

Singapore Myeloma Study Group consensus guidelines for the management of patients with newly diagnosed multiple myeloma

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ABSTRACT

Multiple myeloma (MM) is the second most common haematologic malignancy and remains incurable. Significant advances have been made in both supportive care and definitive therapy for MM, leading to marked improvements in survival and quality of life. The availability of potent novel agent-based induction regimens, as well as methods to assess deeper levels of response, has transformed the landscape of MM therapy. Balancing therapeutic efficacy against toxicities and cost-effectiveness remains a key challenge to be addressed. Here, the Singapore myeloma study group provides consensus recommendations on the management of newly diagnosed MM, incorporating key developments in diagnostics, response assessment, supportive care and definitive therapy.

Keywords: cancer, guideline, haematology, multiple myeloma, Singapore

CLINICAL IMPACT

What is New

- The management of multiple myeloma has seen major advances in the last decade, resulting in improved clinical outcomes.
- The array of diagnostic and treatment modalities available presents a challenge for physicians in delivering high-quality and cost-effective care.

Clinical Implications

- The Singapore Myeloma Study Group provides updated recommendations on the holistic management of patients with newly diagnosed myeloma.
- The guideline highlights data from Singapore studies and provides recommendations based on landmark trials adapted to Singapore.

INTRODUCTION

Multiple myeloma (MM) is the second most common haematologic malignancy worldwide and remains incurable.^{1,2} Approximately 100 to 120 people per year are diagnosed with MM in Singapore. Therapeutic advances with novel agents have changed the treatment landscape; while once largely untreatable, patients with MM now have a higher likelihood of entering remission with prolonged survival. The guidelines produced by the Singapore Myeloma Study Group (SMSG) are evidence-based recommendations for the diagnosis and management of MM.³ These guidelines are intended for medical and allied health

staff caring for patients with MM. They are not meant to be prescriptive and are intended to be used in conjunction with sound clinical judgment. The guidelines focus on the management of newly diagnosed patients and are divided into 5 sections:

- Diagnosis, staging and risk stratification of MM
- Supportive care in patients with MM
- Response assessment and monitoring
- Management of transplant-eligible patients
- Management of patients ineligible for autologous stem cell transplantation

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METHOD

The SMSG performed a review of key English language literature from inception until December 2024, including MEDLINE and Cochrane Library, and proceedings of major meetings from the American Society of Hematology, American Society of Clinical Oncology, European Hematology Association and the International Myeloma Working Group (IMWG). The literature search focused on MM and included diagnosis, risk stratification, response assessment and management as the key components. Recommendations were formulated based on evidence from randomised controlled trials (RCTs) whenever possible. The strength of the recommendations was evaluated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) nomenclature. The GRADE criteria are available at <http://www.gradeworkinggroup.org>, and the GRADE level of evidence is indicated in the text for all recommendations including those that were based on less robust study designs.⁴ Members of the study group proposed and drafted the content of assigned sections of the guideline. All members then reviewed and approved the recommendations in their final form. Key recommendations from IMWG^{5,6} and British Society for Haematology⁷ have also been incorporated into the current guideline.

These findings were summarised into a draft, and the SMSG revised and proposed recommendations in situations where there were insufficient published data. The SMSG suggests the IMWG guidelines as a reference for readers looking for more details on specific aspects of the management of MM. The SMSG recommends that patients be considered for enrolment in high-quality clinical trials whenever feasible and appropriate.

Section 1. Diagnosis, staging and risk stratification of MM

Background

MM forms part of a spectrum of clonal plasma cell disorders and is typically preceded by monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM).⁵ MGUS and SMM are defined by specific levels of monoclonal protein and clonal bone marrow plasma cells in the absence of organ involvement (called myeloma defining events), and these patients may progress to develop MM at varying rates.⁸ The current approach for the management of these patients is observation until the onset of organ involvement.^{9,10}

Diagnosis of symptomatic MM as defined by IMWG criteria

The diagnosis of MM requires monoclonal plasma cells in the bone marrow ($\geq 10\%$) or biopsy-proven bony

or extramedullary plasmacytoma with any 1 or more of the following myeloma-defining events denoted by the acronym “SLiM-CRAB”.^{5,11}

- **S:** Clonal bone marrow plasma cell percentage $\geq 60\%$
- **Li:** Involved/uninvolved serum free light chain ratio ≥ 100
- **M:** >1 focal lesion ≥ 5 mm in size on magnetic resonance imaging (MRI) studies
- **C:** Hypercalcaemia (> 2.75 mmol/L or >0.25 mmol/L above the upper limit of normal)
- **R:** Renal dysfunction (creatinine clearance <40 mL/min or serum creatinine >177 mmol/L).
- **A:** Anaemia (haemoglobin <10 g/dL or >2 g/dL below the lower limit of normal)
- **B:** Bone disease: One or more osteolytic lesions on bone imaging

It is noteworthy that the presence of a monoclonal paraprotein in the serum is not a requirement for the diagnosis of MM. The IMWG has also revised the definition of plasma cell leukaemia with a cutoff of 5% for the percentage of plasma cells in the peripheral blood in patients who fit the other diagnostic criteria for MM.¹²

Recommendations

1.1 Screening for monoclonal proteins

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.⁵ The finding of a monoclonal protein is also a frequent cause of referrals from other medical specialists who screen patients for monoclonal gammopathies. Serum immunofixation (IFE) is mandatory to confirm monoclonality and the serum free light chain assay (SFLC) is important in the diagnosis of patients with light chain MM who may have CRAB features but have a negative IFE. SFLC is also relevant for the prognostication of patients with MGUS and the identification of patients with high-risk SMM who may be either reclassified as MM or have a very high short-term risk of progression to MM and require closer monitoring. The SMSG recommends using the new reference ranges for SFLC based on the latest IMWG update.¹³

The SMSG recommends that serum protein electrophoresis (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 the authors do not recommend its routine use. The SMSG recommends using SPEP, IFE and SFLC in the format of a “screening panel” for the convenience of clinical and laboratory staff. Twenty-four-hour urinary protein quantification

is helpful in the evaluation of suspected amyloid light-chain amyloidosis or monoclonal gammopathies of renal significance.¹⁴ However, spot urine IFE, M-band quantification or urine FLC are not recommended.

Recommended investigations: Screening for monoclonal proteins (GRADE 1C)

1.1.1 Serum protein electrophoresis

1.1.2 Serum immunofixation

1.1.3 Serum free light chain study

1.2 Investigations for confirmation of diagnosis and risk stratification

Bone marrow aspiration and trephine biopsy (BMAT) are mandatory for the diagnosis of MM, and immunohistochemical assessment of light chain restriction on the trephine specimen is recommended to confirm plasma cell clonality.⁵ Flow cytometric immunophenotyping is not mandatory for the diagnosis of MM, but may be considered on a case-by-case basis, especially if a B-cell lymphoproliferative disorder is part of the differential diagnosis.¹⁵ 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 corrected calcium are essential to confirm the presence of anaemia, renal impairment and hypercalcaemia. Quantification of the serum M protein by densitometry is recommended at diagnosis to provide a baseline quantitative estimation for subsequent response assessment. Immunoglobulin quantification by turbidimetry is recommended in patients with immunoglobulin A, immunoglobulin M or immunoglobulin D paraproteins, which may not be reliably quantified by M protein densitometry.¹⁶

A whole-body skeletal survey (SKS) was the previous standard imaging modality used to screen for lytic skeletal lesions. Whole-body low-dose computed tomography (WBLDCT), whole-body MRI and positron emission tomography (PET) scans have since emerged as more sensitive techniques. In a multicentre study, the IMWG compared SKS and whole-body CT scans of 212 patients with monoclonal gammopathies. They found that WBLDCT identified bone lesions in 25.5% of patients who had a negative SKS.¹⁷ In a cohort of 52 patients with a variety of monoclonal gammopathies, 12 patients (23%) were shown to be positive for osteolytic lesions on WBLDCT despite a negative SKS. These results confirm the increased sensitivity of WBLDCT compared with SKS.¹⁸ WBLDCT is hence recommended by the IMWG and the Asian Myeloma Network consensus as the minimal requirement to screen for bone lesions.^{19,20} If WBLDCT is negative,

and no other myeloma-defining events are present, the IMWG recommends the use of whole-body MRI as an alternative.¹⁹ PET-CT may also be an alternative to WBLDCT or whole-body MRI if the relevant imaging technique is contraindicated or unavailable.¹⁹

An MRI of the spine is specifically indicated if there is a clinical suspicion of spinal cord compression. Whole-body MRI is also recommended for all patients diagnosed with SMM, as finding more than 1 focal lesion >5 mm on MRI will lead to them being reclassified as MM.¹¹ PET-CT maybe an alternative for this purpose if whole-body MRI is not available or contraindicated.²¹ MRI or PET-CT are also important tools in distinguishing truly solitary bone plasmacytoma from MM by identifying additional occult bone lesions.¹⁹ Specifically, a whole-body MRI is recommended for solitary bone plasmacytoma, while a PET scan is recommended for extramedullary plasmacytoma.¹⁹

It is noteworthy that when the clinical suspicion is MM, the above imaging (WBLDCT/MRI/PET-CT) should all be performed without any intravenous contrast due to the risk of contrast nephropathy.²² The lack of contrast does not affect the imaging efficiency in discerning MM bone or marrow lesions when recommended imaging techniques are employed (for example, fluorodeoxyglucose [FDG] PET without contrast or diffusion-weighted MRI without gadolinium). The Asian Myeloma Network's imaging guidelines for myeloma provide more information on each of these modalities and alternatives in resource-constrained situations.²⁰

Risk stratification and staging

Risk stratification of MM has traditionally been based on the international staging system (ISS) where albumin and β 2-microglobulin (β 2M) were used to generate the prognostic score.²³ Genetic information obtained through bone marrow karyotyping and fluorescent in situ hybridisation (FISH) is also an important prognostic factor.²⁴ Specifically, the presence of t(4; 14), 17p13(del), t(14; 16), t(14; 20), 1p loss and 1q gain have been shown to carry an adverse prognosis.²⁴ These can all be detected by FISH performed on CD138-enriched plasma cells from the bone marrow. Conventional metaphase karyotyping has low yield (informative karyotypes in less than 30% of patients) and an inability to detect some prognostically relevant abnormalities such as t(14;16).²⁵ Although it is useful in the absence of FISH, the utility of metaphase karyotyping in the presence of FISH is limited.

The revised international staging system (R-ISS) that incorporates the prognostic value of the ISS, genetics and lactate dehydrogenase (LDH) has been revised since the publication of the previous guideline.^{26,27} The latest International Myeloma Society (IMS)/

IMWG risk stratification defines high-risk MM by the presence of specific combinations of chromosomal abnormalities and/or high $\beta 2M$ (>5.5 mg/dL) with normal creatinine (Table 1).⁶ The SMSG proposes using the updated IMS/IMWG risk stratification as the current standard for staging and prognostication. The SMSG recommends the following investigations for diagnosis, risk stratification and pretreatment evaluation.

Table 1. International Myeloma Society/International Myeloma Working group criteria for high-risk myeloma.

Del(17p) and/or TP53 mutation
One of these translocations—t(4;14) or t(14;16) or t(14;20)—co-occurring with +1q and/or del(1p32)
Monoallelic del(1p32) along with +1q, or biallelic del(1p32)
High $\beta 2M$ (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL)
$\beta 2M$: $\beta 2$ -microglobulin

Recommended investigations for confirmation of diagnosis and risk stratification

1.2.1 Blood investigations (GRADE 1C)

1.2.1.1 Serum M protein quantification (in addition to SPEP/SFLC and IFE)

1.2.1.2 FBC, serum electrolytes and renal function assessment including urea/creatinine and corrected calcium

1.2.1.3 Serum $\beta 2M$, albumin and LDH

1.2.2 Bone marrow investigations (GRADE 1C)

1.2.2.1 Bone marrow aspirate and trephine biopsy

1.2.2.2 FISH myeloma panel including the following probes: fibroblast growth factor receptor 3/multiple myeloma SET domain t(4;14), MAF-B t(14;20) and MAF-C t(14;16) translocations, and copy number changes for 17p, 1q and 1p

1.3 Imaging

1.3.1 WBLDCT as the minimum first line screening modality (GRADE 1B).

1.3.2 Non-contrasted diffusion-weighted whole-body MRI or non-contrasted FDG PET-CT to be considered if WBLDCT is not conclusive or unavailable (GRADE 1C).

1.3.3 Whole-body MRI is the modality of choice when evaluating patients with SMM for

high-risk biomarkers, which may result in upstaging to active MM (GRADE 1B). PET-CT is an alternative if whole-body MRI is not feasible (GRADE 2B).

1.3.4 Whole-body PET-CT scan if there is suspected extramedullary disease (GRADE 1B).

Recommendations for pretreatment evaluation (GRADE 1C)

The pretreatment evaluation suggested below is recommended for all patients with newly diagnosed MM. The protocol for financial assessment and assistance may vary between institutions.

- (1) Height, weight and body surface area to be recorded
- (2) Urine human chorionic gonadotrophin test for females of childbearing age
- (3) Liver function tests
- (4) Viral serologic screen: hepatitis B surface antigen, anti-hepatitis B core antibody (polymerase chain reaction for hepatitis B deoxyribonucleic acid [DNA] would be required if the core antibody is positive), anti-hepatitis C virus and human immunodeficiency virus serology
- (5) Glucose-6 phosphate dehydrogenase quantification
- (6) Dental assessment
- (7) 25-OH vitamin D level
- (8) Red cell phenotyping if CD38 monoclonal antibody therapy is planned
- (9) Pre-chemotherapy counselling according to institutional protocol
- (10) Financial assessment and referral to social worker if necessary

Section 2. Supportive care in patients with MM

Supportive care is essential to ensure that patients remain minimally affected by the complications of MM and its treatment. The SMSG proposes the following recommendations for supportive care in conjunction with references made to published guidelines.²⁸⁻³⁰

2.1 Hypercalcaemia

Osteoclast-mediated bone destruction in MM may lead to hypercalcaemia, which can present with a variety of clinical manifestations.³¹ Hydration with intravenous normal saline is usually adequate for mild hypercalcaemia ($Ca^{2+}=2.6$ to 2.9 mmol/L), while bisphosphonates are recommended for moderate to severe hypercalcaemia ($Ca^{2+} >2.9$ mmol/L),³² ideally after dental clearance. Steroids such as dexamethasone, along with intravenous (IV) hydration, can help resolve even moderately severe hypercalcaemia

promptly and can also be used as first-line treatment (GRADE 1C recommendation).

Zoledronic acid was found to be superior to pamidronate in the treatment of malignancy-related hypercalcaemia (GRADE 1B recommendation),³³ while denosumab is an option for hypercalcaemia refractory to zoledronic acid.²⁹ However, the use of bisphosphonates in patients with renal dysfunction needs careful consideration, in discussion with renal physicians, due to the potential for further kidney damage. Close monitoring of renal function, appropriate dose modification and use of a slow infusion of pamidronate are suggested (due to slightly lower renal risk compared to zoledronate).²⁹ Calcitonin can also be considered as an adjunctive therapy in hypercalcaemia refractory to bisphosphonates or when bisphosphonates are contraindicated (GRADE 2C recommendation).³⁴ Close monitoring of fluid balance is crucial, and expectant diuresis should also be considered (GRADE 2C recommendation).³² Prompt initiation of definitive antimyeloma treatment, is of vital importance in conjunction with these supportive measures.

2.2 Renal complications

Renal impairment is associated with an increased risk of mortality in patients with MM³⁵ and occurs as a result of light chain cast nephropathy.³⁵ There is a pressing need to curtail further worsening of renal function and possibly reverse renal injury to avoid the need for long-term renal replacement therapy in these patients. While adequate hydration, management of hypercalcaemia and the avoidance of nephrotoxic agents are important, early institution of anti-myeloma treatment may reverse renal complications in up to 50% of patients.³⁶

Three RCTs evaluated high cut-off (HCO) dialysis compared to standard dialysis in patients with suspected light chain cast nephropathy.^{37–39} None of these studies conclusively demonstrated the superiority of HCO over standard dialysis. A meta-analysis including 2 of the aforementioned clinical trials, as well as 3 retrospective cohort studies, showed that although HCO dialysis resulted in faster clearance of free light chains, there was no significant benefit in terms of renal recovery.⁴⁰

With regard to plasmapheresis (PLEX), 3 RCTs^{41–43} evaluated PLEX compared to standard MM treatment in light chain cast nephropathy with mixed results and no clear demonstration of superior renal recovery. While a meta-analysis of 147 patients with MM-related renal impairment suggested an improved renal outcome in patients treated with chemotherapy and PLEX rather than chemotherapy alone.⁴⁴ Taken together, there is currently insufficient evidence to support the routine use of HCO dialysis or PLEX in all patients with suspected light chain cast nephropathy.

These interventions may be considered on a case-by-case basis for patients with severe renal injury, in discussion with nephrologists (GRADE 2C recommendation).

2.3 Anaemia

Anaemia is a frequent complication of MM and may significantly impair quality of life.^{45,46} A thorough clinical evaluation to exclude other causes of anaemia such as haematinic deficiency or blood loss is required. Erythropoiesis stimulating agents (ESAs) were once recommended for the management of anaemia in patients with cancer; however, studies have shown an increased risk of thrombotic events and increased mortality.^{47–49} The SMSG therefore recommends ESAs in MM only if the anaemia does not respond adequately to definitive MM therapy (GRADE 2C recommendation),⁵⁰ especially when there is associated renal dysfunction. The additional thrombotic risk of immunomodulatory therapy is an important consideration in weighing the risk/benefit of the use of ESAs.⁵¹ If ESAs are deemed necessary, the aim of therapy is to increase the haemoglobin to a level at which symptoms of anaemia are addressed and transfusion is avoided (GRADE 2C recommendation).⁵⁰ Erythropoietin alpha or beta and darbepoetin, as well as the equivalent biosimilar agents, are acceptable options (GRADE 2C recommendation).^{48,50} ESAs should be discontinued if no response (increase in haemoglobin by at least 1–2 g/dL) is observed after 6 to 8 weeks (GRADE 1B recommendation).⁵⁰

2.4 Bone disease and related complications

Osteolytic bone lesions occur in up to 80% of patients with newly diagnosed MM,²⁹ and can result in pain, pathologic fractures and spinal cord compression.⁵² The management of bone disease in MM can be divided into bone directed medical therapy and the management of acute skeletal events.

2.4.1 Bone-directed therapy and maintenance of bone health

Treatment of vitamin D deficiency is a crucial aspect of bone health maintenance.²⁹ The SMSG recommends the measurement of 25 hydroxyvitamin D levels in all patients at diagnosis. Vitamin D and calcium replacement is indicated in patients with vitamin D deficiency and/or those who are on bisphosphonate treatment (GRADE 1A recommendation). Vitamin D or calcium replacement is contraindicated in patients with hypercalcaemia until normalisation of serum calcium levels.²⁹

All patients with symptomatic MM, regardless of the presence of bone lesions, should be treated with a bisphosphonate—the first choice being zoledronic

acid (GRADE 1A recommendation).²⁹ Beyond bone health, zoledronic acid has been shown to have antimyeloma activity, with improvements in overall survival (OS) seen in patients on treatment.⁵³ Pamidronate at a monthly dose of 30 mg is an option in patients with a creatinine clearance <30 mL/min. The minimum duration of bisphosphonate therapy is 12 months at monthly dosing (GRADE 1B recommendation). For patients achieving a very good partial response (VGPR) or better, reduction in the frequency of bisphosphonate therapy to every 3 months for the next year can be considered.^{29,54} Discontinuation of bisphosphonate after 2 years of therapy can be considered if the response of VGPR or better is maintained, and bisphosphonates should be restarted at the time of relapse to prevent new skeletal events.²⁹

Denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand, was shown in a Phase III randomised trial to be at least of equivalent efficacy to zoledronic acid.⁵⁵ These findings remained consistent in a subgroup analysis of Asian patients,⁵⁶ supporting the broader application of denosumab across ethnic groups. Denosumab is a reasonable alternative to bisphosphonates and may be a consideration in patients with creatinine clearance <30 mL/min, albeit with close monitoring²⁹ (GRADE 1B recommendation). The potential rebound effect on osteoclasts when denosumab is discontinued is an important consideration. Administration of a bisphosphonate 6 months after discontinuation of denosumab has been proposed as a means to overcome the rebound effect,²⁹ but further studies are required to define the optimal strategy to mitigate this effect. The risk of serious hypocalcaemia associated with denosumab can be reduced by commencing it after vitamin D is replete.

Given the risk of medication-related osteonecrosis of the jaw (MRONJ) with both bisphosphonates and denosumab, all patients should undergo dental assessment prior to initiating these agents and at least annually while on treatment²⁹ (GRADE 1C recommendation). Bone-directed therapy should be paused prior to dental procedures and restarted 4 to 6 weeks after the procedure, depending on the state of the dentition and urgency of need for anti-resorptive therapy.⁵⁷ Prompt referral to an oral-maxillofacial surgeon is required if patients develop symptoms suggestive of MRONJ.⁵⁷

2.4.2 Management of fractures

Long bone fractures may require surgical stabilisation⁵⁸ and consideration of subsequent radiotherapy⁵⁹ (GRADE 1B recommendation). Local radiotherapy with 8 Gy in a single fraction has been shown to be an effective and safe dose for pain control.⁶⁰ Use of cross-sectional imaging can help identify areas of

imminent fracture (large or unstable lytic lesions) that should prompt an orthopaedic opinion to consider preemptive surgical management, helping to reduce fracture associated morbidity and healthcare/rehabilitation costs.⁵⁸ Kyphoplasty or vertebroplasty are also options for painful vertebral compression fractures.^{61,62} The presence of neuro-logical symptoms and spinal stability is a key deciding factor in the optimal management of vertebral fractures. A dedicated bone disease directed multidisciplinary team comprised of spinal/orthopedic surgeons, interventional radiologists, haematologists, radiation oncologists and pain management specialists, could be invaluable in making individualised management decisions.

2.4.3 Management of spinal cord compression

If there is any clinical suspicion of spinal cord compression, an urgent MRI scan of the spine should be performed, and orthopaedic/spinal surgeon consulted about the need for immediate surgical intervention⁶³ (GRADE 1A recommendation). Corticosteroid therapy should be commenced as soon as possible in addition to spinal nursing. Radiotherapy is appropriate for spinal cord compression due to plasmacytomas while surgery should be considered if the spinal cord is unstable or if the compression is due to retropulsed bone fragments.⁶³

2.5 Infective complications

The combination of MM-related hypogammaglobulinaemia and treatment-related immunosuppression increases the susceptibility to and severity of infections in MM patients.³² Infections are an important cause of mortality in patients with MM, and the risk is highest during the first 3 months after diagnosis.³⁰

Antiviral prophylaxis using acyclovir is recommended for patients receiving proteasome inhibitors or monoclonal antibodies, while both antiviral and *Pneumocystis jirovecii* pneumonia prophylaxis is recommended for patients receiving high-dose steroids^{30,64,65} (GRADE 4C recommendation). For patients who are seropositive for the hepatitis B core antibody, seronegative for hepatitis B surface antigen and have no detectable viral load, prophylactic antiviral therapy based on institutional protocols is recommended^{30,66} (GRADE 4C recommendation). Consultation with hepatology is recommended for patients with active hepatitis B. The routine use of antibacterial and antifungal prophylaxis in MM patients cannot be recommended given the equivocal evidence supporting their use at the time of publication.⁶⁷ An exception to this is the neutropenic phase of the stem cell transplant where fluoroquinolone prophylaxis should be considered (GRADE 4C recommendation). Management of neutropenic fever should be carried out according to institutional protocols.

The recommendation regarding intravenous immunoglobulin (IVIG) has been updated based on data questioning the efficacy of prophylactic IVIG at reducing infection rates in the modern era.^{68,69} Rather than recommending IVIG replacement in all patients with hypogammaglobulinaemia and infection, the SMSG suggests IVIG replacement in a selected group of patients—specifically for those with serum IgG less than 400 mg/dL and recurrent or severe infections with encapsulated bacteria despite adequate antimicrobial prophylaxis and immunisation³⁰ (GRADE 2A recommendation). IVIG as post-exposure prophylaxis in patients who are exposed to varicella, hepatitis A and herpes zoster may be considered on a case by case basis³⁰ (GRADE 2B recommendation).

2.5.1 Immunisations

Although immune paresis associated with MM may lead to impaired responses to vaccination, they do confer a benefit of reducing the frequency of infections and resulting hospitalisations.^{70,71} The seasonal influenza and pneumococcal vaccines have been used widely for MM patients and have a favourable safety profile.⁷² Patients with MM should receive inactivated vaccines rather than live vaccines in view of their immunocompromised status³⁰ (GRADE 2B recommendation). The SMSG recommends using the influenza vaccine annually, and the *Streptococcus pneumoniae* vaccine (PCV13) followed by PPSV23 based on institutional protocols (GRADE 2B recommendation). Vaccination against other encapsulated organisms like *H. influenzae* as well as the inactivated shingles vaccine and COVID-19 vaccinations can also be considered following institutional/national guidelines⁷³ (GRADE 2B recommendation). Patients should also undergo revaccinations post autologous stem cell transplant according to international guidelines/institutional protocols^{72,74} (GRADE 2B recommendation).

2.6. Thrombotic complications

The risk of venous thromboembolism (VTE) in MM is dependent on patient, disease and treatment related factors.⁷⁵ VTE is more common in newly diagnosed patients with more extensive disease, and immunomodulator based therapy increases thrombotic risk, especially in combination with immobility, steroids or chemotherapy.^{51,76,77} The risk of VTE with proteasome inhibitor/immunomodulator based triplet combinations has been reported at 2–5%.^{78–80} Although there is no prospective RCT data supporting the use of thromboprophylaxis in MM, retrospective analyses of VTE incidence in published RCT cohorts provide adequate grounds for its implementation.^{81,82} There are also no head-to-head comparisons between the various thromboprophylactic agents (low molecular

weight heparin versus aspirin versus target-specific oral anticoagulants). The SMSG proposes the following recommendations with reference to the risk assessment model suggested by the IMWG (Table 2).⁵¹

- Consider aspirin prophylaxis for all MM patients treated with immunomodulator-based combinations (GRADE 2B recommendation).
- For all MM patients treated with immunomodulator-based combinations with 2 other risk factors, consider low molecular weight heparin (LMWH) prophylaxis (GRADE 2B recommendation).
- Rivaroxaban or apixaban prophylaxis may be considered on a case-by-case basis (GRADE 2C recommendation).

It is noteworthy that the incidence of VTE in Asian MM patients treated with immunomodulators may be lower than that of their western counterparts.^{83,84} There is hence a need for VTE prediction scores developed and validated in Asian patients. More recently developed predictive models including IMPEDE-VTE⁸⁵ and SAVED⁸⁶ are promising options which need to be evaluated further in the Asian context. Our recommendations should be applied bearing in mind the individualised risk/benefit ratio for thromboprophylaxis.

Recommendations

A multidisciplinary approach is crucial to ensure holistic supportive care and maximise the benefits from treatment. Our recommendations for supportive care under the domains of hypercalcaemia, anaemia, renal impairment, bone disease, infection and thrombosis are presented in Table 3.

Section 3. Response assessment and monitoring

3.1 Response definitions

Standard response assessment for MM relies on paraprotein quantification using M protein densitometry and the SFLC assay in light chain disease.⁸⁷ Bone marrow studies are required for confirmation of complete response (CR) and stringent CR.⁸⁷ The SMSG recommends following the uniform response criteria defined by the IMWG,⁸⁷ summarised in Table 4 (GRADE 1A recommendation). There have been significant developments in the field of response assessment for MM since the publication of the previous guideline. These pertain to the concepts of minimal residual disease and imaging which are discussed below.

3.2 Minimal residual disease (MRD) assessment

The use of potent targeted drug combinations has resulted in deep responses for patients with MM, prompting the evolution of techniques to detect clonal plasma cells at levels beyond the resolution

Table 2. Risk factors for venous thromboembolism in multiple myeloma patients.

Individual factors	Obesity		BMI ³ 30 kg/m ²
	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
	Therapy related	High-dose dexamethasone (>480 mg dexamethasone equivalent per month)	
		Doxorubicin	
		Multiagent chemotherapy	

VTE: venous thromboembolism

Table 3. Summary of recommendations for supportive care of patients with multiple myeloma.

Domains	Recommendations for supportive care	
Hypercalcaemia		
Mild hypercalcaemia	IV N/S	Monitor fluid status.
Moderate-severe hypercalcaemia	IV N/S	Monitor fluid status.
CrCl >30 mL/min	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 3.0 mg - CrCl <30 mL/min: use is not recommended To consider IV pamidronate if significant renal impairment.
CrCl <30 mL/min	IV pamidronate 30 mg over 4–6 hours	There is limited pharmacokinetic data in patients with CrCl <30 mL/min. - Suggested dose for CrCl <30 mL/min and extensive bone disease: 90 mg (or consider reduced dose) over 4–6 hours. - Consider reduced initial dose if renal impairment pre-existing.
Refractory hypercalcaemia	SC calcitonin 4 units/kg every 12 hours	
	SC denosumab 120 mg 4 weekly	Suggest monitoring calcium levels prior to each dose; dental clearance is recommended prior to initiation of therapy.
Renal impairment		
All patients with renal impairment	Optimise hydration	
	Avoid nephrotoxic agents	
	Definitive treatment for MM	Bortezomib-based therapy is recommended.
Requiring renal replacement therapy with high SFLC	Consider plasmapheresis or HCO dialysis	Consider on case-by-case basis.

Table 3. Summary of recommendations for supportive care of patients with multiple myeloma. (Cont'd)

Domains	Recommendations for supportive care	
Hypercalcaemia		
Anaemia		
Hb <10 g/L	Erythropoietin	To consider erythropoietin stimulating agents if anaemia does not respond to definitive MM therapy. Consider stopping therapeutic trial if no response after 6–8 weeks.
Skeletal complications		
Spinal cord compression	Consider surgical intervention/RT IV dexamethasone	
Bone protection	Monthly zoledronic acid	See above for dosage adjustment for CrCl.
Infective complications		
Antimicrobial prophylaxis		
• Bortezomib	Acyclovir prophylaxis	
• High-dose steroid	Co-trimoxazole prophylaxis	NA
Management of hypogammaglobulinaemia	IVIg	To consider in patient with serum IgG less than 400 mg/dL and recurrent or severe infections despite adequate antimicrobial prophylaxis and immunisation.
Thromboprophylaxis		
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	

CrCl; creatinine clearance; Hb: haemoglobin; HCO: high cut-off ; IgG: immunoglobulin G; IV: intravenous; IVIg: intravenous immunoglobulin; LMWH: low molecular weight heparin; MM: multiple myeloma; N/S: normal saline; PO: by mouth; RT: radiotherapy; SC: subcutaneous; SFLC: serum free light chain assay; OM: every morning

of light microscopy.⁸⁸ The IMWG recommends MRD assessment via next-generation flow cytometry (NGF) or next-generation sequencing (NGS) using variable-diversity-joining rearrangement also known as V(D)J rearrangements to identify clonal plasma cells.⁸⁷ MRD negativity is defined by the IMWG as the absence of phenotypically aberrant plasma cells using a validated NGF or NGS technique with a sensitivity of at least 1 in 10⁵ nucleated cells.⁸⁹ MRD positivity has been established as an important adverse prognostic factor in MM, with MRD negativity even proposed to overcome adverse cytogenetic risk.^{90,91}

While the prognostic value of MRD is clear, the optimal methodology for MRD assessment in routine clinical practice remains uncertain. The EuroFlow 8-colour NGF panel was validated on patients treated in the PETHEMA/GEM2012MENOS65 trial⁹¹ and is recommended as the standard NGF platform by

the IMWG.⁸⁷ Other centres have also developed multiparametric flow cytometry panels reporting equivalent sensitivity⁹² although their use is not as widespread as that of the EuroFlow panels. NGS platforms have shown similar levels of sensitivity to NGF and have the advantage of requiring a smaller number of cells⁸⁸. NGS is however more costly, requires a longer turnaround time, a baseline sample and significant bioinformatics support.⁸⁸

A number of clinical trials have explored MRD-based adaptation of therapy in newly diagnosed MM.^{93,94} These trials have demonstrated the feasibility of applying MRD-adapted treatment protocols as well as the value of attaining MRD negativity, especially in patients with high cytogenetic risk MM. The optimal time point at which to assess MRD, however, remains to be determined. While the prognostic impact of MRD pre-maintenance⁹⁵ has been established, the

Table 4. International Myeloma Working Group definitions of response categories.

Response sub-category	Response criteria
Sustained MRD-negative CR	MRD negativity in the bone marrow by NGF and/or NGS, and by imaging as defined below, confirmed on at least 2 time points 1 year apart. The duration of negativity can be described based on subsequent evaluations, e.g. MRD-negative at 3 years.
MRD- and imaging-negative CR	MRD negativity in the bone marrow by NGF and/or NGS, in addition to resolution of all areas of PET tracer uptake detected at baseline to less than the mediastinal blood pool SUV or to less than the surrounding normal tissues.
Flow MRD-negative CR	Absence of phenotypically aberrant clonal plasma cells by NGF on a bone marrow aspirate using the EuroFlow standard operating protocol for MRD detection in MM, with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher.
Sequencing MRD-negative CR	Absence of clonal plasma cells by NGS on a bone marrow aspirate in which the presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing using the LymphoSIGHT (Sequentia/Adaptive) platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher.
Stringent CR	CR as defined below plus • Normal SFLC ratio • Absence of phenotypically aberrant PC by MPFC
CR	• Negative IFE on serum and urine • Disappearance of any soft tissue plasmacytomas • ≤5% bone marrow PC
VGPR	• Serum and urine M-protein detectable by IFE but not on SPEP; or • ≥90% reduction in serum M-protein plus reduction in 24 hr urine M-protein by ≥90% or to <100 mg/24 hr
PR	• ≥50% reduction of serum M-protein and reduction in 24 hr urinary M-protein by >90% or to <200 mg/24 hr
Stable disease	• Not meeting criteria for CR, VGPR, PR or PD
Progressive disease	• >25% increase in serum M-protein in 3 months (absolute increase must be >5 g/L) • >25% increase in urine M-protein in 3 months (absolute increase must be >200 mg/24 hr) • >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 >100 mg/L) • >25% increase in bone marrow plasma cell percentage (absolute percentage must be >10%) • Development of new bone lesions or soft tissue plasmacytoma • Development of hypercalcaemia

CR: complete response; DNA: deoxyribonucleic acid; hr: hour; IFE: immunofixation electrophoresis; MM: multiple myeloma; MPFC: multiparameter flow cytometry; MRD: minimal residual disease; NGF: next-generation flow cytometry; NGS: next-generation sequencing; PC: clonal plasma cells; PD: progressive disease; PET: positron emission tomography; PR: partial response; SFLC: serum free light chain; SPEP: serum protein electrophoresis; SUV: standardised uptake value; VGPR: very good partial response

PRIMER study suggests that pre-transplant MRD negativity may not have the same prognostic value.⁹⁶

MRD assessment from bone marrow samples fails to account for patchy marrow involvement as well as spatial heterogeneity of the tumour cells⁹⁷ that are typical in MM. The invasive nature of bone marrow sampling and the associated costs means that MRD assessment at multiple time points may be unacceptable for some patients. Although peripheral blood-based MRD monitoring platforms are being developed, these are not ready for clinical application at the time of publication.⁹⁸ Importantly, bone marrow-based or blood-based MRD assessment does not take into account extramedullary disease.⁸⁷

3.3 Imaging for response assessment

Since the previous SMSG guideline, evidence has emerged on the value of sensitive imaging techniques to detect progression of bone lesions and extramedullary disease.^{19,99} As suggested by the IMWG, a WBLDCT should be considered before the initiation of maintenance therapy as a baseline if it was not performed at diagnosis. A repeat WBLDCT can be considered at the point of serologic relapse, or if there are clinical symptoms suggestive of new bone lesions¹⁹ If there is a suspicion of extramedullary relapse, or the patient had PET imaging at diagnosis, PET would be the recommended modality of imaging at relapse.¹⁹ The finding of new bone lesions during

an otherwise biochemical relapse may help decision-making regarding initiation of treatment.

As mentioned in section 3.2, currently available modalities for assessment of MRD fail to account for extramedullary disease. The combination of bone marrow MRD assessment using NGF/NGS with sensitive imaging to document the absence of extramedullary disease is therefore attractive. The adverse prognostic value of FDG avid lesions on post-treatment PET has been demonstrated in prospective clinical trials.^{21,100} The IMWG defines the “imaging plus MRD-negative” status as the achievement of MRD negativity by NGF/NGS plus disappearance or reduction in standard uptake value (SUV) of all FDG avid lesions seen on the baseline 18F-FDG-PET-CT. Whole-body MRI and WBLDCT have limited value in the setting of imaging MRD assessment or detection of extramedullary disease.

Although the rationale for a composite MRD assessment is strong, there remain many unanswered questions. Specifically, at what time points and how often should the MRD assessments be done, and should all modalities be used at each time point? Most importantly, there is currently insufficient data to support guiding treatment decisions based on MRD results alone and this is strongly discouraged outside of a clinical trial context.

Recommendations

- The SMSG recommends following the current IMWG consensus criteria for response assessment⁸⁹ (GRADE 1A).
- PET imaging is recommended for patients with non-secretory MM and to assess extramedullary disease/plasmacytomas (GRADE 1B).
- The SMSG does not recommend routine assessment of MRD outside of clinical trials. If MRD assessment is used on a case-by-case basis, we recommend NGF using the EuroFlow-8 colour panel. The rationale for this recommendation is that the expertise to conduct this analysis is available locally, in addition to the faster turnaround time and lower cost compared to NGS (GRADE 2C).
- The SMSG strongly discourages starting new therapy/changing therapies based on MRD results alone (GRADE 2C).

Section 4. Management of transplant-eligible patients with MM

4.1 Background and definition of transplant eligibility

High-dose melphalan followed by autologous stem cell transplant (ASCT) has been shown to prolong progression-free survival (PFS) in several large RCTs. The key RCTs supporting the use of ASCT in

the modern era are the IFM2009,⁸⁰ EMN02 H95¹⁰¹ and DETERMINATION¹⁰² trials. In this section, the authors discuss the evidence base for management of transplant eligible patients with MM and provide recommendations on the optimal treatment options.

4.2 Choice of induction therapy

4.2.1 Proteasome inhibitor/immunomodulator-based triplet combinations

A meta-analysis of Phase III RCTs comparing bortezomib and non-bortezomib containing induction regimens showed a superior response rate and PFS for the bortezomib containing regimens.¹⁰³ The combination of bortezomib with thalidomide and dexamethasone (VTD) was shown to be superior to bortezomib/cyclophosphamide/dexamethasone (VCD) in terms of response rates pre ASCT.¹⁰⁴ Bortezomib, lenalidomide, dexamethasone (VRD) has been proposed as the optimal choice of proteasome inhibitor-based triplet combination.^{105,106} Although there are no RCTs directly comparing VRD with VTD, an integrated analysis of 4 RCTs suggested superior response rates with VRD compared to VTD pre pre-ASCT.¹⁰⁷ While carfilzomib-based triplet regimens have been studied in the first-line setting for transplant eligible patients,^{108,109} the only RCT that compared KRD with VRD was not able to show a significant PFS benefit over VRD.⁷⁹ It is noteworthy however that this study did not include patients with high cytogenetic risk MM. Among the triplet regimens, the SMSG recommends VRD as the first choice, with VTD as an alternative option.

4.2.2 Daratumumab-based quadruplet combinations

Daratumumab (DARA) is an anti-CD38 human immunoglobulin G kappa monoclonal antibody, which induces apoptosis of malignant plasma cells via a variety of mechanisms.¹¹⁰ DARA-based quadruplet regimens have been evaluated as induction therapy pre-ASCT in the CASSIOPEIA (DARA-VTD), GRIFFIN (DARA-VRD) and PERSEUS (DARA-VRD) trials.¹¹¹⁻¹¹³ All 3 RCTs showed a benefit for DARA-VTD and DARA-VRD (DVRD) over VTD and VRD, respectively, in terms of stringent complete response rate and PFS.^{111,112} Importantly, the DARA-based quadruplets in all 3 trials resulted in superior rates of MRD negativity, which has emerged as an important predictor of long-term outcomes.^{114,115} The superiority of DARA-based quadruplets (with regard to response rates and PFS) over standard triplet induction regimens has been confirmed in systematic reviews and meta analyses.^{116,117} Given the excellent results obtained with DARA-based quadruplet therapy, the SMSG recommends that DARA-VTD or DARA-VRD be considered as options for pre-ASCT induction. The recommended regimens for induction therapy

are summarised in Table 5, and dose adjustments for toxicity are summarised in Appendix S1.

Table 5. Options for induction therapy in transplant-eligible patients with newly diagnosed multiple myeloma.

Triplet regimens	Quadruplet regimens
Bortezomib/lenalidomide/ dexamethasone (preferred option)	Daratumumab-VTD
Bortezomib/thalidomide/dexamethasone	Daratumumab-VRD

VRD: bortezomib/lenalidomide/dexamethasone; VTD: bortezomib/thalidomide/dexamethasone

Recommendation

- The SMSG recommends VRD, DARA-VTD or DARA-VRD as the preferred regimens for induction therapy pre ASCT (GRADE 1A).

4.3 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 in CR having the best outcome.^{118,119} The minimum response required before proceeding to ASCT is a partial response (PR). If a PR is not achieved after 4 cycles of induction therapy, a further 2 cycles should be considered. If a PR is not achieved after 6 cycles or there is progressive disease at any time point during induction, a change of therapy is recommended^{120,121} (GRADE 1B recommendation).

4.4 Mobilisation chemotherapy and stem cell collection

High-dose cyclophosphamide (CY) at 4–7 g/m² with granulocyte colony-stimulating factor (GCSF) has been shown to be effective for haematopoietic progenitor cell (HPC) mobilisation.¹²² Vinorelbine 25 mg/m² in combination with cyclophosphamide 1500 mg/m² (i.e. VINO-Cy) was shown to be comparable to high-dose cyclophosphamide mobilisation in retrospective analyses and has less haematologic toxicity.^{121,123,124} Pegylated GCSF may also be an equally effective and more convenient alternative to conventional GCSF.¹²⁵

The use of lenalidomide and CD38 monoclonal antibodies can limit the harvest, especially if the patient has had multiple cycles of treatment. However, timing the harvest in relation to these agents and the use of plerixafor have enabled safe and effective collection of CD34-positive cells in adequate quantities in these patients. In general, based on prospective trials using the above agents in combination, the quantum of CD34-positive cells collected has been lower and use of rescue plerixafor higher in DARA-containing arms. Given the current cost of plerixafor, rescue use of plerixafor seems the most economical

approach in the Singapore context, although preemptive use to enable higher quantum collection possibly with reduced number of apheresis sessions and associated hospital stay remains a good strategy.¹²⁶

4.5 The SMSG recommends one of the following mobilisation protocols (GRADE 1B):

- Vinorelbine 25 mg/m² on day 1, cyclophosphamide 1500 mg/m² on day 2 with pegylated GCSF 6 mg on Day 4. Or
- Cyclophosphamide 1500 mg/m² on day 1 and 2 and conventional GCSF 10 mcg/kg/day from day 5 onwards.

An HPC collection adequate for 2 SCTs should be the target, this is conventionally accepted to be greater than 5×10^6 per kg/body weight.¹²⁷

4.6 Conditioning regimen and early versus delayed ASCT

Melphalan 200 mg/m² is the standard conditioning regimen for ASCT in MM.^{106,128} While the addition of bortezomib¹²⁹ or busulfan¹³⁰ to melphalan conditioning has been studied, these trials have not shown conclusive clinical benefits. Dose modification of melphalan is recommended in some situations, such as in renal dysfunction and in patients >70 years of age.¹³¹ Indeed, there is data suggesting that the outcomes with melphalan 140 mg/m² and 200 mg/m² are comparable in patients who have achieved VGPR or better with induction therapy.¹³²

The IFM2009¹³³ and DETERMINATION¹⁰² trials demonstrated that patients having ASCT in first remission enjoyed a markedly improved PFS when compared to the non-ASCT arm with VRD induction and lenalidomide maintenance therapy. The lack of an OS benefit in these trials has however triggered the debate as to whether delayed transplant is a reasonable alternative. Furthermore, there is no guarantee that patients will retain their performance status and fitness for ASCT if they choose to wait until relapse. Importantly, access to therapies at relapse in the Singapore context is different to their availability in the countries where these trials were conducted. Given the marked PFS benefit and the challenges of demonstrating an OS benefit in MM (due to the potent salvage options available), the SMSG recommends ASCT in first remission as the standard.

Recommendations

- Melphalan 200 mg/m² remains the standard conditioning regimen (GRADE 1A recommendation).
- Delayed ASCT maybe considered on an individualised basis if there are personal or logistic reasons that prevent a patient from having ASCT in first remission (GRADE 2A recommendation).

4.7 Single versus double ASCT

A randomised study by the Intergroupe francophone du myélome showed that tandem ASCT results in an OS benefit for patients who achieved less than a VGPR after their first ASCT.¹³⁴ This study was however conducted in the pre-novel agent era. Several trials have since evaluated the relative efficacy of single versus tandem ASCT in newly diagnosed MM following novel agent containing induction therapy.^{135–137} A long-term follow-up analysis of patient-level data from 3 Phase III trials comparing single versus tandem ASCT using bortezomib-based induction regimens demonstrated that the greatest benefit was for patients with high-risk cytogenetics and a suboptimal response to induction therapy.¹³⁸

Recommendation

- Double ASCT should be discussed as an option and considered in patients who have achieved less than VGPR after first ASCT, especially in patients with high-risk disease (GRADE 2C).

4.8 Role of consolidation therapy

While older studies reported a PFS benefit for bortezomib or lenalidomide as consolidation therapy,^{139,140} the patients in these trials did not receive a proteasome inhibitor/immunomodulator based induction which is considered standard today. Since the publication of the previous SMSG guideline, 2 large RCTs have evaluated post-ASCT consolidation therapy. The STAMINA trial compared 4 cycles of VRD consolidation against tandem ASCT and single ASCT followed by continuous lenalidomide maintenance.¹⁴¹ The EMN02/H095 trial compared VRD consolidation with no consolidation in patients who had undergone either bortezomib/melphalan/prednisolone (VMP) or single/double ASCT followed by lenalidomide maintenance.¹⁴² Neither trial demonstrated a PFS or OS benefit for consolidation therapy. While consolidation therapy has been employed in RCTs evaluating DARA-based quadruplet induction, none of them included a randomisation at consolidation.^{113,143,144}

Recommendation

- There is inadequate evidence to recommend the routine administration of consolidation therapy, although it may be considered on a case-by-case basis for patients not achieving at least a VGPR post-ASCT, using the same regimen used for induction therapy (GRADE 2C).

4.9 Maintenance therapy post-autologous stem cell transplantation

Lenalidomide maintenance has been shown to prolong PFS and OS post-ASCT,¹⁴⁵ in 4 key RCTs.^{139,146–148} All 4 trials showed a significant PFS benefit in favour of

lenalidomide with the CALGB 100104 and MRC XI trials also showing an OS benefit. The OS benefit was confirmed by a meta-analysis including patients from all the trials except MRC XI,¹⁴⁹ establishing lenalidomide as the standard of care for post-ASCT maintenance therapy.

Although the evidence base for thalidomide maintenance is not as strong as that for lenalidomide, it remains an option for patients who cannot tolerate lenalidomide.¹⁵⁰ Single-agent bortezomib maintenance has only been assessed in 1 prospective trial where the standard arm was treated with vincristine, doxorubicin, dexamethasone induction, ASCT and thalidomide maintenance.¹⁵¹ While bortezomib-based maintenance is frequently used in high-risk MM, this recommendation is not supported by RCT data.^{152,153} Close monitoring for peripheral neuropathy is crucial if bortezomib or thalidomide are used for maintenance therapy.³²

Ixazomib presents an alternative maintenance option based on the TOURMALINE MM-3 study,¹⁵⁴ which showed a modest PFS benefit in favour of ixazomib over placebo. DARA was investigated as maintenance therapy in the second randomisation of the CASSIOPEIA trial where PFS was significantly longer in the DARA maintenance group than the observation group.¹⁴³ DARA could therefore be considered in patients who are unable to receive lenalidomide maintenance. Although there are no RCTs comparing lenalidomide, ixazomib and DARA maintenance against each other, a recent meta-analysis suggests that lenalidomide remains the preferred option.¹⁵⁵

The optimal duration of maintenance therapy remains an area of uncertainty. Although the key trials evaluating lenalidomide employed continuous maintenance until progression,^{139,145,147,156} long-term toxicities including second primary malignancies are an important concern. Ongoing trials are evaluating the role of individualised maintenance therapy based on response to treatment, especially MRD adapted approaches,¹⁵⁷ which may be incorporated into future treatment algorithms. Based on currently available data, maintenance therapy for 2 years is considered an acceptable standard, with consideration of extended duration in individuals with manageable toxicity profiles.¹⁵⁸

Recommendation

- The SMSG recommends lenalidomide maintenance as the standard of care for standard risk patients (GRADE 1A), while for high-risk patients, lenalidomide- and/or bortezomib-based therapy can be considered (GRADE 2C). We do not recommend the routine use of DARA maintenance

given the lack of clear evidence at the present time that it is superior to lenalidomide.

- Bortezomib, thalidomide or ixazomib maintenance maybe considered on an individualised basis when lenalidomide maintenance is not tolerated or contraindicated (GRADE 2B).
- The SMSG suggests 2 years of maintenance therapy as the standard duration, with consideration of longer duration on a case-by-case basis depending on toxicities (GRADE 2C).

4.10 Role of allogeneic transplant

Allogeneic SCT (allo-SCT) is currently the only curative therapy available for MM, however it is associated with a high transplant-related mortality (TRM) of 20–30%.¹⁵⁹ The high TRM, together with the exponentially increasing treatment options in MM was the reason for allogeneic SCT falling out of favour in the last decade. However, with the move from more myelosuppressive regimens to more immunosuppressive, reduced intensity regimens in conditioning, better supportive therapy, earlier allo-SCT and less prior chemotherapy the TRM has been reduced. Long-term survival was achieved in 10–25% of the patients and the plateau in survival curve was observed in 1 study.^{160,161}

Recommendation

- Given the plethora of agents currently available, allo-SCT would be considered investigational in the upfront setting; however in selected young, fit patients with ultra-high-risk myeloma at first relapse, it may be an appropriate consideration (GRADE 3C).

Section 5. Management of patients ineligible for autologous stem cell transplantation

5.1. Patient selection

The determination of transplant eligibility and fitness for treatment should be based on a comprehensive functional assessment rather than age alone. Geriatric assessment is of increasing importance in MM, and comprehensive frailty evaluation has become a standard of care to optimise the safety of treatment and minimise the impact on quality of life.¹⁶² Stratification of patients by frailty enables treatment to be tailored to individual patients' tolerance of therapy. The IMWG frailty score is the current standard for geriatric assessment in MM, incorporating age, comorbidities and functional measures.¹⁶³ Frailty scoring systems used or being developed in MM are summarised in Table 6.

Recommendation

- The SMSG suggests using the IMWG frailty score, while awaiting further validation of the newer frailty scoring systems (GRADE 2B).

5.2. Induction therapy for transplant ineligible patients

Many of the currently used transplant-ineligible induction regimens build on the lenalidomide/dexamethasone (Rd) backbone established by the FIRST trial, which showed the superiority of Rd to the prior standard of melphalan/prednisolone/thalidomide (MPT).¹⁸³ It is noteworthy that this effect was more apparent for continuous therapy with Rd compared to time-limited Rd given for 18 months.¹⁸³ The VRD regimen was compared against RD for transplant ineligible MM patients in a randomised study (SWOG S0777), which resulted in VRD becoming a standard of care induction regimen.¹⁸⁴ It is noteworthy, however, that the population included in this trial was younger than the typical transplant-ineligible population in the Singapore context.

DARA-based induction therapy in transplant-ineligible patients was first evaluated in the ALCYONE trial, which demonstrated a PFS and OS benefit for DARA+VMP over VMP.¹⁸⁵ The MAIA trial compared the DARA/lenalidomide/dexamethasone (DRd) regimen in a continuous fashion against Rd.¹⁸⁶ DRd resulted in a marked PFS benefit over Rd (median PFS not reached for DRd versus 34.4 months for Rd (hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.43–0.66; $P < 0.0001$)).¹⁸⁶ Notwithstanding the caveats of the MAIA study,¹⁸⁷ the remarkable results have led to DRd being considered one of the standard of care regimens in transplant-ineligible MM patients.

CD38 monoclonal antibody-based quadruplet induction has been investigated in the IMROZ and BENEFIT trials (Isatuximab-VRD),^{188,189} and the ongoing CEPHEUS trial (DARA-VRD),¹⁹⁰ with MRD negativity as the primary end point. All 3 trials have shown superiority of the quadruplets with regard to efficacy, with a favourable toxicity profile. It is however noteworthy that these trials did not enrol frail patients, hence the use of these regimens may be limited to a subset of fit, transplant-ineligible patients.

Isatuximab-VRD and DARA-VRD are currently not approved for induction therapy in transplant-ineligible patients but may become viable options in the near future. Recommended treatment protocols for induction therapy are summarised in Table 7 and dose adjustments based on frailty status and toxicity are summarised in Table 8 and Appendix S1. Doublet regimens such as bortezomib, dexamethasone¹⁹¹ and RD¹⁸³ are also reasonable options in frail patients. It is noteworthy that dexamethasone-sparing induction regimens are under active investigation¹⁹² and may become an option for frail patients in the future.

If a triplet regimen is being used, SMSG recommends induction therapy for 8–9 cycles until a response plateau. Subsequently, options include continuing the triplet until disease progression or stepping down to

Table 6. Comparison of the frailty scoring systems in multiple myeloma.

Score	Reference	Variables	Frailty/outcome groups defined	Validation
Fried phenotype	Fried ¹⁶⁴	• Unintentional weight loss • Weakness • Poor endurance and exhaustion • Slowness • Low physical activity	• Frail group (≥3 frail criteria) • Intermediate-frail (1–2 criteria)	• No internal validation cohort
Clinical frailty index	Rockwood ¹⁶⁵	• Modified Mini-Mental State Examination • Cumulative Illness Rating Scale • History of falls, delirium, cognitive impairment or dementia • CSHA definition of frailty • CSHA Frailty Index • CSHA Function Scale	• Very fit • Well • Well, with treated comorbid disease • Apparently vulnerable • Mildly frail • Moderately frail • Severely frail	• Longitudinal follow-up of original cohort
Hematopoietic cell transplantation-specific comorbidity index	Sorrø ¹⁶⁶	• Atrial fibrillation or flutter, sick sinus syndrome or ventricular arrhythmias • Coronary artery disease, congestive heart failure, myocardial infarction or EF ≤50% • Crohn's disease or ulcerative colitis • Diabetes requiring treatment with insulin or oral hypoglycaemics but not diet alone • Transient ischaemic attack or cerebrovascular accident • Depression or anxiety requiring psychiatric consult or treatment • Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN • Patients with a body mass index > 35 kg/m² • Infection requiring continuation of antimicrobial treatment after day 0 • SLE, RA, polymyositis, mixed CTD or polymyalgia rheumatica • Peptic ulcer requiring treatment • Serum creatinine >2 mg/dL, on dialysis, or prior renal transplantation • DLco and/or FEV1 66–80% or dyspnoea on slight activity • Prior solid tumour treated at any time point in the patient's history, excluding nonmelanoma skin cancer • Heart valve disease except mitral valve prolapse • DLco and/or FEV1 ≤65% or dyspnoea at rest or requiring oxygen • Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	• 0 • 1–2 • >2	• Internal validation; training (n=708), validation (n=347). • External validation in multiple studies^{167,171}
International Myeloma Working Group	Palumbo ¹⁷²	• Age • CCI • IADL • ADL	• Fit • Intermediate-fit • Frail	• No internal validation cohort • External validation by 125 patients in a single institution¹⁷³

Table 6. Comparison of the frailty scoring systems in multiple myeloma. (Cont'd)

Score	Reference	Variables	Frailty/outcome groups defined	Validation
Simplified Frailty scale	Facon ¹⁷⁴	- Age - CCI - ECOG	- Non frail - Frail	- Retrospective analysis of the patients in the Phase III FIRST trial - External validation in a population-based cohort¹⁷⁵
Revised myeloma comorbidity index	Engelhardt ¹⁷⁶	- Age - eGFR - Lung disease - Karnofsky Performance Status - Frailty - Cytogenetics	- Fit - Intermediate-fit - Frail	- Internal validation; training (n=552) and validation (n=249) - External validation¹⁷⁷
Myeloma risk profile	Cook ¹⁷⁸	- Age - Performance status - C-reactive protein - International Staging System	- Low risk - Medium risk - High risk	- Internal validation with the NCRI Myeloma XI study [NCRI-XI, n=1852] and externally validated using the MRC Myeloma IX study [MRC-IX, n=520]) - External validation in prospective and retrospective studies^{179, 180}
Mayo Clinic Frailty	Milani ¹⁸¹	- Age - Performance status - NT-BNP	- I - II - III - IV	No external validation studies
Carolina Frailty Index	Guerard ¹⁸²	- IADL - Physical function - Comorbidities - Number of daily medications - Vision - Hearing - Nutrition - Mental health - Social activity - Measure of physical function and cognition	- Robust - Pre-frail - Frail	No external validation studies

ADL: activities of daily living; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CCI: Charlson Comorbidity Index; CSHA: Canadian Study of Health and Aging; CTD: connective tissue disease; DLco: diffusion capacity of lung; eGFR: estimated glomerular filtration rate; ECOG: Eastern Cooperative Oncology Group; EF: ejection fraction; FEV1: forced expiratory volume in 1 second; IADL: instrumental activities of daily living; IMWG: International Myeloma Working Group; MRC: Medical Research Council; NCRI: National Cancer Research Institute; NT-BNP: N-terminal pro-B-type natriuretic peptide; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ULN: upper limit of normal

maintenance therapy. This decision should be guided by the disease risk stratification, depth of response to treatment, toxicities, financial circumstances and patient preference.^{193,194}

Recommendations

- The SMSG recommends DRd or VRD as preferred induction regimens, while RD or VD can be considered for frail patients (GRADE 1A).
- Continuous therapy or de-escalation to single-agent maintenance after 8–9 cycles are both reasonable strategies (GRADE 2C).

5.3 Maintenance therapy

Lenalidomide maintenance has shown consistent PFS benefit across clinical trials and is considered the standard of care for maintenance therapy.^{156,195} Notably, for intermediate-fit elderly patients treated with Rd, stepping down to lenalidomide maintenance was shown to be comparable to continuous Rd with regard to efficacy and avoided the additional toxicities of continuous Rd.¹⁹⁶ Thalidomide maintenance has also been shown to prolong PFS but peripheral neuropathy can be a limiting factor; furthermore, a

network meta-analysis suggested that lenalidomide maintenance maybe superior to thalidomide.^{197,198} Hence, thalidomide should only be considered if lenalidomide maintenance is not tolerated.

Ixazomib maintenance was compared to placebo in transplant ineligible patients in the TOURMALINE-MM4 trial where the ixazomib arm showed a modest PFS benefit (median 17.4 months for ixazomib versus 9.4 months for placebo (HR 0.659, 95% CI 0.542–0.801; $P < 0.001$).¹⁹⁹ A recent meta-analysis also suggested that lenalidomide maintenance is superior to ixazomib maintenance.¹⁵⁵ There is no evidence supporting the use of bortezomib maintenance in the transplant ineligible setting. The SMSG therefore proposes lenalidomide as the standard of care, while bortezomib-based maintenance can be considered on a case-by-case basis for patients with high-risk MM, based on extrapolation from the transplant-eligible patient data.

Recommendations

- SMSG recommends lenalidomide as the preferred maintenance option for transplant-ineligible patients (GRADE 1A).

Table 7. Frontline treatment options for transplant-ineligible multiple myeloma patients.

Fit	Daratumumab, lenalidomide, dexamethasone Bortezomib, lenalidomide, dexamethasone
Frail	Bortezomib, lenalidomide, dexamethasone with dose reduction Bortezomib, dexamethasone Lenalidomide, dexamethasone
Unfit	VD or RD tailored according to patient frailty with appropriate dose attenuation

RD: lenalidomide, dexamethasone; VD: bortezomib, dexamethasone

Table 8. Dose adjustments in elderly patients with multiple myeloma.

Drug	Initial/standard dose	Reduced dose	Further reduction if required
Dexamethasone ^a	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
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
Bortezomib ^b	1.3 mg/m ² D1, 8, 15, 22 every 28 days	1.0 mg/m ² D1, 8, 15, 22 every 28 days	0.7 mg/m ² D1, 8, 15, 22 every 28 days
Cyclophosphamide	500 mg once weekly	300 mg weekly	200 mg weekly

(Adapted from Palumbo A, Mina R. Management of older adults with multiple myeloma. *Blood Rev* 2013;27:133-42.)

EOD: every other day; EON: every other night; ON: at night

^a Dexamethasone should be commenced at the reduced dose (20 mg once weekly) in patients above the age of 70 years.

^b To consider using bortezomib 1.3 mg/m² twice weekly on D1, 4, 8, 11 every 3 weeks in selected patients who require rapid reduction of paraprotein levels.

- Thalidomide or ixazomib maintenance can be considered as alternatives when lenalidomide is not tolerated (GRADE 2B).
- The SMSG suggests 2 years of maintenance therapy as the standard duration, with consideration of longer duration on a case-by-case basis depending on toxicities (GRADE 2C).

Supplementary material

Appendix S1. Drug toxicity and dose adjustments for induction and maintenance therapy in multiple myeloma.

Ethics statement

Not applicable as no study participants were involved.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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