PROTOCOLS OF CONDUCT

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UPDATES ON THE MANAGEMENT OF MULTIPLE MYELOMA: GUIDELINES BY THE HEMATOLOGY AND BONE MARROW TRANSPLANT UNIT AT HOSPITAL UNIVERSITÁRIO WALTER CANTÍDIO

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ABSTRACT

Multiple Myeloma (MM) is a mature hematological neoplasm characterized by histological infiltration (bone marrow and/or extramedullary plasmacytomas) by clonal plasma cells and the presence of one or more defining events, including anemia, renal impairment, osteolytic lesions, and hypercalcemia. The management of MM has drammaticaly evolved over the past few years. However, new drugs are not available in the Brazilian public health service and treatment is still a challenge, especially in the relapsed/refractory setting. We herein summarize the updates in MM management and make recommendations for care in an optimal scenario and in the Brazilian public health service.

Keywords: Multiple Myeloma. Public Health. Brazil.

INTRODUCTION

Multiple Myeloma (MM) is a mature hematological neoplasm characterized by histological infiltration (bone marrow and/or extramedullary plasmacytomas) by clonal plasma cells and the presence of one or more defining events, including anemia, renal impairment, osteolytic lesions, and hypercalcemia. The production of monoclonal proteins, whether heavy and/or light chain, is very common; however, about 3% of cases present as non-secretory MM.[1]

The presence of bone marrow infiltration by ≥60% clonal plasma cells, a ratio of involved/uninvolved light chain ≥100, and the presence of > 1 focal lesion on magnetic resonance imaging (MRI) larger than 5mm are associated with over 70% progression within 2 years for defining lesions of MM. According to the 2014 consensus of the International Myeloma Working Group (IMWG), these biomarkers should also be considered as MM-defining events.[1]

Care must be taken to differentiate cases of MM from other related plasma cell disorders, as shown in Table 1:

MM: Multiple Myeloma. MGUS: Monoclonal Gammopathy of Undetermined Significance. AL: Light Chain Amyloidosis. AHL: Heavy and Light Chain Amyloidosis. AH: Heavy Chain Amyloidosis. DM: Diabetes Mellitus. *Not all patients meeting the criteria will have POEMS; a temporal relationship between the findings and the absence of other attributable causes is necessary. &There is no established cutoff value; the IMWG recommends using a threshold of 3-4 times the reference value to count as a major criterion.

TABLE 1- Diagnostic criteria for Multiple Myeloma (MM) and other monoclonal gammopathies

Monoclonal Gammopathies	Diagnostic criteria	Progression rate	Main progression events
non-IgM MGUS	**All three criteria must be met:** Serum monoclonal protein <3 g/dL; Clonal plasma cells in bone marrow <10%; Absence of defining lesions for multiple myeloma.	1%/year	MM, solitary plasmacytoma, Amyloidosis (AL, AHL, AH)
IgM MGUS	**All three criteria must be met:** • Monoclonal IgM protein <3 g/dL; • Clonal lymphoplasmacytic cells in bone marrow <10%; • Absence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly or other organ damage that can be attributed to an underlying lymphoproliferative disorder.	1,5%/year	Waldenstrom Macroglobulinemia, Amyloidosis (AL, AHL, AH)
Light-chain MGUS	**All criteria must be met:** • Abnormal kappa/lambda ratio (<0.26 or >1.65); • In addition to the altered ratio, the absolute value of the involved light chain must be elevated; • Absence of monoclonal heavy chain on immunofixation; • Urinary monoclonal protein <500 mg/dL; • Clonal plasma cells in bone marrow <10%; • Absence of AL amyloidosis and defining events for multiple myeloma.	0,3%/year	MM, AL Amyloidosis

Smoldering MM	**Both criteria must be met:** • Serum monoclonal protein (IgG or IgA) ≥3 g/dL, urinary monoclonal protein ≥500 mg/24 h, or clonal plasma cells in bone marrow 10-59%; • Absence of MM-defining events.	5-24%/year according to risk stratification	MM
MM	**Both criteria must be met:**	---	---
	Clonal plasma cells in bone marrow ≥10% or biopsy-proven plasmacytoma.		
	At least one of the defining events for multiple myeloma must be present: • Hypercalcemia (total calcium >11 mg/dL or >1 mg/dL above the normal upper limit); • Renal impairment: creatinine >2 mg/dL or creatinine clearance <40 mL/min; • Anemia: hemoglobin <10 g/dL or decrease in hemoglobin >2 g/dL; • Bone lesions: one or more osteolytic lesions on CT, PET-CT, or X-ray; • Clonal plasma cells in bone marrow ≥60%; • Ratio of involved to uninvolved light chains ≥100, with involved light chain ≥100 mg/L; • More than one focal lesion (≥5 mm) on MRI.		
Plasma cell leukemia	The patient meets the criteria for MM and presents ≥5% plasma cells in peripheral blood.	---	---
Solitary plasmacytoma	**All criteria must be met:** • Biopsy of bone or soft tissue showing infiltration by clonal plasma cells; • Bone marrow without infiltration by clonal plasma cells; • CT and/or MRI without other lesions; • Absence of defining lesions for multiple myeloma.	10% in 3 years	MM
Solitary plasmacytoma with minimal marrow involvement.	**All criteria must be met:** • Biopsy of bone or soft tissue showing infiltration by clonal plasma cells; • Presence of <10% clonal plasma cells in bone marrow; • CT and/or MRI without other lesions; • Absence of MM-defining events.	60% (bone) or 20% (soft tissue) in 3 years	MM

POEMS Syndrome*	**Mandatory criteria:** • Polyneuropathy; • Clonal plasma cell proliferative disorder (almost always lambda).	---	---
	Major criteria (at least one must be present): • Sclerotic bone lesions; • Castleman disease; • Elevated levels of VEGF.&;		
	Minor criteria (at least one must be present): • Organomegaly (hepatomegaly or splenomegaly); • Lymphadenopathy; • Signs of congestion (edema, pleural effusion, or ascites); • Endocrinopathy, except for hypothyroidism and diabetes mellitus (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic); • Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocyanosis, flushing, white nails); • Papilledema; • Thrombocytosis or polycythemia.		
AL Amyloidosis	**All criteria must be met:** • Presence of a systemic syndrome related to amyloid deposition (involvement of the kidneys, liver, heart, gastrointestinal tract, or peripheral nervous system); • Tissue biopsy showing positive Congo red amyloid deposition; • Evidence that the amyloid deposit is composed of light chains (mass spectrometry or immunoelectron microscopy); • Evidence of monoclonal gammopathy (serum or urinary monoclonal protein, abnormal kappa/lambda ratio, clonal plasma cells in bone marrow).	---	Some patients may develop MM.

Adapted from Rajkumar SV et al.[1], 2014; Rajkumar, 2016[2]; and Lakshman et al., 2018[3].

Laboratory and Imaging Work-up

At diagnosis, patients with Multiple Myeloma (MM) should undergo the following tests:

Blood Tests

- Complete blood count with reticulocyte count;
- Peripheral blood smear analysis (to assess the presence of circulating plasma cells);
- Urea, creatinine, sodium, potassium, calcium, magnesium, phosphorus;
- Serum protein electrophoresis and immunofixation;
- Measurement and ratio of free light chains;
- Measurement of immunoglobulins: IgG, IgA, and IgM;
- Albumin, β2-microglobulin, and LDH;
- Fasting glucose and/or HbA1c;
- AST, ALT, GGT, alkaline phosphatase, ESR;
- Serologies for HIV 1 and 2, HTLV 1 and 2, Hepatitis B and C, Chagas disease, and Syphilis;
- Beta-HCG for women of childbearing age;
- Erythrocyte phenotyping (in patients considered for monoclonal anti-CD38 antibody therapy).

Evaluation of Bone Marrow or Other Tissues

- Bone marrow aspirate and biopsy with immunohistochemistry. Send samples for immunophenotyping by flow cytometry to quantify clonal plasma cells, and if available, FISH;
- Biopsy with immunohistochemistry of lesions suspected of plasmacytoma;
- Fat pad biopsy with Congo red staining when amyloidosis is suspected.

Urinary Tests

Urinalysis;

24-hour proteinuria with electrophoresis;

Urinary protein immunofixation when no monoclonal serum component is identified.

Cardiac Evaluation

Electrocardiogram;

Echocardiogram with strain assessment to evaluate signs of cardiac amyloidosis;

NT-pro-BNP and troponin I when AL amyloidosis is suspected.

Imaging Studies

Whole-body CT or MRI or PET-CT;
Chest X-ray (PA and lateral views);
Additional X-rays as clinically indicated.

Risk Stratification

All patients diagnosed with Multiple Myeloma (MM) should be stratified according to the International Staging System, whether in its original version or in the first (R-ISS) or second revision (R2-ISS). Another very useful approach in clinical practice, particularly when FISH testing is not available, is the assessment of functional risk, which identifies patients who are refractory or who experience early progression (within 12 to 18 months) after the initiation of an appropriate first-line treatment[4]. Additionally, the Mayo Clinic group has developed a risk stratification method based solely on cytogenetic abnormalities, referred to as mSMART[5].

TABLE 2- Risk Stratification in Multiple Myeloma

ISS	R-ISS	R2-ISS	Other risk factors
Stage I: Beta-2-microglobulin < 3.5 µg/L and albumin > 3 g/dL; **Stage II:** No criteria for Stage I or III; **Stage III:** Beta-2-microglobulin > 5.5 µg/L.	**Stage I:** ISS-I + normal LDH and absence of t(4;14), t(14;16), and del(17p) by FISH; **Stage II:** No criteria for Stage I or III; **Stage III:** ISS-III + one of the following: • Elevated LDH • High-risk alterations: t(4;14), t(14;16), and del(17p) by FISH.	Additive score: ISS II = 1 point ISS III = 1.5 points Del(17p) = 1 point Elevated LDH = 1 point t(4;14) = 1 point Gain 1q = 0.5 points Risk groups: **Low risk:** 0 points; **Intermediate-low:** 0.5-1 point; Intermediate-high: 1.5-2.5 points; High risk: 3-5 points.	Genetic alterations: • Deletion and mutation of TP53; • Del(1p); Extramedullary disease; Circulating clonal plasma cells in flow cytometry; Plasma cell leukemia or related disorders; High-risk gene expression profile.

Adapted from Gay F et al, 2023[4]

TABLE 3 - Mayo Clinic Risk Stratification for Multiple Myeloma (mSMART).

RISK GROUP	PERCENTAGE OF NEWLY DIAGNOSED MM PATIENTS
Standard risk • Trisomies; • t(11;14); • t(6;14);	60%
High risk • t(4;14); • t(14;16); • t(14;20); • del(17p); • gain(1q); • del(1p); • Double-hit: 2 high risk mutations; • Triple-hit: 3 or more high risk mutations.	40%

INFECTIOUS PROPHYLAXIS

Patients with Multiple Myeloma (MM) are susceptible to infections, particularly pneumococcal infections, due to immunoparesis associated with the disease itself and treatment-related immunosuppression. The period of highest infectious risk occurs during the first three months following diagnosis. Patients who are relapsed/refractory and have undergone multiple lines of treatment also exhibit a significantly increased risk of infection.[6]

Vaccination is crucial for the prevention of infections and should ideally be administered during stages of monoclonal gammopathy prior to the onset of MM (such as Monoclonal Gammopathy of Undetermined Significance, smoldering MM, or solitary plasmacytoma), when immunization efficacy is likely to be higher. In patients diagnosed at the MM stage, vaccines should be administered as soon as possible, preferably 14 days before the initiation of treatment. If treatment has already begun, vaccination should occur only after achieving at least a partial response with recovery of uninvolved immunoglobulins.[6] This text will not cover the topic of post-autologous stem cell transplantation vaccination.

The recommended vaccination schedule includes the following (note that vaccines should be inactivated):

• **Pneumococcal** conjugated vaccine (for example PCV13) followed by Pneumococcal polysaccharide vaccina (PPSV23) at least two months later, and then PPSV23 every five years.

> Note: If the patient has already received PPSV23, a minimum of one year should be waited before administering PCV13.

• **Influenza:** annually (it is also recommended to vaccinate close contacts of the patient).

• **Haemophilus influenzae:** one dose.

• **Recombinant herpes zoster vaccine** (inactivated), if available.

Clinical practices regarding pharmacological prophylaxis vary significantly. In our center, we recommend the use of acyclovir 400 mg every 12 hours daily and sulfamethoxazole-trimethoprim 800+160 mg every 12 hours on Mondays, Wednesdays, and Fridays. Attention should be given to the potential need for dose adjustment in cases of renal dysfunction.

ASSESSMENT OF FRAILTY

All patients diagnosed with Multiple Myeloma (MM) should undergo frailty assessment as recommended by the International Myeloma Working Group (IMWG), which classifies patients into three groups: Fit, Intermediate-fitness, and Frail. This classification is based on age, comorbidities (Charlson comorbidity index), and the ability to

perform basic activities (Katz scale) and instrumental activities (IADL scale). A calculator to facilitate this assessment is available at the following link:http://www.myelomafrailtyscorecalculator.net/Geriatric.aspx.

This frailty assessment is predictive of mortality and treatment-related toxicity, hence dose adjustments are needed according to Table 4. Patients classified as Fit should be referred for eligibility evaluation for autologous stem cell transplantation by the bone marrow transplant team. Patients who are not Fit but were previously functional, whose scores are attributable to active MM, should be reassessed after approximately four cycles in those who have achieved at least a partial response.

TABLE 4. Dose adjustments of antineoplastic drugs according to frailty

DRUG	FIT	INTERMEDIATE FITNESS	FRAIL OR AGE >75
BORTEZOMIB	1,3mg/m^2	1,3mg/m^2	1,0 mg/m^2
DEXAMETHASONE	40mg	40mg 20mg as of cycle 4	20mg
THALIDOMIDE	100mg	100mg	100mg
CYCLOPHOSPHAMIDE	300mg/m^2 (maximum: 500mg/dose)	300mg/m^2 (consider omitting D22) (maximum: 500mg/dose)	300mg/m^2, omit D22 (maximum: 500mg/dose)
MELPHALAN	9mg/m^2	6,75mg/m^2	4,5mg/m^2
LENALIDOMIDE	25mg	15-25mg	10-25mg

First-Line Treatment Selection for Patients Eligible for Stem Cell Transplantation

The treatment of Multiple Myeloma (MM) has significantly improved over the past decades with the emergence of new medications. Recently, quadruplet therapy has shown benefits in terms of measurable residual disease (MRD) and progression-free survival (PFS).[8,9] In an ideal scenario, we recommend the use of the Dara-VRD protocol for four induction cycles, followed by high-dose melphalan and stem cell transplantation, along with two consolidation cycles of Dara-VRD. Maintenance therapy with daratumumab has not demonstrated significant benefits in patients who have already received the drug during induction and consolidation.[10] Therefore, we recommend maintenance therapy with lenalidomide until disease progression or unacceptable toxicity occurs, as it has shown benefits in terms of progression-free survival (PFS) and overall survival (OS).[11,12] Ongoing clinical trials are further evaluating the role of maintenance with anti-CD38 antibodies.[13,14]

Unfortunately, many medications are still not available through the Brazilian Unified Health System (SUS). Thus, among the therapeutic arsenal of the public system, we recommend the VTd regimen as first-line treatment, as it has shown higher rates of very good partial response (VGPR) compared to VCd in a prospective study[15], although without PFS or OS evaluations. In cases of women of childbearing age, significant prior neuropathy (grade 2 or higher), very high thrombotic risk (such as bedridden patients and/or those who have undergone orthopedic surgery), or suspicion of systemic amyloidosis, the VCd regimen should be considered as first-line therapy.

Patients who live very far from our institution may struggle with transportation to the hospital in order to receive weekly doses of bortezomib. Some of them even refuse therapy due to such difficulty. It is

important to contact the social service to explore alternatives to meet this demand. Another option, if available, would be to replace bortezomib with the oral proteasome inhibitor ixazomib, either during induction or maintenance therapy, with the aim of reducing the number of visits the patient must make to the healthcare facility. However, it should not be overlooked that these patients still need to attend the hospital in order to be monitored for toxicities and treatment response.

CYCLES EACH 28 DAYS

TABLE 5 - Summary of VTd and VCd regimens.

VTD	DAYS	VCd	DAYS
BORTEZOMIB 1,3mg/m^2 SC	D1, D8, D15, D22	BORTEZOMIB 1,3mg/m^2 SC	D1, D8, D15, D22
DEXAMETHASONE 40mg VO 1xdia	D1,D8, D15, D22	DEXAMETHASONE 40mg VO 1xdia	D1,D8, D15, D22
THALIDOMIDE* 100mg VO 1xdia	D1 até D28	CYCLOPHOSPHAMIDE 300mg/m^2 IV/PO (maximum: 500mg/dose)	D1, D8, D15, D22

IMPORTANT: Delay the start of the cycle if neutrophils <1000/mm^3 or platelets <70,000/mm^3. If the cycle has already started, delay the dose if neutrophils <750/mm^3 or platelets <30,000/mm^3. If it is necessary to delay 2 doses in a cycle, reduce bortezomib to 1 or 0.7 mg/m^2. **NOTE**: In patients who have not yet achieved at least a partial response and/or whose cytopenias are ascribed to massive bone marrow infiltration, consider proceeding with chemotherapy despite cytopenias and prescribe G-CSF 2-3 times per week and/or transfusion support if needed. **DO NOT FORGET**: *Patients on thalidomide should receive thromboprophylaxis, preferably with enoxaparin 40 mg/day subcutaneously or unfractionated heparin 5000 UI every 12 hours subcutaneously; if unavailable, use aspirin 100 mg/day.

Laboratory tests:

Collect a complete blood count on D1 and D15 of each cycle. Collect creatinine, urea, electrolytes, AST, ALT, bilirubins on D1 of each cycle.

In the case of significant alterations, repeat tests in the following week or sooner according to clinical judgment. If it is necessary to delay a dose, repeat tests in the following week.

Adjustments for renal function:

Bortezomib: Monitor tests weekly if creatinine clearance (CrCl) <20 mL/min;
Cyclophosphamide: If CrCl >20 mL/min, 100% of the dose; if 10-20 mL/min, 75% of the dose; if <10 mL/min, 50% of the dose.

Adjustments for hepatic function:

Bortezomib: If total bilirubin >1.5 times the upper limit of normality (ULN), start with 0.7 mg/m^2 and increase as tolerated;
Cyclophosphamide: Not recommended if AST or ALT >3 times ULN or bilirubin alterations.

In patients eligible for stem cell transplantation (SCT), regimens containing melphalan, such as VMP, should be avoided, particularly prior to the collection of hematopoietic progenitor cells.[16] The selected regimen should be administered for 4-6 cycles, followed by autologous SCT. Patients who do not achieve at least a very good partial response (VGPR) after SCT should undergo an additional 2-4 cycles of consolidation therapy.

Due to the unavailability of lenalidomide in the Brazilian Unified Health System (SUS), maintenance therapy may be performed with thalidomide at a

dose of 100 mg daily, which has demonstrated safety and a benefit in progression-free survival (PFS) in a smaller study.[17] There is evidence of an increased risk of venous and arterial thrombotic events even during the maintenance phase.[11,18] Therefore, aspirin at a dose of 100 mg daily should be prescribed, except in patients with an increased risk of bleeding or those who are already indicated for anticoagulation, such as in recent thrombosis.

In cases of plasma cell leukemia (defined as MM with 5% or more circulating plasma cells) or exuberant extramedullary disease, the VTD-PACE protocol with tandem autologous SCT is one of the most commonly utilized regimens for eligible patients.[5] Tandem SCT appears to be more beneficial in patients with del(17p); however, in many cases, this strategy is extrapolated to other high-risk cytogenetic abnormalities. Nonetheless, not all patients eligible for SCT are suitable for intensified treatment followed by tandem SCT, thus necessitating a more thorough screening from both physical and psychological perspective. Recently, aggressive protocols incorporating new drugs have been described, such as in the OPTIMUM study (4 Dara-VCRd -> bortezomib-intensified autologous SCT -> 18 Dara-VR(d) -> Dara-R until progression).[19]

FIRST-LINE TREATMENT SELECTION FOR PATIENTS INELIGIBLE FOR STEM CELL TRANSPLANTATION

The assessment of eligibility is critical for the management of patients with MM; however, it should not be viewed as a fixed label, especially when functional deterioration is ascribed to disease activity at diagnosis. Consequently, we recommend reevaluating eligibility for autologous SCT after four cycles of chemotherapy in patients who have achieved at least a partial response.

In patients considered intermediate-fitness or frail, we regard the DRd regimen as the first choice due to the outcomes of the MAIA study, which reported a median PFS of 61.9 months and a median overall survival (OS) that has not yet been reached.[20] The VRd regimen also demonstrated favorable results in the SWOG S0777 study[21]; however, a recent real-world retrospective study suggested the superiority of DRd over VRd.[22] Nonetheless, there is currently no randomized clinical trial directly comparing the two regimens, which would be ideal to establish superiority. Therefore, VRd remains an adequate option, particularly for patients with low-risk cytogenetics.[23]

Despite the success of quadruplet therapy in patients eligible for SCT, ineligible patients should undergo meticulous selection for this therapy. Two recent randomized clinical trials have demonstrated benefits in PFS and depth of response with the Isa-VRd regimen.[24,25] Although they excluded patients over 80 years of age, these studies included only ineligible patients with a median age of 72-73 years, using age >65 years or comorbidities as criteria for ineligibility for SCT. The CEPHEUS study is currently underway to investigate the use of Dara-VRd in this context, considering age >70 years or comorbidities as criteria for SCT ineligibility, while allowing for the inclusion of eligible patients under 70 years who refuse SCT. Quadruplet therapy containing carfilzomib should be avoided, even in fit patients, due to evidence of increased mortality related to infections with the use of Dara-KRd, despite the higher rate of negative measurable residual disease (MRD).[26]

Within the therapeutic arsenal of the SUS, the VTd regimen would again be the first choice, followed by VCD and VMP, in that order. Even in patients without planned progenitor cell collection, there is concern regarding the use of melphalan due to the risk of secondary myeloid neoplasms.[23] However, in the context of lack of alternatives, VMP may be an option, particularly in patients with a limited life expectancy, where the risk of secondary neoplasms becomes less relevant.

RESPONSE ASSESSMENT

All patients should undergo treatment response assessment according to the criteria established by the International Myeloma Working Group (IMWG). This process requires serum protein electrophoresis with quantification of the monoclonal peak. If this test becomes negative, serum protein immunofixation and free light chain measurements should be requested. If the monoclonal protein in serum protein electrophoresis is below 0.5 g/dL at diagnosis, the response assessment should be conducted using serum free light chain measurements. In our facility, response assessment is primarily performed through serum tests; however, urinary protein electrophoresis and immunofixation may be requested in selected cases.

TABLE 6- Response assessment to Multiple Myeloma treatment

IMWG RESPONSE CRITERIA	
Progression	**One or more of the following criteria:** An increase of 25% from the lowest confirmed response in one or more of the following criteria: • Serum M-protein (absolute increase must be ≥0.5 g/dL); • Increase in serum M-protein ≥1 g/dL if the lowest M-component was ≥5 g/dL; • Urinary M-protein (absolute increase must be ≥200 mg/24 h); • In patients without measurable levels of serum and urinary M-protein, the difference between the involved and uninvolved free light chain (absolute increase must be >10 mg/dL); • In patients without measurable levels of serum and urinary M-protein and without measurable levels of involved free light chains, the percentage of plasma cells in the bone marrow regardless of baseline status (absolute increase must be ≥10%); • Appearance of new lesion(s), an increase of ≥50% from nadir in the sum of diameters of >1 lesion, or an increase of ≥50% in the longest diameter of a prior lesion >1 cm in the short axis; • An increase of ≥50% in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.
Stable disease	Does not meet the criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Minimal response	• Reduction of ≥25% but ≤49% in serum M-protein and a reduction in urinary M-protein of 50–89%. • In addition to the criteria listed above, if previously present, a reduction of ≥50% in the size (sum of diameters) of soft tissue plasmacytomas is also required.
Partial response	• ≥50% reduction in serum M-protein along with a reduction in urinary M-protein over 24 hours of ≥90% or to <200 mg over 24 hours; • If serum and urinary M-protein are not measurable, a reduction of ≥50% in the difference between involved and uninvolved free light chain levels is required instead of the M-protein criteria; • If serum and urinary M-protein are not measurable, and the serum free light chain test is also not measurable, a reduction of ≥50% in plasma cells is required instead of M-protein, provided that the baseline percentage of plasma cells in the bone marrow was ≥30%. In addition to these criteria, if present at diagnosis, a reduction of ≥50% in the size (sum of diameters) of soft tissue plasmacytomas is also required.
Very good partial response (VGPR)	• Detectable serum and urinary M-protein by immunofixation but not by electrophoresis, or ≥90% reduction in serum M-protein with urinary M-protein levels <100 mg over 24 hours.
Complete response (CR)	Negative immunofixation in serum and urine, disappearance of any soft tissue plasmacytoma, and <5% plasma cells in bone marrow aspirates.
Stringent complete response (sCR)	Complete response as defined above + normal free light chain ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).

Adapted from Kumar S et al, 2016[27]

SECOND-LINE TREATMENT SELECTION IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM)

Clinical relapses of MM, characterized by new onset of defining events, indicate the initiation of a new therapeutic line. Conversely, biochemical relapses can often be monitored with intervals of no more than two months. The indications for treatment in patients with biochemical relapses are as follows[28]:

- Doubling of serum monoclonal protein (MP) within a two-month period, provided the absolute increase is > 0.5 g/dL;
- Absolute increase of serum MP > 1 g/dL;
- Absolute increase of urinary MP > 500 mg/24h;
- Absolute increase of the involved light chain > 20 mg/dL (assuming the K/L ratio is altered) or a relative increase of 25% (whichever is greater).

Historically, the IMWG definition of refractoriness to a specific agent includes cases of progression during treatment or within 60 days following the last dose.[29] Based on these criteria, patients with RRMM should be categorized as either refractory/intolerant or sensitive to lenalidomide. Among patients sensitive to lenalidomide, several meta-analyses identify the DRd regimen as the most effective[30,31], despite the absence of direct comparisons with other triplet regimens. Other options include DKd, Isa-Kd, and for those unable to receive anti-CD38 agents, KRd and ERd. For patients who can still receive bortezomib, DVd, PVd, and VRd can be utilized, although these regimens have shown lower PFS compared to the aforementioned combinations, also lacking direct comparisons.

In patients who are refractory or intolerant to lenalidomide, there are no studies directly comparing two triplet regimens; however, evidence suggests that using a triplet therapy that includes an anti-CD38 agent is preferable.[32] In this context, the Isa-Kd protocol has demonstrated the longest PFS among triplet regimens that do not utilize lenalidomide[33], albeit with results comparable to DKd, making these two regimens the most recommended. Other alternatives include DPd and Isa-Pd, which should be considered particularly in patients with cardiac conditions who cannot use carfilzomib. For patients unable to utilize anti-CD38 agents, KCd or KPd are viable alternatives.[5]

Unfortunately, the SUS only provides the same drugs available for first-line treatment in different combinations for relapsed/refractory disease. Patients who are primarily refractory to a triplet regimen containing bortezomib have no adequate therapy options. Those who have responded and have not progressed after 60 days since their last bortezomib dose may be re-exposed. Given the scarcity of alternatives, a second SCT may be considered for patients relapsing 18 months, ideally 24 months, after the first autograft, based on retrospective data from our institution[34]. Another retrospective study indicated that high-risk cytogenetic patients or those relapsing early after the first SCT have a lower likelihood of response; however, the 18-month cutoff was not significant, and no alternative cutoffs were suggested.[35] For patients who underwent maintenance therapy after the first SCT, a cutoff of 36 months has been proposed.[5] Again, the VMP protocol should be avoided in patients scheduled for progenitor cell collection for a second SCT, although it remains a possible treatment option for ineligible patients.

Cycles each 35 days

TABLE 7- Summary of VMP regimen.

VMP	DAYS
BORTEZOMIB 1,3mg/m^2 SC	D1, D8, D15, D22
MELPHALAN 9mg/m^2/day	D1 until D4
PREDNISONE 60mg/m^2/day	D1 until D4

IMPORTANT: Delay the start of the cycle if neutrophils <1000/mm^3 or platelets <70,000/mm^3. If the cycle has already started, delay the dose if neutrophils <750/mm^3 or platelets <30,000/mm^3. If it is necessary to delay 2 doses in a cycle, reduce bortezomib to 1 or 0.7 mg/m^2. **NOTE**: In patients who have not yet achieved at least a partial response and/or whose cytopenias are ascribed to massive bone marrow infiltration, consider proceeding with chemotherapy despite cytopenias and prescribe G-CSF 2-3 times per week and/or transfusion support if needed.

Laboratorytests:

Collect a complete blood count on D1 and D15 of each cycle. Collect creatinine, urea, electrolytes, AST, ALT, bilirubins on D1 of each cycle.

In the case of significant alterations, repeat tests in the following week or sooner according to clinical judgment. If it is necessary to delay a dose, repeat tests in the following week.

Adjustments for renal function:

Bortezomib: Monitor tests weekly if creatinine clearance (CrCl) <20 mL/min;
Melphalan: If CrCl >50 mL/min, 100% of the dose; if 10-50 mL/min, 75% of the dose; if <10 mL/min, 50% of the dose.

Adjustments for hepatic function:
Bortezomib: If total bilirubin >1.5 times the upper limit of normality (ULN), start with 0.7 mg/m^2 and increase as tolerated;
Melphalan: Consider dose reduction or drug replacement in next cycles if total bilirubin >1,5 ULN or if AST or ALT >3 times ULN

TREATMENT OF RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM) FROM THE THIRD LINE AND BEYOND

The prospective observational study LocoMMotion, which included patients with RRMM who had been exposed to anti-CD38 and had received three or more lines of treatment or who had been double-refractory to an immunomodulator and a proteasome inhibitor, demonstrated a median progression-free survival (PFS) and overall survival (OS) of 4.6 and 12.4 months, respectively.[29] In addition, the MAMMOTH study retrospectively evaluated patients refractory to anti-CD38 therapy and also found markedly poor outcomes, with median PFS and OS of 3.4 and 9.3 months.[36]

In this context, the CAR-T cell therapy targeting B cell maturation antigen (BCMA) ciltacabtagene autoleucel (cilta-cel) stands out as the first choice for eligible patients, achieving a median PFS of 34.9 months and an OS that is yet to be reached after a median follow-up of 33.4 months in the single-arm CARTITUDE-1 study[37], with similar inclusion criteria as in the LocoMMotion study. This result is significantly superior to other treatments investigated in RRMM. The ongoing randomized clinical trial CARTITUDE-4 included patients even in the second line of therapy, with immature data but already demonstrating a PFS benefit of 75.9% with cilta-cel versus 48.6% with standard therapy, with a median follow-up of 15.9 months.[38] The academic Spanish CAR-T product ARI-002 has been studied with a fractionated two-dose scheme and presents encouraging preliminary results, with a PFS of 75.9% after a median follow-up of 12.1 months. At 100 days, 80% of patients achieved at least a very good partial response, and 100% exhibited some degree of response.[39] These results are comparable to those observed with cilta-cel; however, the ARI-002 study included only patients in the third line of treatment or higher who were refractory to the last line, potentially representing a more challenging patient profile. Our center's collaboration with the Spanish group may, in the future, facilitate access to CAR-T therapy for SUS patients at a more feasible cost.

However, there is concern regarding patients with rapidly progressive disease who may not tolerate waiting for the vein-to-vein manufacturing time of CAR-T. In such cases, bridging therapy with talquetamab (a bispecific targeting GPRC5D) to enable CAR-T therapy when the disease is more controlled would be the optimal choice. If CAR-T cell therapy is unavailable, treatment until progression or unacceptable toxicity with talquetamab or BCMA-targeting bispecifics, such as teclistamab and elranatamab, is recommended. However, it is important to note that CAR-T cell therapy becomes less effective in patients who have previously undergone anti-BCMA therapy, with an overall response rate of 60% and a median duration of response of 11.5 months.[40]

Patients in this context who depend on the SUS face even greater limitations in therapeutic options, often lacking any adequate treatment. Exceptions are

cases of more indolent disease that exhibit durable remissions and may be re-exposed to previous treatments. However, many patients succumb between treatment lines, especially if they do not receive appropriate therapy. This phenomenon is termed "attrition" and explains why we should not reserve more effective treatments for subsequent lines, since many patients may not survive long enough to receive them.[41] Since CAR-T cell therapy and bispecifics are approved by ANVISA (Brazilian regulatory agency) for triple class-exposed patients, SUS users often do not even meet the prerequisites to access the most indicated treatments.

PERIPHERAL NEUROPATHY

The incidence of neuropathy associated with bortezomib or thalidomide, of all grades, approaches 70% in studies, with a minority progressing to more advanced grades. There is no evidence for any medication that can prevent chemotherapy-associated neuropathy[42,43]; therefore, early detection is essential, actively questioning the patient at each consultation.

Peripheral neuropathy associated with bortezomib (PNAB) typically occurs early, almost always by the 5th or 6th cycle[44]. Re-exposure to bortezomib in subsequent treatment lines is considered safe, with only 16-39% developing neuropathy. Studies administering bortezomib weekly via subcutaneous injection have shown lower rates of neuropathy compared to administration twice weekly and/or via the intravenous route[42], without compromising clinical outcomes.[45] Weekly administration of bortezomib is preferred, except in the initial cycles when rapid disease control is necessary, such as in cases of moderate to severe renal impairment, given the importance of this drug in reversing renal involvement.[46] The recommendations for bortezomib dose adjustments are outlined in the table below:

TABLE 8 - Recommended dose adjustments for bortezomib-induced peripheral neuropathy

NEUROPATHY SEVERITY	FINDINGS	RECOMMENDATION
Grade 1	Paresthesia or hypo-/areflexia, without pain or interference with function.	No adjustment.
Grade 1 with pain	Same as above + pain.	Reduce to 1mg/m².
Grade 2 without pain	Interference with function, but the patient is able to satisfactorily perform daily activities.	
Grade 2 with pain	Same as above + pain.	Withhold until symptoms resolve and restart with 0,7mg/m².
Grade 3	The patient is not able to satisfactorily perform daily activities.	
Grade 4	Generally mixed (sensory and motor) and the patient is significantly limited in their daily activities.	Stop bortezomib and do not restart.

Adapted from Argyriou AA et al, Blood 2008.[47]

Following the discontinuation of bortezomib, neuropathy typically resolves with a median duration of approximately three months. However, there are reports of patients taking up to two years to improve or, more rarely, remaining with sequelae indefinitely.[47] If there is advanced-grade neuropathy or in cases that do not respond quickly to dose adjustments or discontinuation, the use of duloxetine may be considered, although it has primarily been studied in the context of neurotoxicity induced by platinum-based compounds and taxanes.[43]

Peripheral neuropathy associated with thalidomide (PAT) may occur early when used at a dose of 200 mg/day; however, at the initial recommended dose in our protocol (100 mg/day), PAT generally develops with prolonged use, necessitating increased vigilance for the onset of neuropathy in patients re-exposed to the drug. Given the higher likelihood of irreversible sequelae, any neuropathy that arises after the sixth cycle of treatment should prompt a reduction in the dose of thalidomide to 100 mg on alternate days and, in severe cases, discontinuation and a switch to cyclophosphamide. Until the fifth cycle, sensory neuropathy should initially be managed by adjusting the bortezomib dosage. In refractory cases that impact quality of life, thalidomide doses should be reduced even in the early cycles. Considering the higher incidence of motor neuropathy (muscle weakness, tremors) with thalidomide compared to bortezomib, the emergence of motor neuropathy at any time should lead to a switch from thalidomide to cyclophosphamide.

It is crucial to differentiate neuropathy findings that predate the initiation of treatment to avoid unnecessary dose reductions.

MANAGEMENT OF BONE DISEASE

Patients with precursor monoclonal gammopathies, without defining lesions of multiple myeloma (MM), should undergo bone densitometry to investigate the presence of osteoporosis. In such cases, the use of bisphosphonates is indicated only for the treatment of osteoporosis, aiming to improve bone density in these patients who are at an increased risk of progressing to MM.[48]

Bone disease in MM occurs through various mechanisms. In addition to producing cytokines that stimulate osteoclast activity, clonal plasma cells interact with the bone marrow stromal cells, leading them to do the same. Stromal cells increase the production of RANKL and reduce the production of osteoprotegerin, resulting in exaggerated osteoclast activation. Furthermore, clonal plasma cells secrete dickkopf-1 and sclerostin, which inhibit osteoblast activity.[49] Due to this lack of bone regeneration, alkaline phosphatase levels and bone scintigraphy will not show alterations in MM.

Dental evaluation is essential before initiating bisphosphonate therapy, whether in newly diagnosed MM cases or in monoclonal gammopathies with osteoporosis, to reduce the risk of osteonecrosis of the jaw. An exception is made for patients with hypercalcemia, who require urgent bisphosphonate treatment. All patients on chronic bisphosphonate therapy should receive vitamin D supplementation of 1000 IU/day and calcium carbonate 500 mg every 12 hours, except in cases of hypercalcemia. This dosage may be increased during treatment in cases that progress to hypocalcemia or borderline calcium levels.

The bisphosphonate of choice is zoledronic acid, not only because of its faster infusion, but mainly for its benefit in overall survival. Thus, it should be administered regardless of the presence of bone lesions. Zoledronic acid should be given monthly for at least one year. After this period, if there is at least a VGPR, the frequency may be reduced to every three months, six months, or even discontinued. Discontinuation after one year of use may be considered, especially in patients who have received quadruplet therapy and maintain at least VGPR. The medication should be reinitiated every three months in cases of biochemical relapse, prior to symptomatic disease, in order to prevent skeletal events.[48]

When zoledronic acid is unavailable, pamidronate is an alternative; however, its benefits are primarily established in patients with bone lesions to prevent skeletal events. Denosumab, a monoclonal antibody against RANKL, is particularly useful in patients with severe renal impairment, for whom the use of zoledronic acid is not recommended.[48]

TABLE 9- Dosing and administration of bisphosphonates in Multiple Myeloma.

Baseline creatinine clearance (mL/min)	Zoledronic acid dose	Pamidronate dose
>60	4mg	30mg
50-60	3,5mg	
40-49	3,3mg	
30-39	3,0mg	
<30	Not recommended	
Infusion	Dilute with 100mL saline 0,9% and administer in 15-20min	Dilute with 250mL saline 0,9% and administer in 2h

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REFERENCES

1. Rajkumar SV, Palumbo A, Anderson KC. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-48.
2. Rajkumar SV. Updated diagnostic criteria and staging system for multiple myeloma. Am Soc Clin Oncol Educ Book. 2016:35:e418-23.
3. Lakshman A, Kumar S, Mateos MV, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J. 2018 Jun 12;8(6):59.
4. Gay F, Palumbo A, Lentzsch S. A rational approach to functional high-risk myeloma. Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):433-442.
5. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2024;1-23.
6. Raje NS, Agha M, Abonour R, et al. Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group. Lancet Haematol. 2022;9:143-61.
7. Palumbo A, Anderson K, Blade J, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015 Mar 26;125(13):2068-74.
8. Sonneveld P, Palumbo A, van der Holt B, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024 Jan 25;390(4):301-313.
9. Gay F, Palumbo A, Gallo E, et al. Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone vs Carfilzomib-Lenalidomide-Dexamethasone as pre-transplant induction and

post-transplant consolidation in newly diagnosed multiple myeloma patients. Blood. 2023;142(Supplement 1):4.

10. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 Jul 6;394(10192):29-38.

11. Attal M, Harousseau JL, Leleu X, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012 May 10;366(19):1782-91.

12. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. J Clin Oncol. 2017 Oct 10;35(29):3279-3289.

13. Goldschmidt H, Palumbo A, Chanan-Khan A, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. Lancet Haematol. 2022 Nov;9(11).

14. Krishnan A, Lentzsch S, Kaur I, et al. Phase III study of daratumumab/rhuph20 (nsc-810307) + lenalidomide or lenalidomide as post-autologous stem cell transplant maintenance therapy in patients with multiple myeloma (MM) using minimal residual disease to direct therapy duration (DRAMMATIC study): SWOG S1803. Blood. 2020;136(Supplement 1):21-22.

15. Moreau P, Attal M, Hulin C, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016 May 26;127(21):2569-74.

16. Bik To L, Palumbo A, Kumar S, et al. How I treat patients who mobilize hematopoietic stem cells poorly. Blood. 2011;118(17):4530-4540.

17. Murakami H, Nishimura Y, Kato K, et al. Thalidomide maintenance therapy in Japanese myeloma patients: a multicenter, phase II clinical trial (COMET study). Int J Hematol. 2019 Apr;109(4):409-417.

18. De Stefano V, Azzarà A, Di Renzo N, et al. Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an ad hoc expert panel. Haematologica. 2022 Nov 1;107(11):2536-2547.

19. Kaiser M, Gahrton G, Palumbo A, et al. Diagnosis and initial treatment of transplant-eligible high-risk myeloma patients: A British Society for Haematology/UK Myeloma Society Good Practice Paper. Br J Haematol. 2024;00:1-7.

20. Weisel K, Moreau P, Mateos MV, et al. Daratumumab plus lenalidomide and dexamethasone (D-RD) versus lenalidomide and dexamethasone (RD) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the Phase 3 MAIA study. Hemasphere. 2023 May;7(Suppl):14-15.

21. Durie B, Palumbo A, Dimopoulos M, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017 Feb 4;389(10068):519-527.

22. Gordon LN, Mateos MV, Landgren O, et al. Progression-free survival of daratumumab versus bortezomib triplet combination with lenalidomide and dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma: TAURUS chart review study. Clin Lymphoma Myeloma Leuk. 2024 Jan;24(1):55-63.

23. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022 Aug;97(8):1086-1107.

24. Facon T, Palumbo A, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024 Jun 3. doi: 10.1056/NEJMoa2400712.

25. Leleu X, Facon T, et al. Isatuximab, lenalidomide, dexamethasone, and bortezomib in

transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. Nat Med. 2024 Jun 3. doi: 10.1038/s41591-024-03050-2. Online ahead of print.

26. Mateos MV, Palumbo A, et al. GEM2017FIT trial: Induction therapy with bortezomib-melphalan and prednisone (VMP) followed by lenalidomide and dexamethasone (Rd) versus carfilzomib, lenalidomide, and dexamethasone (KRd) plus/minus daratumumab (D), 18 cycles, followed by consolidation and maintenance therapy with lenalidomide and daratumumab: phase III, multicenter, randomized trial for elderly fit newly diagnosed multiple myeloma (NDMM) patients aged between 65 and 80 years. Blood. 2023;142(Supplement 1):209.

27. Kumar S, Rajkumar SV, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8).

28. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. Haematologica. 2016 Apr;101(4):396-406.

29. Kastritis E, Palumbo A, et al. How I treat relapsed multiple myeloma. Blood. 2022 May 12;139(19):2904-17.

30. van Beurden-Tan CHY, et al. Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma. J Clin Oncol. 2017 Apr 20;35(12):1312-9.

31. Minakata D, Oda Y, et al. Relapsed and refractory multiple myeloma: a systematic review and network meta-analysis of the efficacy of novel therapies. Br J Haematol. 2023 Mar;200(6):694-703.

32. Mohyuddin GR, Palumbo A, et al. A systematic review and network meta-analysis of randomized data on efficacy of novel therapy combinations in patients with lenalidomide-refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2021 Jul;21(7):489-96.

33. Martin T, Palumbo A, et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized Phase 3 study. Blood Cancer J. 2023 May 9;13(1):72.

34. Medeiros AF, Duarte FB. Evaluation of patients with multiple myeloma undergoing the second autologous transplantation of hematopoietic stem cells in a reference hospital in the state of Ceará. Rev Med UFC. 2024;64(1).

35. Abbi KKS, Krishnan A, et al. Second autologous stem cell transplant: an effective therapy for relapsed multiple myeloma. Biol Blood Marrow Transplant. 2015 Mar;21(3):468-72.

36. Mateos MV, Palumbo A, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia. 2022 May;36(5):1371-1376.

37. Martin T, et al. Ciltacabtagene autoleucel, an anti–B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. J Clin Oncol. 2023;41:1265-1274.

38. San-Miguel J, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. N Engl J Med. 2023 Jul 27;389(4):335-347.

39. Oliver-Caldez A, et al. Fractionated initial infusion and booster dose of ARI0002h, a humanized, BCMA-directed CAR T-cell therapy, for patients with relapsed or refractory multiple myeloma (CARTBCMA-HCB-01): a single-arm, multicenter, academic pilot study. Lancet Oncol. 2023 Aug;24(8):913-924.

40. Cohen A, et al. Efficacy and safety of cilta-cel in patients with progressive multiple myeloma after exposure to other BCMA-targeting agents. Blood. 2023 Jan 19;141(3):219-230.

41. Fonseca R, et al. Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. BMC Cancer. 2020 Nov 10;20(1):1087.

42. Richardson PG, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. Leukemia. 2012;26(3):595-608.

43. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol. 2020;38(8):859-871.

44. Richardson PG, et al. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. Br J Haematol. 2009 Mar;144(6):895-903.

45. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk stratification, and management. Am J Hematol. 2024;1-23.

46. Dimopoulos MA, Palumbo A, et al. Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors. Clin Lymphoma Myeloma. 2009;9(4):302-6.

47. Argyriou AA, et al. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. Blood. 2008;112(5):1593-9.

48. Terpos E, et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. Lancet Oncol. 2021;22(3):e119-30.

49. Terpos E, et al. Mechanisms of bone destruction in multiple myeloma. Eur J Cancer Care (Engl). 2017;26(6)