure holistic patient care and maximise the benefits from treatment. Our recommendations for supportive care in MM are summarised in Table 5.

## **III. MANAGEMENT OF TRANSPLANT-ELIGIBLE PATIENTS**

### **Background**

Approximately 35% of patients with MM are below the age of 65 years.<sup>(40)</sup> High-dose therapy followed by autologous stem cell transplantation (ASCT) has been shown to prolong survival in both the pre-novel agent and novel agent eras.<sup>(41,42)</sup> In this consensus statement, we summarise the evidence for treatment of transplant-eligible patients with MM and provide recommendations on the optimal treatment options.

### **Definition of transplant eligibility**

Patients below 65 years of age with an acceptable comorbidity profile and performance status are considered transplant eligible.<sup>(43)</sup> Selected patients above 65 years with good performance status and minimal comorbidities may be considered for reduced intensity transplant.<sup>(44,45)</sup>

### **Indications for treatment**

Clinical features defining symptomatic MM and/or one or more of the three high-risk biomarkers in patients who would previously have been classified as SMM are considered treatment indications.<sup>(5,6)</sup> Clinical features defining symptomatic MM and high-risk biomarkers are described in detail in Section I.



## Response definitions

The response definitions are based on the uniform response criteria recommended by the IMWG, as summarised in Table 6.<sup>(8)</sup>

## Choice of induction therapy

Cavo et al demonstrated that bortezomib, thalidomide, dexamethasone (VTD) produced a significantly higher rate of complete remission before stem cell transplantation (SCT) compared to thalidomide/dexamethasone.<sup>(46)</sup> Bortezomib, cyclophosphamide, dexamethasone (VCD) has also been shown to produce impressive response rates and survival.<sup>(47,48)</sup> A meta-analysis of phase 3 trials comparing bortezomib and non-bortezomib-containing induction regimens showed a superior response rate and progression-free survival (PFS) for the bortezomib-containing regimens.<sup>(49)</sup> Therefore, we recommend that PI-based induction should be considered in all patients. There is growing evidence that VTD may be superior to VCD. This has been shown in a retrospective analysis by Leiba et al<sup>(50)</sup> and more recently in a prospective randomised study by the Intergroupe Francophone du Myelome (IFM).<sup>(51)</sup> At present, we would recommend both VTD and VCD as options for induction therapy, depending on the physician's choice. If PI-based induction therapy is not possible, at least one novel agent should be a component of the induction regimen.<sup>(40)</sup> The bortezomib, lenalidomide, dexamethasone (VRD) regimen has shown activity in high-risk patients,<sup>(52,53)</sup> but has not been shown to be superior to VCD or VTD. VRD may be considered in certain high-risk patients, with consideration given to the significant cost of this protocol.

We suggest the following protocols as options for PI-based induction therapy:

- Bortezomib, thalidomide, dexamethasone (VTD) (Table 7);<sup>(46)</sup>
- Bortezomib, cyclophosphamide, dexamethasone (VCD) (Table 8, modified from Reeder et al<sup>(47)</sup>);
- Bortezomib, lenalidomide, dexamethasone (VRD) (Table 9).<sup>(52,53)</sup>

***Options for patients for whom PI-based induction therapy is not possible***

The intensive therapy arm of the UK MRC IX study showed that cyclophosphamide, thalidomide, dexamethasone (CTD) was superior to cyclophosphamide, vincristine, doxorubicin, dexamethasone in terms of response rate.<sup>(54)</sup> For patients who, for whatever reason, are not able to receive PI-based induction, we recommend that at least one novel agent be included in the induction regimen.

We recommend the following treatment protocols as options when PI-based induction is not possible:

- Cyclophosphamide, thalidomide, dexamethasone (CTD) (Table 10).<sup>(54)</sup> (Dexamethasone dose is lower than that used in the original study [Day 1–4 and 12–15], based on data of increased mortality with higher doses of dexamethasone).<sup>(55)</sup>
- Thalidomide, dexamethasone (TD) (Table 11).<sup>(56)</sup> (Dexamethasone dose is lower than that used in the original study [Day 1–4, 9–12, 17–20], based on data of increased mortality with higher doses of dexamethasone).<sup>(55)</sup>

**Number of cycles of induction and response before stem cell harvest**

The depth of response pre-transplant correlates with event-free survival and overall survival, with patients who show a CR having the best outcome.<sup>(57,58)</sup> The minimum response required before proceeding to ASCT is a partial response (PR). If a PR is not achieved after four

cycles of induction therapy, a further two cycles should be considered. If a PR is not achieved after six cycles or there is progressive disease at any time point during induction, a change of therapy is recommended.<sup>(12,40)</sup>

### **Mobilisation chemotherapy and stem cell collection**

High-dose cyclophosphamide (Cy) at 4–7 g/m<sup>2</sup> with granulocyte colony-stimulating factor (GCSF) has been shown to be effective for haematopoietic progenitor cell mobilisation despite associated haematologic toxicity.<sup>(59)</sup> Vinorelbine 25 mg/m<sup>2</sup> in combination with Cy 1,500 mg/m<sup>2</sup> (Vino-Cy) was shown to be comparable to Cy mobilisation in a study using historical controls.<sup>(12,60)</sup> We recommend one of the following mobilisation protocols:

- Vinorelbine 25 mg/m<sup>2</sup> on Day 1, Cy 1,500 mg/m<sup>2</sup> on Day 2 with pegylated GCSF 6 mg on Day 4,  
or
- Cy 1,500 mg/m<sup>2</sup> on Day 1 and 2 and GCSF 10 mcg/kg/day from Day 5 onwards

A haematopoietic progenitor cell collection adequate for two SCT should be the target; this is conventionally accepted to be greater than  $5 \times 10^6$  per kg/body weight.<sup>(61)</sup>

### **Conditioning regimen**

ASCT is the standard of care for transplant-eligible patients with MM. This was demonstrated in two pivotal randomised studies in the pre-novel agent era, as well as two studies in the novel agent era.<sup>(41-43,62)</sup> Melphalan 200 mg/m<sup>2</sup> is the standard conditioning regimen.<sup>(41)</sup> The addition of bortezomib to melphalan conditioning has been shown in a phase II study to be associated with higher CR rates compared to historical controls.<sup>(63)</sup> However,

there is no randomised trial data to show a benefit of this combination, and thus we do not recommend it outside of clinical trials.

### **Single versus double ASCT**

A randomised study by the IFM showed that tandem ASCT results in overall survival benefit for patients who achieved less than a VGPR after their first ASCT.<sup>(64)</sup> This study was, however, in the pre-novel agent era, and there is limited data to support this practice in the novel agent era.

Tandem ASCT should not be routinely offered, but considered only in patients who have achieved less than VGPR after their first ASCT, especially in patients with high-risk disease.

### **Disease monitoring**

We recommend that the following parameters be monitored after each cycle of treatment:<sup>(12)</sup> M protein level; FBC; renal function; calcium; immunoglobulin level (if IgA MM); SFLC level (instead of M protein quantification and immunoglobulin level) for light chain myeloma; and bone marrow studies if aiming to confirm CR or to investigate unexplained cytopenia.

### **Role of consolidation therapy**

As there is no clear evidence of an overall survival benefit from bortezomib or lenalidomide consolidation, they are not routinely recommended. Bortezomib and lenalidomide have both been shown to prolong PFS and are therefore options for consolidation in selected patients; in those with only a PR after ASCT, two further cycles of a regimen similar to the induction can

be given for consolidation.<sup>(65,66)</sup>

### **Role of maintenance therapy**

Lenalidomide maintenance has been shown to prolong PFS and overall survival after ASCT in one randomised clinical trial.<sup>(67)</sup> It should, therefore, be considered an option for patients after a thorough discussion of the risks, benefits and costs. In view of the risk of second primary malignancy, the duration of lenalidomide maintenance should be limited to two years.

Thalidomide maintenance has also been shown to prolong PFS after ASCT in patients who achieved less than a VGPR.<sup>(68)</sup> Thus, it may be considered in patients who have achieved less than a VGPR after ASCT. The duration of thalidomide maintenance should be limited to one year in view of the risk of neuropathy.<sup>(69)</sup>

Single-agent bortezomib maintenance has only been assessed in one prospective phase III study where the standard arm was treated with vincristine, adriamycin, dexamethasone induction, high-dose therapy and thalidomide maintenance. It is, therefore, not possible to recommend bortezomib maintenance outside of a clinical trial at this point.<sup>(42)</sup>

### **Role of allogeneic transplant**

Allogeneic SCT is currently the only curative therapy available for MM; however it is associated with high transplant related mortality of 20%–30%.<sup>(70)</sup> Allogeneic SCT may be considered in an upfront setting or at first relapse for young, fit patients with high-risk disease, especially 17p del. Very young patients (e.g. < 40 years) with standard risk disease are another group for whom this approach is a consideration.<sup>(71)</sup>

## **Conclusion**

ASCT remains the standard of care for transplant-eligible MM patients. The depth of response pre-ASCT correlates with long-term outcome.<sup>(57)</sup> Delivering the optimal novel agent-based induction regimen (bearing in mind the cost of these drugs) can be a challenge, as options for funding vary between institutions. We recommend that patients be included in high-quality randomised studies if they are eligible. With improved risk stratification and the availability of highly potent novel agents, the role of ASCT in MM is likely to evolve over the next few years.

## **IV. MANAGEMENT OF TRANSPLANT-INELIGIBLE PATIENTS**

### **Patient selection**

Patients aged > 65 years or who have significant comorbidities are generally ineligible for high-dose therapy. Categorisation of fitness to receive intensive treatment should be based on comorbidities and performance status, which may be assessed using a validated score (Table 1).<sup>(16)</sup> The Charlson Comorbidity Index and Modified Barthel Index, which are used to assess activities of daily living, are recommended by the IMWG to determine fitness for therapy.<sup>(72,73)</sup>

### **Frontline management strategy for newly diagnosed transplant-ineligible MM**

The goal of therapy is to maximise treatment responses while minimising treatment-related toxicities. All patients should be considered for enrolment into clinical trials where available. The inclusion of a novel agent into frontline therapy for transplant-ineligible MM patients has been shown to result in more rapid disease control as well as improved survival. These regimens are also generally well tolerated.<sup>(74)</sup> Outside of a clinical trial, we recommend PI-based induction, given its superior response rates and overall survival data.<sup>(75)</sup> The FIRST

trial showed that lenalidomide dexamethasone (RD) is superior to melphalan, prednisolone, thalidomide (MPT) as a frontline regimen for transplant-ineligible MM patients. It is noteworthy that this effect was more apparent for continuous therapy with RD and there has been no randomised study comparing RD to a PI-based regimen.<sup>(76)</sup> However, RD should be considered a potential frontline option for transplant-ineligible MM patients. The VRD regimen was compared against RD for transplant-ineligible MM patients in a randomised study, which showed superiority of VRD.<sup>(77)</sup> Although this represents another potential treatment option, it is noteworthy that VRD has not been compared to other bortezomib-based combinations. Suggested treatment protocols are summarised and the regimens described in Table 13. A comparison of the efficacy of various treatments is also summarised in Table 14. Very fit patients between the ages of 65 and 75 years old may be considered for reduced intensity autologous transplant (e.g. melphalan 100 mg/m<sup>2</sup>).<sup>(45)</sup>

### **Monitoring of response to therapy**

We recommend that M-protein quantification, immunoglobulin level, FBC, renal function and calcium levels should be monitored after each cycle. SFLC levels, instead of M-protein quantification, may be used for light chain myeloma. Once an M-protein plateau is reached, M-protein quantification may be performed every two to three months. Bone marrow studies should be used to confirm complete remission when applicable or for the investigation of unexplained cytopenia.<sup>(12)</sup>

### **Duration of induction therapy**

We recommend treatment until at least a PR and m-band plateau is achieved. This is defined as three consecutive m-band results, which qualify for at least a PR, and stable with no new CRAB features. As a guide, 9–12 cycles of therapy is recommended if no maintenance is

planned and 6–9 cycles if maintenance is planned. The decision to continue treatment should be balanced against toxicity.<sup>(78)</sup>

### **Maintenance therapy**

Thalidomide and lenalidomide maintenance have been shown to prolong progression-free survival, but overall survival benefit remains controversial.<sup>(69,79)</sup> Thalidomide maintenance may be considered, but it should be limited to a one-year duration in view of the risk of neuropathy.<sup>(69)</sup> The FIRST trial has demonstrated the efficacy and tolerability of continuous RD in transplant-ineligible patients. In this study, the continuous RD arm had improved response rates, progression-free survival and overall survival at interim analysis as compared to MPT.<sup>(76)</sup> Single-agent bortezomib maintenance has not been assessed in the transplant-ineligible population. Bortezomib, thalidomide (VT) or bortezomib prednisolone (VP) maintenance following bortezomib, thalidomide, prednisolone (VTP) or bortezomib, melphalan, prednisolone (VMP) induction showed better response and progression-free survival as compared to the VMP regimen without maintenance, but there was no overall survival benefit. However, comparison of VP and VT in this study is difficult in view of the different induction regimens used.<sup>(80)</sup> It is, therefore, not possible to recommend bortezomib maintenance at this point.

The achievement of an overall survival benefit through maintenance therapy may be difficult to demonstrate due to the availability of effective salvage treatment at relapse.<sup>(81)</sup> There is emerging evidence to suggest the efficacy of the continuous use of lenalidomide-dexamethasone rather than a fixed duration of an alkylator-based regime.<sup>(76)</sup> As for other induction regimens, there is currently insufficient data to justify the routine use of maintenance therapy outside of clinical trials. A thorough discussion of the financial aspects and quality of



life considerations with the patient should be undertaken when offering the option of maintenance therapy.

### **Suggested protocols**

We suggest the following treatment protocols as options for transplant-ineligible patients with MM. The protocols are described in detail in respective tables.

- Bortezomib, melphalan, prednisolone (VMP)<sup>(75,80)</sup> (Table 15)
- Bortezomib, cyclophosphamide, dexamethasone (VCD)<sup>(47,48)</sup> (Table 16)
- Bortezomib, dexamethasone (VD)<sup>(82)</sup> (Table 17)
- Cyclophosphamide/thalidomide/dexamethasone attenuated (CTDa)<sup>(54)</sup> (Table 18)
- Melphalan, prednisolone, thalidomide (MPT)<sup>(83)</sup> (Table 19)
- Thalidomide, dexamethasone (TD)<sup>(84)</sup> (Table 20)
- Bortezomib, lenalidomide, dexamethasone (VRD) (Table 9)<sup>(77)</sup>
- Lenalidomide, dexamethasone (RD)<sup>(76)</sup> (Table 21)

Dose adjustment guidelines depending on patient fitness are summarised in Table 22.<sup>(85)</sup>

### **Conclusion**

The management of transplant-ineligible MM patients should be individualised. The approach should take into consideration the patient's disease burden, comorbidities and the likelihood of treatment-related toxicities. While attaining best disease response with treatment is a goal, the treating physician should not neglect the goals of minimising adverse effects and providing adequate supportive care.

The introduction of novel agents – bortezomib, thalidomide and lenalidomide – has changed the treatment practices of transplant-ineligible MM. They are effective with

manageable toxicities. The armamentarium has since undergone exponential expansion with the advent of second-generation PIs (ixazomib, carfilzomib) and immunomodulators (pomalidomide), as well as the introduction of immunotherapy (such as daratumumab and checkpoint inhibitors).<sup>(86-90)</sup> However, while such potent drugs may be available, the physician is tasked to justify the added benefits in administering these treatments with the financial burdens they may bring.

## **V. DRUG TOXICITY AND DOSE ADJUSTMENTS**

This section provides guidance on the dosages and administration of drugs commonly used in treating MM. Recommendations for dose adjustments in renal and hepatic impairment, as well as information on common toxicities, are also provided. The source of this information is the manufacturers' package insert and recent publications in the field. We recommend that an oncology trained pharmacist be responsible for dispensing these agents.

### **Bortezomib**

Bortezomib is currently the first choice for standard PI-based induction. For cycle 1, FBC should be assessed 24 hours prior to the first and third dose of bortezomib. For subsequent cycles, FBC should be assessed at least twice per cycle. More regular monitoring may be considered on a case by case basis, depending on the severity of cytopenia at the beginning of the cycle and concurrent cytotoxic therapy. Prior to initiating a new cycle of therapy (Table 23): platelet count should be  $> 70 \times 10^9/L$ ; absolute neutrophil count should be  $> 1.0 \times 10^9/L$ ; non-haematological toxicities should have resolved to Grade 1 or baseline; and renal and liver function should be checked before each cycle.

### **Melphalan**

Melphalan is indicated as part of the VMP and MPT protocols, as well as in conditioning for SCT. Significant haematologic and gastrointestinal toxicities are well known. Dose adjustment for renal impairment is recommended (Table 24).

### **Thalidomide**

Thalidomide is an important component of multiple treatment protocols in both transplant-eligible and -ineligible patients. Peripheral neuropathy, constipation, sedation and hypothyroidism are significant toxicities (Table 25).

### **Cyclophosphamide**

Cyclophosphamide is indicated in the VCD and CTD regimens. The main toxicity is haematologic, and adjustment is required for renal and hepatic impairment. (Table 26).

### **Lenalidomide**

The recommended starting dose of lenalidomide is 25 mg once daily on days 1–21 of a 28-day cycle. The recommended dose of dexamethasone is 40 mg orally once daily on day 1, 8, 15 and 22.<sup>(55)</sup> Prior to initiating a new cycle of therapy (Table 27): Platelet count should be  $> 75 \times 10^9/L$ ; absolute neutrophil count should be  $> 1.0 \times 10^9/L$ ; *OR* dependent on bone marrow infiltration by plasma cells, platelet count should be  $> 30 \times 10^9/L$ .

### **Carfilzomib\***

Carfilzomib is administered as an intravenous injection over 2–10 minutes, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15 and 16), followed by a 12-

day rest period every 28 days. In cycle 1, carfilzomib is given at a dose of 20 mg/m<sup>2</sup>. If tolerated, the dose should be escalated to 27 mg/m<sup>2</sup> in subsequent cycles.

Prior to each dose in cycle 1, administer 250–500 mL of intravenous normal saline, and an additional 250–500 mL of intravenous fluids as needed, following carfilzomib administration. Continue intravenous hydration is required in subsequent cycles to ensure adequate hydration while preventing fluid overload.

Pre-medicate with oral or intravenous dexamethasone 4 mg prior to all doses of carfilzomib in cycle 1 and prior to all doses during the first cycle of dose escalation to 27 mg/m<sup>2</sup>, to reduce the incidence and severity of infusion-related reactions. Reinstate dexamethasone premedication if these symptoms develop or reappear during subsequent cycles (Table 28).

*\*Exemption supply (check with institutional pharmacy for cost and forms for application of drug)*

## **Conclusion**

The details regarding dose adjustments for each drug are described in the aforementioned tables. We suggest that prescribing physicians refer to the relevant drug package insert for a more comprehensive review of toxicity and dose adjustments. We reiterate the importance of good communication and collaboration with the haemato-oncology pharmacy team when using these agents.

## SUMMARY OF RECOMMENDATIONS

**Table 1. International Staging System (ISS).**

Stage	Criteria	Median survival (mth)
I	Serum $\beta 2$ -microglobulin < 3.5 mg/L and serum albumin $\geq$ 3.5 g/dL	62
II	Not stage I or III	44
III	Serum $\beta 2$ -microglobulin $\geq$ 5.5mg/l	29

**Table 2. Revised International Staging System (R-ISS).**

	Revised ISS Stage I	Revised ISS Stage II	Revised ISS Stage III
Parameter	ISS I and no high risk CA; normal LDH.	Not R-ISS stage I or III.	ISS III and either high-risk CA by FISH* or high LDH
5-year Overall Survival (%)	82	62	40

\*High-risk CA by FISH defined as deletion 17p, and/or t (4; 14), and/or t (14; 16). CA: cytogenetic abnormalities; FISH: fluorescence in situ hybridisation; LDH: lactate dehydrogenase

**Table 3. Incidence of myeloma related organ and tissue involvement at diagnosis.<sup>(3)</sup>**

Complications	Incidence (%)
Anaemia (Hb < 12 g/dL)	65
Hypercalcaemia ( $\text{Ca}^{2+}$ > 2.75 mmol/L)	23
Renal impairment (Cr > 180 $\mu\text{mol/L}$ )	13
Bone lesions	75

Ca: calcium; Cr: creatinine; Hb: haemoglobin

**Table 4. Risk factors for venous thromboembolism (VTE) in MM patients.<sup>(15)</sup>**

Type of risk factors		
Individual factors	Obesity	Body mass index $\geq$ 30 kg/m <sup>2</sup>
	Comorbidities	Cardiac disease; renal disease; diabetes mellitus; blood clotting disorders/previous VTE; acute infection; immobilisation
	Surgical issues	General surgery/anaesthesia; trauma
	Medications	Erythropoietin
Myeloma-related	Disease factors	Hyperviscosity; high dose dexamethasone (> 480 mg dexamethasone equivalent/mth); doxorubicin; multi-agent chemotherapy

**Table 5. Summary of recommendations for supportive care of patients with multiple myeloma.**

Table 3: Summary of Recommendations for supportive care of patients with multiple myeloma		
Parameter	Recommendation	
<b>Hypercalcaemia</b>		
Mild	IV normal saline	Monitor fluid status
Moderate-severe	IV normal saline	Monitor fluid status
<i>CrCl &gt; 30 mL/min</i>	IV zoledronic acid 4 mg over 15 min	Suggested dose adjustment for renal impairment: - CrCl 50 to 60 mL/min: Reduce dose to 3.5 mg - CrCl 40 to 49 mL/min: Reduce dose to 3.3 mg - CrCl 30 to 39 mL/min: Reduce dose to 3 mg - CrCl < 30 mL/min: Use is not recommended To consider IV pamidronate if significant renal impairment
<i>CrCl &lt; 30 mL/min</i>	IV pamidronate 30 mg over 4–6 hr	Limited pharmacokinetic data in patients with CrCl < 30 mL/min Suggested dose for CrCl < 30 mL/min and extensive bone disease: 90 mg over 4–6 hours Consider reduced initial dose if renal impairment is pre-existing
Refractory	S/C calcitonin 4 units/kg every 12 hr	
<b>Renal Impairment</b>		
All patients with renal impairment	Optimise hydration	
	Avoid nephrotoxic agents	
	Definitive treatment for	Bortezomib based therapy recommended

	MM	
Requiring RRT with high SFLC	Consider plasmapheresis or HCO dialysis	Not evidence-based Consider on case-by-case basis
<b>Anaemia</b>		
Hb < 10 g/L	Erythropoietin	To start at S/C erythropoietin alfa 40,000 units or S/C erythropoietin beta 30,000 units/wk Not to exceed Hb < 12 g/L Consider stopping therapeutic trial if no response after 6–8 wk
<b>Skeletal complications</b>		
Cord Compression	Consider surgical intervention or RT IV dexamethasone	
Bone protection	Monthly zoledronic acid	See above for dosage adjustment for CrCl
<b>Infective complications</b>		
Antimicrobial prophylaxis		
<i>Bortezomib</i>	Acyclovir prophylaxis	
<i>High-dose steroid</i>	Cotrimoxazole prophylaxis	
> 2 infective episodes/yr	IVIg	Consider monthly IVIg 0.4 g/kg for 6 mth
<b>Thromboprophylaxis</b>		
Newly diagnosed MM treated with thalidomide/lenalidomide	PO Aspirin 100 mg OM	
MM patients treated with thalidomide/lenalidomide in combination with steroids/chemotherapy	PO Aspirin 100 mg OM	
MM on thalidomide/lenalidomide with ≥ 2 other risk factors	LMWH at prophylactic dose	
<i>CrCl</i> : creatinine clearance; <i>Hb</i> : haemoglobin; <i>IV</i> : intravenous; <i>IVIg</i> : intravenous immunoglobulin; <i>LMWH</i> : low molecular weight heparin; <i>MM</i> : multiple myeloma; <i>OM</i> : once per day; <i>PO</i> : per oral; <i>RRT</i> : renal replacement therapy; <i>RT</i> : radiotherapy; <i>S/C</i> : subcutaneous; <i>SFLC</i> : serum free light chain		

Table 6. International Myeloma Working Group definitions of response categories.

Response sub-category	Response criteria
Stringent Complete Response (SCR)	<ul style="list-style-type: none"> <li>CR as defined below plus:               <ul style="list-style-type: none"> <li>Normal SFLC ratio</li> <li>Absence of phenotypically aberrant PC by MPFC</li> </ul> </li> </ul>
Complete Response (CR)	<ul style="list-style-type: none"> <li>Negative IFE on serum and urine</li> <li>Disappearance of any soft tissue plasmacytomas</li> <li>≤ 5% bone marrow PC</li> </ul>
Very Good Partial Response (VGPR)	<ul style="list-style-type: none"> <li>Serum and urine M-protein detectable by IFE but not on SPEP; <u>OR</u></li> <li>≥ 90% reduction in serum M-protein plus reduction in 24 hr urine M-protein by ≥ 90% or to &lt; 100 mg/24 hr</li> </ul>
Partial Response (PR)	<ul style="list-style-type: none"> <li>≥ 50% reduction of serum M-Protein and reduction in 24 hr urinary M-protein by &gt; 90% or to &lt; 200 mg/24hr</li> </ul>
Stable Disease (SD)	<ul style="list-style-type: none"> <li>Not meeting criteria for CR, VGPR, PR or PD</li> </ul>
Progressive Disease (PD)	<ul style="list-style-type: none"> <li>25% increase in serum M-protein in 3 mth (absolute increase must be &gt; 5 g/L)</li> <li>25% increase in urine M-protein in 3 mth (absolute increase must be &gt; 200 mg/24hr)</li> <li>25% increase in the difference between involved and uninvolved SFLC levels (applicable only to patients without measurable serum and urine M- protein (absolute increase must be &gt;100 mg/l)</li> <li>25% increase in bone marrow plasma cell percentage (absolute percentage must be &gt; 10%)</li> <li>Development of new bone lesions or soft tissue plasmacytoma</li> <li>Development of hypercalcaemia</li> </ul>

IFE: immunofixation; MPFC: Multiparameter Flow Cytometry; SFLC: serum free light chain; SPEP: serum protein electrophoresis

**Table 7. VTD (bortezomib, thalidomide, dexamethasone) protocol.**

Day	Drug	Route	Dose
1–28 or 1–21	Thalidomide	Per os	100–200 mg
1, 8, 15, 22 or 1, 4, 8, 11	Bortezomib	Subcutaneous	1.3 mg/m <sup>2</sup>
1, 2, 8, 9, 15, 16, 22, 23 or 1, 2, 4, 5, 8, 9, 11, 12	Dexamethasone	Per os	40 mg

*Cycle length: 28 days for weekly bortezomib. Subcutaneous bortezomib should be used in all patients. IV bortezomib and twice weekly dosing maybe considered in patients who require a rapid reduction in paraprotein level, e.g. patients with renal impairment.*

**Table 8. VCD (bortezomib, cyclophosphamide, dexamethasone) protocol.**

Day	Drug	Route	Dose
1, 8, 15, 22	Cyclophosphamide	Per os	300 mg/m <sup>2</sup>
1, 8, 15, 22	Bortezomib	Subcutaneous	1.3 mg/m <sup>2</sup>
1, 8, 15, 22	Dexamethasone	Per os	40 mg

*Cycle length: 28 days. Bortezomib 1.3 mg/m<sup>2</sup> on day 1, 4, 8, 11 can be considered in patients requiring a rapid reduction in paraprotein level and renal impairment. If bortezomib is given twice weekly, the dexamethasone dose should be 40 mg daily on days 1–4, 9–12 and 17–20.*

**Table 9. VRD (bortezomib, lenalidomide, dexamethasone) protocol.**

Day	Drug	Route	Dose
1–14	Lenalidomide	Per os	25 mg
1, 4, 8, 11	Bortezomib	Subcutaneous	1.3 mg/m <sup>2</sup>
1, 8, 15 or *1–5 and 8–12	Dexamethasone	Per os	40 mg

*Cycle length: 21 days. To be considered in high risk patients with aggressive disease. \*If dexamethasone is given on days 1–5 and 8–12, dosing for cycles 1–4 should be 20 mg and 10 mg for subsequent cycles.<sup>(53,77)</sup>*

**Table 10. CTD (cyclophosphamide, thalidomide, dexamethasone) protocol.**

Day	Drug	Route	Dose
1, 8, 15	Cyclophosphamide	Per os	500 mg
1–21	Thalidomide	Per os	100 mg
1, 8, 15	Dexamethasone	Per os	40 mg

*Cycle length: 21 days. Dexamethasone dose is lower than that used in the original study (1–4 and 12–15) based on data of increased mortality with higher doses of dexamethasone.<sup>(55)</sup>*

**Table 11. TD (thalidomide, dexamethasone) protocol.**

Day	Drug	Route	Dose
1–28	Thalidomide	Per os	100 mg
1, 8, 15, 22	Dexamethasone	Per os	40 mg

*Cycle length: 28 days. Dexamethasone dose is lower than that used in the original study (1–4, 9–12, 17–20) based on data of increased mortality with higher doses of dexamethasone.<sup>(55)</sup>*

**Table 12: Fitness for therapy patient categorisation.**

Patient category	Charlson Comorbidity Index score	Modified Barthel Index score
Fit	0–3	75–59
Intermediate*	≥ 2 with MBI score < 49	49–74
Unfit	≥ 4	0–48

*\*Case by case decision on fitness required.*

**Table 13: Frontline treatment options for transplant-ineligible MM patients.**

Patient fitness level	Treatment option	
Very fit	Consider induction (e.g. VCD) followed by reduced intensity autologous transplant	
Fit	Proteasome inhibitor-based	VMP; VCD; VD; VRD
	Non-proteasome inhibitor-based	MPT; CTDa; TD; RD
Unfit	Tailored according to patient with appropriate dose attenuation	

CTDa: cyclophosphamide, thalidomide, dexamethasone (attenuated); MPT: melphalan, prednisolone, thalidomide;  
 RD: lenalidomide, dexamethasone; TD: thalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone;  
 VD: bortezomib, dexamethasone; VMP: bortezomib, melphalan, prednisolone

**Table 14. Comparison of the response rates with the protocols described.**

Response	VCD	VMP	VD	CTD	MPT	TD
CR (%)	10–39	30	6–20	22.5	10–15	4–25
≥ PR (%)	84–88	70	65–85	72.5	60–70	63

CR: complete remission; CTD: cyclophosphamide, thalidomide, dexamethasone; MPT: melphalan, prednisolone, thalidomide;  
 PR: partial remission; TD: thalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; VD: bortezomib, dexamethasone; VMP: bortezomib, melphalan, prednisolone

**Table 15. VMP (bortezomib, melphalan, prednisolone) protocol.**

Day	Drug	Route	Dose
1, 8, 15, 22	Bortezomib	Subcutaneous	1.3 mg/m <sup>2</sup>
1–4	Melphalan	Per os	9 mg/m <sup>2</sup> /day
1–4	Prednisolone	Per oc	60 mg/m <sup>2</sup> /day

Cycle length: 35 days

**Table 16. VCD (bortezomib, cyclophosphamide, dexamethasone) protocol, as modified from Reeder et al.<sup>(47)</sup>**

Day	Drug	Route	Dose
1, 8, 15, 22	Bortezomib	Subcutaneous	1.3 mg/m <sup>2</sup>
1, 8, 15, 22	Cyclophosphamide	Per os	300 mg/m <sup>2</sup>
1, 2, 8, 9, 15, 16, 22, 23	Dexamethasone	Per oc	20 mg

Cycle length: 28 days

**Table 17. VD (bortezomib, dexamethasone) protocol, as modified from Girnius et al.<sup>(82)</sup>**

Day	Route	Route	Dose
1, 8, 15, 22	Drug	Subcutaneous	1.3 mg/m <sup>2</sup>
1, 2, 8, 9, 15, 16, 22, 23	Bortezomib	Per os	20 mg

Cycle length: 28 days

**Table 18. CTDa (cyclophosphamide, thalidomide, dexamethasone) attenuated protocol, as modified from Morgan et al.<sup>(54)</sup>**

Day	Drug	Route	Dose
1, 8, 15, 22	Cyclophosphamide	Per os	500 mg
1–28	Thalidomide	Per os	100 mg
1–4 and 15–18	Dexamethasone*	Per os	20 mg

Cycle length: 28 days \*In patients for whom “pulsed” dexamethasone is considered unsuitable, dexamethasone 20 mg on days 1, 8, 15 and 22 can be considered.

**Table 19. MPT (melphalan, prednisolone, thalidomide) protocol, as modified from Palumbo et al.<sup>(83)</sup>**

Day	Drug	Route	Dose
1–7	Melphalan	Per os	4 mg/m <sup>2</sup> /day
1–7	Prednisolone	Per os	40 mg/m <sup>2</sup> /day
1–28	Thalidomide	Per os	50–100 mg/day

Cycle length: 28 days

**Table 20. TD (thalidomide, dexamethasone) protocol.**

Day	Drug	Route	Dose	Cycle
1–28	Thalidomide	Per os	200 mg/day	
1–4	Dexamethasone	Per os	40 mg/day	Odd
1–4, 15–18	Dexamethasone	Per os	40 mg/day	Even

Cycle length: 28 days



**Table 21. RD (lenalidomide, dexamethasone) protocol.**

Day	Drug	Route	Dose
1-21	Lenalidomide	Per os	25 mg per day
1,8,15,22	Dexamethasone	Per os	40 mg per day

*Cycle length: 28 days*

**Table 22. Dose adjustments in elderly patients with MM, as adapted from Palumbo et al.<sup>(85)</sup>**

Drug	Initial/standard dose	Reduced dose	Further reduction if req.
Dexamethasone	40 mg/day D1, 8,15, 22 every 28 days	20 mg/day D1, 8, 15, 22 every 28 days	10 mg/day D1, 8, 15, 22 every 28 days
Melphalan	0.25 mg/kg or 9 mg/m <sup>2</sup> D1-4 every 4-6 wk	0.18 mg/kg or 7.5 mg/m <sup>2</sup> D1-4 every 4-6 wk	0.13 mg/kg or 5 mg/m <sup>2</sup> D1-4 every 4-6 wk
Thalidomide	100 mg ON	50 mg ON	50 mg EON
Lenalidomide (used with dexamethasone)	25 mg D1-21 every 28 days	15 mg D1-21 every 28 days	10 mg D1-21 every 28 days
Lenalidomide (used with melphalan/prednisolone)	10 mg D1-21 every 28 days	5 mg D1-21 every 28 days	5mg EOD D1-21 every 28 days
Bortezomib*	1.3 mg/m <sup>2</sup> D1, 8, 15, 22 every 28 days	1.0 mg/m <sup>2</sup> D1, 8, 15, 22 every 28 days	0.7 mg/m <sup>2</sup> D1, 8, 15, 22 every 28 days
Cyclophosphamide	500 mg once weekly	300 mg weekly	200 mg weekly

*\*To consider using bortezomib 1.3 mg/m<sup>2</sup> twice weekly on D1, 4, 8, 11 every 3 wk in selected patients with renal impairment or those who require rapid reduction in paraprotein levels. EON: every other night; EOD: every other day*

**Table 23. Dose adjustment and toxicity of bortezomib [VELCADE® (bortezomib) injection package insert].**

Bortezomib dosage adjustment based on organ dysfunction				
Renal impairment	<ul style="list-style-type: none"><li>Dose adjustments not necessary in renal impairment</li><li>Administer bortezomib after dialysis. Dialysis may reduce drug concentrations</li></ul>			
Hepatic impairment	<b>Liver dysfunction</b>	<b>Bilirubin level</b>	<b>AST levels</b>	<b>Modification of starting dose</b>
	Mild	$\leq 1.0\times$ ULN	$> \text{ULN}$	None
		$> 1.0\times - 1.5\times$ ULN	Any	
	Moderate	$> 1.5\times - 3\times$ ULN	Any	Reduce to $0.7 \text{ mg/m}^2$ in cycle 1. Consider dose escalation to $1.0 \text{ mg/m}^2$ or further dose reduction to $0.5 \text{ mg/m}^2$ in subsequent cycles based on tolerability
	Severe	$> 3\times$ ULN	Any	
Bortezomib dosage adjustment based on drug-induced toxicity				
Haematological toxicity	<ul style="list-style-type: none"><li>If platelet counts <math>&lt; 25 \times 10^9/\text{L}</math> or ANC <math>&lt; 0.5 \times 10^9/\text{L}</math> on dosing day (other than Day 1), bortezomib therapy should be withheld</li><li>If several doses in a cycle are withheld (<math>\geq 3</math> doses during twice weekly administration or <math>\geq 2</math> doses during weekly administration), the dose of bortezomib should be reduced by one dose level (from <math>1.3 \text{ mg/m}^2 \rightarrow 1 \text{ mg/m}^2</math> or from <math>1 \text{ mg/m}^2 \rightarrow 0.7 \text{ mg/m}^2</math>)</li></ul>			
Neuropathy (neuropathic pain and/or peripheral sensory or motor neuropathy)	<b>Severity of neuropathy</b>	<b>Modification of dose and regime</b>		
	Grade 1	No modification		
	Grade 2	Change to weekly dosing. If administered IV, change to S/C. If already on weekly S/C, reduce dose by one dose level (from $1.3 \text{ mg/m}^2 \rightarrow 1 \text{ mg/m}^2$ or from $1 \text{ mg/m}^2 \rightarrow 0.7 \text{ mg/m}^2$ )		
	Grade 3	Hold dose until resolution of toxicity, then restart at one dose level down or $0.7 \text{ mg/m}^2$		
	Grade 4	Discontinue treatment		

*ANC: absolute neutrophil count; AST: aspartate aminotransferase test IV: intravenous; S/C: subcutaneous; ULN: upper limit of normal*

**Table 24. Dose adjustment and toxicity of melphalan [ALKERAN™ (melphalan) injection package insert].**

Table 2. Dose adjustment and toxicity of melphalan (Table 2) (melphalan) injection package insert.

Melphalan dosage adjustment based on organ dysfunction				
Renal impairment	<ul style="list-style-type: none"><li>Oral/IV low dose melphalan:<ul style="list-style-type: none"><li>- CrCl: 30–50 mL/min: dose reduce by 50%</li><li>- CrCl: &lt; 30 mL/min: clinical decision<ul style="list-style-type: none"><li>For high doses (&gt; 100 mg/m<sup>2</sup>) and in moderate renal impairment (CrCl: 30–50 mL/min), dose reduction of 50% is usual (ALKERAN™ (melphalan) Injection Package Insert)</li></ul></li><li>High-dose melphalan is reduced to 140 mg/m<sup>2</sup> if creatinine clearance is less than 60 mL/min<sup>(20)</sup></li></ul></li></ul>			
Hepatic impairment	No dose reduction necessary			
Melphalan dosage adjustment based on drug-induced toxicity				
Haematological toxicity	<ul style="list-style-type: none"><li>Monitor FBC 14 days after melphalan in first and second cycles</li></ul>			
	Platelets x 10 <sup>9</sup> /L		ANC x 10 <sup>9</sup> /L	No. of days of melphalan on subsequent courses
	> 75	and	> 1.3	Proceed with next cycle on schedule, no dose adjustments required
	Plt <75 and/or ANC <1.3			Delay next cycle (for up to 2 wk) and if FBC shows marked thrombocytopenia/ neutropenia at day 14, adjust melphalan as below:
	25–75	and/or	0.5–1.0	Reduce melphalan dose to 3 days in subsequent cycle
	< 25	and/or	< 0.5	Reduce melphalan dose to 2 days in subsequent cycle
	<ul style="list-style-type: none"><li>If neutrophils &lt; 1.3 x 10<sup>9</sup>/L and/or platelets &lt; 75 x 10<sup>9</sup>/L 6 wk after the last chemotherapy was given, consider alternative therapy</li></ul>			
ANC: ANC: absolute neutrophil count; FBC: full blood count; CrCl: creatinine clearance; Plt: platelet count				

**Table 25. Dose adjustment and toxicity of thalidomide.**

<b>Thalidomide dosage adjustment based on organ dysfunction</b>											
Renal impairment	<ul style="list-style-type: none"> <li>No dose adjustment required</li> <li>No supplemental dose required if on haemodialysis<sup>(91,92)</sup></li> </ul>										
Hepatic impairment	<ul style="list-style-type: none"> <li>No recommendations for dosage adjustments in manufacturer's labelling</li> </ul>										
<b>Management of drug-induced toxicities</b>											
Peripheral neuropathy (PN)	<ul style="list-style-type: none"> <li>Monitor for PN, especially in first few months of therapy</li> <li>Thalidomide-induced neuropathy can be irreversible, thus patient should be informed to stop treatment if significant numbness or paraesthesia occurs</li> </ul> <table border="1"> <thead> <tr> <th>Severity of neuropathy</th><th>Modification of dose</th></tr> </thead> <tbody> <tr> <td>Grade 1</td><td>No modification</td></tr> <tr> <td>Grade 2</td><td>Reduce dose by 50% or hold therapy till resolution of toxicity, then restart at 50% of dose</td></tr> <tr> <td>Grade 3</td><td>Stop till resolution of toxicity, restart at low dose when PN grade 1</td></tr> <tr> <td>Grade 4</td><td>Discontinue treatment</td></tr> </tbody> </table>	Severity of neuropathy	Modification of dose	Grade 1	No modification	Grade 2	Reduce dose by 50% or hold therapy till resolution of toxicity, then restart at 50% of dose	Grade 3	Stop till resolution of toxicity, restart at low dose when PN grade 1	Grade 4	Discontinue treatment
Severity of neuropathy	Modification of dose										
Grade 1	No modification										
Grade 2	Reduce dose by 50% or hold therapy till resolution of toxicity, then restart at 50% of dose										
Grade 3	Stop till resolution of toxicity, restart at low dose when PN grade 1										
Grade 4	Discontinue treatment										
Sedation	<ul style="list-style-type: none"> <li>Decreases with continued administration of constant dose</li> <li>'Hangover effect' can be minimised by administering in the evening, approximately 3–4 hr before bedtime</li> </ul>										
Constipation	<ul style="list-style-type: none"> <li>Significant at higher doses</li> <li>Can be overcome by extra dietary fibre and laxatives</li> </ul>										
Hypothyroidism	<ul style="list-style-type: none"> <li>Monitor thyroid function and manage hypothyroidism accordingly</li> </ul>										

**Table 26. Dose adjustment and toxicity of cyclophosphamide [ENDOXAN® (cyclophosphamide) package insert].**

<b>Cyclophosphamide dosage adjustment based on organ dysfunction</b>	
Renal impairment	<ul style="list-style-type: none"> <li>CrCl ≥ 10 mL/min: no dose adjustment required</li> <li>CrCl &lt; 10 mL/min: administer 50% (package insert) to 75% (up to date) of normal dose</li> <li>Cyclophosphamide is moderately dialysable</li> <li>Haemodialysis: administer 50% of normal dose, post-haemodialysis</li> <li>Continuous ambulatory peritoneal dialysis (CAPD): administer 75% of normal dose</li> <li>Continuous renal replacement therapy (CRRT): administer 100% of normal dose</li> </ul>
Hepatic impairment	<ul style="list-style-type: none"> <li>Serum bilirubin 3.1–5 mg/dL or transaminases &gt; 3 times ULN: administer 75% of dose</li> </ul>

	<ul style="list-style-type: none"><li>• Serum bilirubin &gt; 5 mg/mL: avoid use</li><li>• Severe hepatic impairment may reduce conversion of cyclophosphamide to its active metabolite, potentially reducing efficacy of treatment</li></ul>		
cyclophosphamide dosage adjustment based on drug induced toxicity			
Haematological toxicity	<ul style="list-style-type: none"><li>• Recommendations for dose adjustment in myelosuppression (mainly for cyclophosphamide as <u>monotherapy</u>)</li></ul>		
	Platelets x 10 <sup>9</sup> /L	WBC x 10 <sup>9</sup> /L	No. of days of melphalan on subsequent courses
	> 100	> 4.0	100% of normal dose
	50–100	2.5–4.0	50% of normal dose
	< 50	< 2.5	Hold till counts recover
CrCl; creatinine clearance; ULN: upper limit of normal; WBC: white blood cell			

**Table 27. Dose adjustment and toxicity of lenalidomide.**

<b>Lenalidomide dosage adjustment based on organ dysfunction</b>														
Renal impairment	<ul style="list-style-type: none"> <li>Mild renal impairment: no dose adjustment required</li> <li>Recommended starting doses in moderate or severe impairment or ESRF are as follows:</li> </ul> <table> <tr> <th>Renal impairment</th><th>CrCl (mL/min)</th><th>Dose adjustment (Day 1–21 of a 28 day cycle)</th></tr> <tr> <td>Moderate</td><td>30–50</td><td>10 mg once daily*</td></tr> <tr> <td>Severe</td><td>&lt; 30, not requiring dialysis</td><td>15 mg every other day**</td></tr> <tr> <td>ESRF</td><td>&lt; 30, requiring dialysis</td><td>5 mg once daily Dose should be administered post dialysis</td></tr> </table> <p>*Dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment</p> <p>**Dose may be escalated to 10 mg once daily if the patient is tolerating the treatment</p>		Renal impairment	CrCl (mL/min)	Dose adjustment (Day 1–21 of a 28 day cycle)	Moderate	30–50	10 mg once daily*	Severe	< 30, not requiring dialysis	15 mg every other day**	ESRF	< 30, requiring dialysis	5 mg once daily Dose should be administered post dialysis
Renal impairment	CrCl (mL/min)	Dose adjustment (Day 1–21 of a 28 day cycle)												
Moderate	30–50	10 mg once daily*												
Severe	< 30, not requiring dialysis	15 mg every other day**												
ESRF	< 30, requiring dialysis	5 mg once daily Dose should be administered post dialysis												
Hepatic impairment	<ul style="list-style-type: none"> <li>No recommendations for dosage adjustments in manufacturer's labelling</li> </ul>													
REVLIMID® (lenalidomide) package insert	Starting dose (day 1–21 every 28 days)	25 mg OD												
	Dose level - 1	15 mg OD												
	Dose level - 2	10 mg OD												
	Dose level - 3	5 mg OD												
<b>Lenalidomide dosage adjustment based on drug-induced toxicity</b>														
Thrombocytopenia	<b>When platelets</b> First falls to < 30 x 10 <sup>9</sup> /L Returns to ≥ 30 x 10 <sup>9</sup> /L For each subsequent drop < 30 x 10 <sup>9</sup> /L Return to ≥ 30 x 10 <sup>9</sup> /L	<b>Recommended course</b> Interrupt treatment Resume at dose level - 1 Interrupt treatment Resume at next dose level lower												
Neutropenia	<b>When neutrophils</b> First falls to < 1.0 x 10 <sup>9</sup> /L Returns to ≥ 1.0 x 10 <sup>9</sup> /L, when neutropenia is the only observed toxicity Return to ≥ 1.0 x 10 <sup>9</sup> /L, when dose-dependent haematological toxicities other than neutropenia are observed For each subsequent drop < 1.0 x 10 <sup>9</sup> /L Return to ≥ 1.0 x 10 <sup>9</sup> /L	<b>Recommended course</b> Interrupt treatment Resume at starting dose Resume at dose level - 1 Interrupt treatment Resume at next dose level lower												
<i>CrCl; creatinine clearance; ESRF: end stage renal failure</i>														

**Table 28. Dose adjustment and toxicity of carfilzomib.**

<b>Carfilzomib dosage adjustment based on drug-induced toxicity</b>	
Haematological toxicity (Grade 3/4 neutropenia; Grade 4 thrombocytopenia)	<ul style="list-style-type: none"> <li>Withhold dose</li> <li>Resume at same dose level if counts recover fully before next scheduled dose</li> <li>If recover to Grade 2 neutropenia or Grade 3 thrombocytopenia, reduce dose by one dose level (from 27 mg/m<sup>2</sup> → 20 mg/m<sup>2</sup>, or from 20 mg/m<sup>2</sup> → 15 mg/m<sup>2</sup>)</li> <li>If tolerated, may escalate back to previous dose at physician's discretion</li> </ul>

Cardiac toxicity (Grade 3 or 4, new onset or worsening of: congestive heart failure; decreased left ventricular function; myocardial ischaemia)	<ul style="list-style-type: none"> <li>• Withhold dose until resolved or returned to baseline</li> <li>• After resolution, consider if restarting at a reduced dose is appropriate (from 27 mg/m<sup>2</sup> → 20 mg/m<sup>2</sup>, or from 20 mg/m<sup>2</sup> → 15 mg/m<sup>2</sup>)</li> <li>• If tolerated, may escalate back to previous dose at physician's discretion</li> </ul>
Pulmonary hypertension	<ul style="list-style-type: none"> <li>• Withhold dose until resolved or returned to baseline</li> <li>• Restart at dose used prior to event or reduced dose level (from 27 mg/m<sup>2</sup> → 20 mg/m<sup>2</sup>, or from 20 mg/m<sup>2</sup> → 15 mg/m<sup>2</sup>), at physician's discretion</li> <li>• If tolerated, may escalate back to previous dose at physician's discretion</li> </ul>
Pulmonary complications (Grade 3 or 4)	<ul style="list-style-type: none"> <li>• Withhold dose until resolved or returned to baseline</li> <li>• Consider restarting at next scheduled treatment with one dose level reduction (from 27 mg/m<sup>2</sup> → 20 mg/m<sup>2</sup>, or from 20 mg/m<sup>2</sup> → 15 mg/m<sup>2</sup>)</li> <li>• If tolerated, may escalate dose back to previous dose at physician's discretion</li> </ul>
Hepatic toxicity (Grade 3 or 4 elevation of transaminases, bilirubin or other liver abnormalities)	<ul style="list-style-type: none"> <li>• Withhold dose until resolved or returned to baseline</li> <li>• After resolution, consider if restarting at a reduced dose is appropriate (from 27 mg/m<sup>2</sup> → 20 mg/m<sup>2</sup>, or from 20 mg/m<sup>2</sup> → 15 mg/m<sup>2</sup>), with close monitoring of liver function</li> <li>• If tolerated, may escalate back to previous dose at physician's discretion</li> </ul>
Renal toxicity (Serum creatinine ≥ 2 × baseline)	<ul style="list-style-type: none"> <li>• Withhold dose until recovered to Grade 1 or returned to baseline; monitor renal function</li> <li>• If attributable to drug, restart at next scheduled treatment at reduced dose level (from 27 mg/m<sup>2</sup> → 20 mg/m<sup>2</sup>, or from 20 mg/m<sup>2</sup> → 15 mg/m<sup>2</sup>), at physician's discretion</li> <li>• If not attributable to drug, restart at the dose used prior to event</li> <li>• If tolerated, may escalate back to previous dose at physician's discretion</li> </ul>
Peripheral neuropathy (Grade 3 or 4)	<ul style="list-style-type: none"> <li>• Withhold dose until resolved or returned to baseline</li> <li>• Restart at dose used prior to event or reduced dose level (from 27 mg/m<sup>2</sup> → 20 mg/m<sup>2</sup>, or from 20 mg/m<sup>2</sup> → 15 mg/m<sup>2</sup>), at physician's discretion</li> <li>• If tolerated, may escalate back to previous dose at physician's discretion</li> </ul>

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