Mexican Consensus of Multiple Myeloma

José A. de la Peña-Celaya¹, Jocelyn Aguilar-Luevano², Luisa Ma. Alcivar-Cedeño¹, José L. Álvarez-Vera¹, Irene Anaya-Cuellar³, Erika Añorve-Hernández⁴, Luara L. Arana-Luna¹, Luis Arteaga-Ortiz⁵, Pamela E. Báez-Islas⁶, Luisa I. Banda-García⁷, Ramón A. Bates-Martín⁸, Dafne Itzel Campa-Monroy⁹, Mariela Cardiel-Silva¹⁰, Ángel de Jesús Castillo-Salas¹, Xóchitl Cota-Range⁶, Guillermo Díaz-Vargas¹¹, M. Eugenia Espitia-Ríos¹, Patricia Estrada-Domínguez¹, Denisse Fermín-Caminero¹, Alinka García-Camacho⁹, Carolina García-Castillo¹², Katheryn B. Garzón-Velásquez¹³, Carlos Gil-Rondero¹⁴, Lidia V. Guerra-Alarcón¹⁵, Ana K. Hernández-Colín¹, Eleazar Hernández-Ruiz¹⁶, Areli E. Hernández-Alcántara¹³, Silvia A. Hernández-Cervantes¹, Wilfrido Herrera-Olivares¹⁷, Gregorio Ignacio-Ibarra¹⁸, Sergio I. Inclán-Alarcón¹⁸, Faustino Leyto-Cruz⁴, Juan P. Macías-Flores¹, Andrea Martínez-de la Vega¹⁹, Mario Alberto Martínez-Ramírez⁷, Jorge Martínez-Corone²⁰, Jesús Emanuel Medina-Cora²¹, Lizeth Meza-Dávalos¹, Leire Montoya-Jiménez¹, Alba Morales-Hernández¹, Elizabeth Morales-López²², Javier de Jesús Morales-Adrián²³, Maricruz Morales-de Azcué¹³, Aldo Mújica-Martínez²⁴, Juan L. Murillo-Cruz¹, Jéssica Nájera-Martínez¹³, Iris Mabel Narváez-Sarmiento¹, Lorena Nava-Villegas¹, Marco A. Nava-Alpide¹, Juan J. Orellana Garibay²⁵, Ma. Teresa Palafox-Zaldívar²⁶, Orlando G. Palma-Moreno¹, Eugenia P. Paredes-Lozano⁸, Ma. Luisa Pedraza-Colín²⁷, Juan M. Pérez-Zúñiga¹, Alejandra B. Pérez-Lizard⁹, Flavio Rojas-Castillejos²⁸, Eduardo Romero-Martínez²⁹, Hilda Romero-Rodelo³⁰, Josué Ruiz-Contreras¹, Azucena Saavedra-González³¹, Erick Saucedo-Montes³², Luis G. Silva-Miche⁹, Karina Silva-Vera³³, Óscar Teomitzi-Sánchez¹, Fredy Tepepa-Flores¹, Yanet Ventura-Enríquez²⁴, Atenas Villela-Peña¹, Shendel P. Vilchis-González², Nidia Zapata-Canto¹³, Pedro A. Zárate-Rodríguez³⁴, and Martha Alvarado-Ibarra^{1*}

¹Servicio de Hematología, Centro Médico Nacional 20 de Noviembre, ISSSTE Ciudad de México; ²Servicio de Hematología, Hospital General Regional N.o 2, IMSS, Ciudad de México; ³Servicio de Hematología, Hospital General Lázaro Cárdenas, ISSSTE, Chihuahua, Chih.; ⁴Servicio de Hematología, Hospital Regional Lic. Adolfo López Mateos, ISSSTE, Ciudad de México; ⁵Servicio de Hematología, Hospital General La Paz, ISSSTE, La Paz, B.C.S.; ⁶Servicio de Hematología, Hospital Ángeles Lomas, Huixquilucan, Edo. Méx.; ⁷Servicio de Hematología, Hospital Regional de Alta Especialidad de Veracruz, Ver.; ⁸Servicio de Hematología, Hospital Regional 1. de Octubre, ISSSTE, Ciudad de México; ⁹Servicio de Hematología, Centro Médico Nacional siglo XXI, IMSS, Ciudad de México; ¹⁰Servicio de Hematología, Hospital General de Zona 1, IMSS, Ciudad de México; ¹¹Servicio de Hematología, Centro Oncológico Estatal ISSEMYM, Toluca, Edo. Méx.; ¹²Servicio de Hematología, Hospital Central Militar, SEDENA, Ciudad de México; ¹³Servicio de Hematología, Instituto Nacional de Cancerología, Ciudad de México; ¹⁴Servicio de Hematología, Hospital Dr. Fernando Ocaranza, ISSSTE, Hermosillo, Son.; ¹⁵Centro Regional de Hemato-oncología, Grupo CREHO, Guatemala, Guatemala; ¹⁶Servicio de Hematología, Hospital Regional Presidente Juárez ISSSTE, Oaxaca de Juárez, Oax.; ¹⁷Servicio de Hematología, Hospital Regional de Puebla, ISSSTE, Puebla, Pue.; ¹⁸Servicio de Hematología, Hospital General Regional 1 "Dr. Carlos Mac Gregor Sanchez Navarro" IMSS, Ciudad de México; ¹⁹Servicio de Hematología Centro Médico ABC, Campos Observatorio, Ciudad de México; ²⁰Servicio de Hematología, Hospital Regional "Valentin Gómez Farias" ISSSTE, Guadalajara, Jal.; ²¹Servicio de Hematología, Hospital Civil de Culiacán, Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Sin.; ²²Servicio de Hematología, Hospital General Regional Orizaba (HGRO), IMSS Orizaba, Ver.; ²³Servicio de Hematología Hospital Regional "Elvia Carrillo Puerto," ISSSTE, Merida, Yuc.; ²⁴Servicio de Hematología, Hospital Naval, Ciudad de México; ²⁵Servicio de Hematología, Hospital Regional de Alta Especialidad "Centenario de la Revolución" ISSSTE, Emiliano Zapata, Mor.; ²⁶Servicio de Hematología, Hospital General Saltillo, ISSSTE, Saltillo, Coah.; ²⁷Servicio de Hematología, Hospital de alta especialidad de Morelia, ISSSTE, Morelia, Mich.; ²⁸Servicio de Hematología, Hospital de Especialidades de Salina Cruz, Salina Cruz, Oax.; ²⁹Servicio de Hematología Clínica Hospital 5 de Diciembre, ISSSTE, Mexicali, B.C.; ³⁰Servicio de Hematología, Hospital Fray Junipero Serra, ISSSTE, Tijuana, B.C.; ³¹Servicio de Hematología, Hospital Regional tipo B de Alta Especialidad Bicentenario de la Independencia, ISSSTE, Tultitlán, Edo. Méx.; ³²Servicio de Hematología Hospital General de Tampico, ISSSTE, Tampico, Tamps.; ³³Servicio de Hematología, Hospital General tipo B, ISSSTE, Tultitlán, Edo. Méx.; ³⁴Servicio de Hematología, Hospital Central Sur de Alta Especialidad de PEMEX, Ciudad de México.

Correspondence:

*Martha Alvarado-Ibarra

E-mail: normoblasto@gmail.com

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Abstract

To identify this increasingly common pathology, known as multiple myeloma (MM), it is necessary to refer to the specific factors that characterize it; to this end, the classic criteria known as CRAB (hyperkalemia, renal failure, anemia, and lytic lesions) are available, in which renal failure is one of the most frequent complications. Recently, three indisputable biomarkers have been described for the diagnostic support for MM, which are: more than 10% of clonal plasma cells in bone marrow or, a biopsy that corroborates the presence of a plasmacytoma, light chain ratio ≥ 100 mg/dL and more than one focal lesion on magnetic resonance imaging. A differential diagnosis for plasma cell leukemia, solitary bone plasmacytoma, and extramedullary plasmacytoma should always be considered. Being this an incurable disease, a lot of research has been done regarding its therapeutic management, whose main objective is the disappearance of plasma cells and the patient clinical improvement. Melphalan was the first drug that showed a benefit in 1958 and afterward, with the addition of a steroid as a second drug, it was possible to improve response rates. Subsequently, different molecules were studied, forming multiple combinations, and achieving better rates of overall survival and progression-free survival. Years later, with the arrival of proteasome inhibitors such as bortezomib, and immunomodulators such as thalidomide and lenalidomide, an important turnaround in the disease has been seen, as deeper responses, more prolonged remissions, and improvement in the quality of life of patients have been achieved. This consensus has the purpose of integrating a group of Mexican specialists and promoting the updating of this pathology.

KEY WORDS: Multiple Myeloma. Response. Transplantation. Maintenance. Gammopathy.

Consenso Mexicano de Mieloma Múltiple

Resumen

Para identificar una patología cada vez más común, conocida como mieloma múltiple, es necesario hacer alusión de los factores específicos que la caracterizan. Para ello existen los clásicos criterios conocidos como CRAB (hipercalcemia, insuficiencia renal, anemia y lesiones líticas), siendo la insuficiencia renal una de sus complicaciones más frecuentes. Recientemente se han descrito tres biomarcadores indiscutibles para el apoyo diagnóstico del mieloma múltiple, que son: más del 10% de células plasmáticas clonales en medula ósea o biopsia que corrobora la presencia de un plasmocitoma, relación de cadenas ligeras ≥ 100 mg/dl y más de una lesión focal en resonancia magnética. Se debe tomar siempre en cuenta el diagnóstico diferencial con leucemia de células plasmáticas, plasmocitoma óseo solitario y plasmocitoma extramedular. Al ser una enfermedad incurable, se ha investigado mucho en cuanto al manejo terapéutico, el cual tiene como objetivo principal la desaparición de las células plasmáticas y la mejoría clínica del paciente. El primer fármaco que demostró algún beneficio fue el melfalán en el año 1958 y posteriormente al adicionar un esteroide como segundo fármaco se logró mejorar las tasas de respuesta. Después se fueron estudiando diferentes moléculas, con las que se han realizado múltiples combinaciones, alcanzando mejores tasas de supervivencia global y supervivencia libre de progresión. Años más tarde, con la llegada de los inhibidores de proteosoma como el bortezomib, así como de los agentes inmunomoduladores como la talidomida y la lenalidomida, se presenta un giro importante en la enfermedad, ya que se logran respuestas más profundas, periodo de remisiones más prolongadas y mejoría en la calidad de vida de los pacientes. Este consenso tiene la finalidad de integrar a un grupo de especialistas mexicanos y promover la actualización de esta patología.

PALABRAS CLAVE: Mieloma múltiple. Respuesta. Trasplante. Mantenimiento. Gammopatía.

Module 1

Classification of monoclonal gammopathies

Monoclonal gammopathies are a group of pathologies derived from post-germinal plasma cells which have recovered their replication capacity; these series of conditions are not necessarily sequential. Their clinical spectrum goes from the asymptomatic presence of a monoclonal protein in serum and urine, to disease states with healthy tissue destruction. The symptoms may be the result of the infiltration of clonal plasma cells and the monoclonal protein secreted, or the interaction of the plasma cell with its microenvironment¹.

Monoclonal gammopathies, their diagnostic criteria and their progression rate are covered in table 1:

There are other entities related to monoclonal gammopathies, which are mentioned in the following table 2.

Monoclonal gammopathy of uncertain significance (MGUS)

MGUS is considered the first step before multiple myeloma (MM), it may be present at 8-10 years before the diagnosis. However, up to 25% of the MM patients never had or were never identified with this alteration³.

The incidence increases with age, being estimated from 3 up to 20% in older than 50 years, and it is higher in men and African-American subjects; it is estimated that the risk of progression to MM is 1%/year⁴.

The conversion process implies several steps, some of which take place simultaneously. Initially the post-germinal center plasma cell must suffer chromosomal alterations, mainly hyperdiploidy, as well as translocations in the immunoglobulin's heavy chain (IgH), this results in the activation of the KRAS oncogene, TP53 inactivation, and genomic instability; at the same time, there is rearrangement of the cellular microenvironment, the plasma cell recovers its proliferative capacity, causing monoclonality⁵.

Prognostic criteria

Nowadays, there are two risk prediction models developed by the Mayo Clinic and by the PHETEMA group, which consider the following elements.

Quiescent or asymptomatic MM

Unknown incidence in our country. In the USA, 0.9 cases per 100,000 inhabitants are reported, out of these, 13.7% evolve to symptomatic MM in subjects older than 67 years⁶ (Table 3).

Diagnostic and prognostic criteria

Criteria for a patient to be considered as ultra-high risk are as follows:

- Plasma cells in bone marrow (BM) higher than 60%⁷.
- Relation of free light chains higher than 100⁸.
- Presence of at least one bone lesion, determined by body magnetic resonance imaging or low dose full body computed tomography (CT)⁸.

These criteria increase the risk of progression to more than 70% at 2 years (Table 4).

Solitary plasmacytoma

Solitary plasmacytoma represents 2-5% of monoclonal gammopathies. It is characterized by the plasma cells extramedullary proliferation in the absence of monoclonality in BM or other signs of target organ damage (CRAB)⁹.

Symptomatology depends on the destruction of the tissue affected by the tumor, a balloon sinuplasty (BSP) presents more frequently in axial skeleton, and an exome sequencing project (ESP) is mostly present in nose and oropharynx. This type of tumor has pathognomonic alterations by imaging; therefore, to integrate a definitive diagnosis, proof of monoclonal CP infiltration by biopsy will be needed¹⁰.

Prognostic criteria

- a. Location and tumor size: presence of a BSP implies a lower Marfan syndrome than that provided by an ESP (36.4% vs. 72.1% at 10 years). A tumor larger than 5 cm confers an unfavorable prognosis¹¹.
- b. Paraprotein and light chains: persistence of monoclonal protein, following radiotherapy, is a risk factor related to MM progression¹¹.

Treatment

At present, radiation is the treatment of choice. The dose to be administered may be 40-50 Gy, but it is variable¹¹. The use of surgery and chemotherapy is more controversial than the previous measures.

Table 1. Diagnostic criteria and progression rate of monoclonal gammopathy

Pathologies	Diagnostic criteria	Progression
Non-IgM MGUS	<ul style="list-style-type: none"> – Serum monoclonal protein < 3 g/dl – Clonal plasma cells < 3% – Absence of a target organ 	1%/year
Smoldering type myeloma	<ul style="list-style-type: none"> – Serum monoclonal protein > 3 g/dl or monoclonal protein in urine > 500 mg/24 h and/or clonal plasma cells 10-60% – Absence of myeloma or amyloidosis defining events (**) 	10%/year
IgM MGUS	<ul style="list-style-type: none"> – IgM Serum monoclonal protein < 3 g/dl – Lymphoplasmacytic infiltration in bone marrow < 10% – Absence of target organ damage 	1-5%/year
Light chain MGUS	<ul style="list-style-type: none"> – Light chain ratio < 0.26 or > 1.65 – Increase of involved light chains (kappa relation > 1.65 and lambda < 0.26) – No heavy chain expression on immunofixation – Absence of target organ damage – Clonal plasma cells < 10% – Monoclonal proteins in urine < 500 mg/24 h 	0-3%/year
Solitary plasmacytoma	<ul style="list-style-type: none"> – Bone lesion or soft-tissue biopsy with evidence of clonal plasma cells – Bone marrow without evidence of plasma cells infiltration – Normal skeletal findings – Absence of target organ damage 	10%/3 years
Solitary plasmacytoma with bone marrow involvement	<ul style="list-style-type: none"> – Biopsy of a bone lesion or in soft tissue with evidence of clonal plasma cells – Bone marrow with < 10% plasma cells – Magnetic resonance or tomography of spine and pelvis without lesions – Absence of target organ damage 	60%/3 years (bone marrow) 20%/3 years (soft tissue)

Hypercalcemia higher than 11 mg/dL, renal failure creatinine clearance lower than 40 ml/min, serum creatinine higher than 2 mg/dL, anemia lower than 10 g/dL, lytic lesions detected by X-ray, tomography, or PET-CT.

Table 2. Other conditions related to monoclonal gammopathy

Causes of monoclonal proteins in other diseases	
Associated to different pathologies	Hematologic <ul style="list-style-type: none"> – Lymphoproliferative syndromes (lymphomas, chronic lymphocytic leukemia, or hairy cell leukemia) – Myelodysplastic syndromes – myeloproliferative (chronic myeloid leukemia, polycythemia vera, myelofibrosis) – Paroxysmal nocturnal hemoglobinuria, pure red cell aplasia
	Autoimmune and immunosuppression <ul style="list-style-type: none"> – Systemic erythematosus lupus, rheumatoid arthritis – Scleroderma, polymyositis, thyroiditis – Solid organ transplantation
	Dermatologic <ul style="list-style-type: none"> – Scleroderma, pyoderma gangrenosum, Xanthogranulomatous
	Viral <ul style="list-style-type: none"> – Hepatitis C and HIV viruses
	Endocrinology <ul style="list-style-type: none"> – Hyperparathyroidism
	Other <ul style="list-style-type: none"> – Pulmonary hemosiderosis, sarcoidosis, and neoplasms
Associated to lymphoplasmacytic proliferation	<ul style="list-style-type: none"> – Amyloidosis – Heavy or light chain disease – Macroglobulinemia/lymphoplasmacytic lymphoma – Plasmacytoma or multiple myeloma (Solitary, extramedullary, or POEMS syndrome)

Table 3. A Risk criteria for MGUS

MGUS risk criteria				Follow-up
Risk factors	Risk	Number of factors	Risk of progression at 20 years	
Mayo clinic model				
Non-IgG isotype M Protein > 1.5 g/dL Altered CL's rel	Low	0	5%	Assessment every 6 months for 2 years, yearly thereafter
	Intermediate	1	21%	The above plus bone marrow aspirate, if paraprotein increases > 25% rule out amyloidosis and CRAB
		2	37%	
		High	3	
PETHEMA model			At 5 years	
Abnormal phenotype		0	2%	
Aneuploidy		1	10%	
		2	46%	

Modified from Maciocio et al., 2016.

Table 4. Risk criteria for quiescent Myeloma

Risk criteria for quiescent myeloma					Follow-up
Risk factors	Number of factors		Risk of progression at 5 years	Median TTP	
Mayo clinic model					
Rel. CL a normal PC in BM > 10% M protein > 3.0 g/dL	Low risk	1	25%	10 years	Yearly assessment if paraprotein is not > 25%
	Intermediate risk	2	51%	5 years	Quarterly assessment during the 1 st year ruling out CRAB
	High risk	3	76%	1.9 years	Bimonthly assessment, consider early treatment
PETHEMA model			At 5 years		
> 95% abnormal CP by flow cytometry/ CPMO Immunoparesis	0		4%	NA	
	1		46%	6 years	
	2		72%	1.9 years	

Modified from Maciocio et al., 2016.

Module 2

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy) syndrome, Castleman disease and Waldenström Macroglobulinemia (WM)

POEMS syndrome

POEMS is a para-neoplastic syndrome that presents with plasma cells dyscrasia, its name is derived from the acronym coined by Dr. Bardwick in 1980, to

describe a patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy monoclonal y, and skin changes. However, this syndrome is not limited to the disorders conforming the acronym, diagnostic criteria have been modified to get to a wider classification, since they frequently also present: papilledema, extravascular overload, sclerotic bone lesions, and thrombocytosis/erythrocytosis (PEST)¹.

Pathophysiology of this entity is scarcely known and vascular endothelial growth factor (VEGF) participation is established; nevertheless, it must be differentiated from gammopathies already described due to variations in

Table 1. Diagnostic criteria for POEMS syndrome

Diagnostic criteria for POEMS syndrome	
Mandatory major criteria	1. Demyelinating polyneuropathy
	2. Monoclonal plasma cell dyscrasia
Other major criteria	3. Castleman disease
	4. Sclerotic bone lesions
	5. VEGF serum increase
Minor criteria	6. Organomegaly
	7. Extravascular hydric overload
	8. Endocrinopathy
	9. Skin changes (hyperpigmentation, hypertrichosis, plethora)
	10. Papilledema
Other symptoms	11. Thrombocytosis/polycythemia
	12. Weight loss, hyperhidrosis, pulmonary hypertension, diarrhea

Modified from Dispenzieri, 2017

their management and prognosis. There are established criteria to differentiate it from other blood dyscrasias² (Table 1). Its epidemiology is not well determined due to the scarce number of cases presented even in reference sites; it is estimated that, in Japan, one of the countries with a higher number of reported cases, there are 0.3 cases/100,000 inhabitants³.

The diagnosis requires a large number of tests to determine the damage or grade of involvement in each organ or system known to be probably affected by the syndrome. A complete clinical history, including a thorough physical and neurological examination with emphasis in menstrual disorders in women, or other disorders of probable endocrine origin is very important. On the other hand, imaging and clinical tests must be performed guided by clinical findings and questioning, in such a way to allow us to determine which criteria are met with the smaller amount of used resources.

From the total signs and symptoms that may occur, the most frequent are: neuropathy, in up to 100% of the cases; peripheral edema, skin hyperpigmentation, thrombocytosis, and plasma cells dyscrasias, these in up to 88% of the cases. There are no other specific predictive models for this entity, but it has been shown that its survival, both as progression free and as

overall, is better than that of other gammopathies (overall survival [OS] at 10 years of up to 79%)⁴.

POEMS syndrome treatment will be determined based on the degree of plasma cells infiltration into the BM. In those cases, where the infiltration is scarce or almost null, radiotherapy is considered the standard treatment, with response rates from 50 to 70%, and a noticeable symptomatology improvement⁵. On the other hand, when there is an important plasma cell dyscrasia component, the treatment of choice should be based on those used in this group of diseases. There is no standard treatment and inconclusive results have been reported with different treatment schemes, based on the use of proteasome inhibitors (PI) in combination with an ImiD, such as thalidomide and lenalidomide, with good response rates⁶. However, hematopoietic stem cells (HSC) transplantation still reports response rates of up to 100% with a disease-free survival (DFS) of 72% at 6 years in a Mayo Clinic series⁴.

The follow-up and response assessment are done based on initially involved organs and the treatment administered; hence, in case of a PI plus IMiD is used, the response assessment points should be at 4 months initially, to be re-evaluated at 6 months (Table 2).

Castleman disease and POEMS syndrome

Castleman disease was initially described in the 50's, specifically in the case of patient with mediastinum nodes, fever and weight loss in those with suspicion of diverse pathologies, such as tuberculosis, which were discarded after the description of plasmacytic infiltration found in such nodes, corresponding to what we know as unicentric Castleman disease⁶.

This disease may be related to several pathologies, both, infectious (human immunodeficiency virus [HIV], and human herpesvirus 8) and autoimmune, and in this case, hematologic. Although it is considered a benign disease, it confers an increase in the risk of lymphoma and other neoplasms.

Regarding its pathophysiology, this will depend on the type of disease, we are facing. In both cases, there is an interleukin (IL)-6 increase, with lymphocytic proliferation resulting in the increase of VEGF stimulating factor, and a hyaline-vascular disease, the difference lies in the relation of the formerly mentioned viruses for the multicentric and almost exclusive IL-6 activity for the unicentric presentation. A Castleman variant may be found, in which there are proliferation and infiltration of plasmacytic cells with IgG or IgA overexpression and restriction of the lambda chains, and this

Table 2. Response criteria for POEMS syndrome

Response criteria			
Parameter	CR	Improvement	Progression
Plasma VEGF	Normal	50% decrease from baseline	50% increase from baseline
Hematologic	Negative immunofixation in serum and urine	50% decrease from monoclonal peak	25% increase from baseline
Ascites/edema	Absent	1 point improvement in CTCAE	1 point worsening in CTCAE
Ventricular systolic pressure. By Eco TT	Normal	Below 40 mmHg	NA
Papilledema	Absent	Absent	Present

VEGF: vascular endothelial growth factor; CTCAE: Common Terminology Criteria for Adverse Events.
Modified from Dispenzieri, 2017.

variant should be considered at the moment of making a differential diagnosis between POEMS and WM. This plasmocytic form has been reported in up to 44% of the multicentric Castleman cases⁷.

Diagnosis should consider both approaches the histopathological and the exclusion one. The approach in patients with Castleman or POEMS should basically include the same tests described for the previous syndrome. Furthermore, autoimmune diseases which may be related to the disease should be ruled out. In the specific case of correlation between Castleman and POEMS, the definition is based on the histopathologic report of the first one, with clinical characteristics of the second; this is the point in which several Castleman disease cases with “singular” characteristics really correspond to a Castleman in the POEMS frame. Neuropathy present in Castleman tends to be milder than that in POEMS and remits partially. There is a lambda chain restriction observed in the lab, but with normal IgM levels, tending more toward to an IgG and IgA polyclonal elevation, which helps to the differentiation between WM and MM¹.

Treatment of Castleman disease is varied, there is no standard treatment and most of the regimes used are off-label. In a meta-analysis published in 2016 steroids-based schemes were found, reporting a 2-year survival of up to 88%; other based on chemotherapy, such as cyclophosphamide, with a 2 year survival of 90%, and schemes with rituximab with survival of up to 100% at 2 years. However, bortezomib, immunomodulators (IMiD), and other chemotherapies have been described and used with similar response rates to those reported with more traditional treatments. IL-6 has become the target of some novel treatments, specifically for the multicentric HIV negative type, with variable response rates⁷.

In the case of a documented relationship between POEMS and Castleman, treatment must be oriented to the resolution of the plasmacytic proliferation, with the use of Pls o IMiD, it is known that this relation, observed in 15-25% of the cases, has a favorable response to those treatments⁸.

The response assessment and follow-up do not vary in comparison with those described for the POEMS syndrome; the second-line treatment will depend on the resources available and on the response to the first-line treatment.

WM

Definition

According to the last WHO review in 2016, WM belongs to the group of mature B cells neoplasms, in the subgroup of lymphoplasmacytic lymphomas. WM is a clinical-pathological entity defined by: BM infiltration, lymphoplasmacytic lymphoma, and the presence of a monoclonal IgM component in serum⁹.

Epidemiology and classification

WM has a global incidence of 3/million person-year and represents, approximately 1-2% of non-Hodgkin lymphomas^{10,11}. Age adjusted incidence is 3.4-7.3/million in men, and 1.7-4.2/million in women, in the population of United States of America and Europe, respectively^{11,12}. Opposite to MM incidence, WM prevalence is higher in Caucasian population than in African-Americans¹³. Mean age at presentation is 63-75 years¹³. There is a strong family predisposition, reporting a risk of up to 20 times higher of developing WM in first-degree family members who are WM

Table 3. Diagnostic evaluation for WM

Diagnostic evaluation
Recommended
<ul style="list-style-type: none"> – Clinical history and physical examination <ul style="list-style-type: none"> • Include a familiar history of WM and other lymphoproliferative diseases – Revision by system (symptoms B -14%), organomegalies, hyperviscosity symptoms, neuropathy, Raynaud disease, rash, peripheral edema, dermal anomalies, dyspnea <ul style="list-style-type: none"> • Include fundoscopy in cases of elevated IgM and suspicion of hyperviscosity syndrome – Lab tests: <ul style="list-style-type: none"> • Complete blood count; • Complete metabolic panel; • Immunoglobulins panel (IgA, IgG, and IgM); • B2-microglobulin; • Viral serology (HIV, HBV, and HCV) – Bone marrow aspirate and bone biopsy. <ul style="list-style-type: none"> • Immunohistochemistry (essential); • Flow cytometry (optional, in case immunohistochemistry is not available); • MYD88 gene mutation test • Biopsy of lymph node, or from other involved lymphoid site – Chest, abdomen and pelvis CT (if clinically indicated, and in all patients considered at treatment initiation)
Optional
<ul style="list-style-type: none"> – Cryoglobulins; – Serum viscosity; – Screening of acquired von Willebrand disease; – 24 h proteinuria; – Serum light chains; – NTproBNP, troponins; – Electromyography (seek advice of a neurologist)

carriers¹⁴. In Mexico, there is a reported incidence of 0.18% of all the hematologic diseases, being 11 times less frequent than in the Caucasian population¹⁵.

Although it is considered an incurable disease, the median DFS has improved from 6 years in the 90's-8 years as from 2000¹⁶.

It is important to differentiate it from the MGUS IgM type, MM, mantle lymphoma (ML), chronic lymphocytic leukemia (CLL), and marginal zone lymphoma (MZL). Infections such as hepatitis, HIV, and several rheumatic diseases also elevate IgM levels. The presence of the MYD88 L265P mutation differentiates WM from other B cell chronic lymphoproliferative diseases¹⁷.

Pathogenesis

There are several abnormalities and genetic mutations, the most common include: del(6q) (50%), immunoglobulin heavy variable somatic hypermutation, t(9;14) (p13;q32) (50%), and trisomy 4 (20%). In WM oncogenesis, somatic mutations in genes MYD88

(> 90%) and chemokine type 4 receptor (CXCR4) (30-35%) play a key role¹⁸.

The gene product of the myeloid differentiation primary response (MYD88) is an adaptative protein (connects extracellular and intracellular signals) of the 4 toll-like receptor and the IL-1R and 2 (IL-2R) receptors. It may be activated directly by these receptors or by interaction of the TIR domain adaptative protein and Bruton Tyrosine Kinase, promoting the activation of the NF-κB pathway. There are several somatic variants, being MYD88 L265P (substitution of leucine by proline in position 265) the most frequent, resulting in a gain of function¹⁹. This mutation is rare or is not present in MGUS-IgM (10-60%), MZL (7%), CLL (3%), and MM (0%)²⁰.

The CXCR4 is a G-protein coupled receptor, which plays an important role in cytokine release and chemotaxis. Mutations in this protein result in permanent activation by stromal-derived factor 1-alpha. Suppression of CXCR4 results in the inhibition of migration and adhesion of WM cells. Somatic mutations of this receptor are found in 27% of patients with MW²¹; CXCR4 S338 mutation has shown inferior responses to ibrutinib²².

Table 4. Diagnostic Criteria for Waldenström macroglobulinemia

Diagnostic criteria for Waldenström macroglobulinemia
IgM monoclonal gammopathy (regardless of the concentration); Bone marrow infiltration by lymphoplasmoblasts; Immunophenotype of M.O: CD5-, CD10-, CD19+, CD20+, CD23-; Rule out other mature lymphocyte pathologies

Modified from Mayo Clin Proc. 2010 Sep; 85(9).

Table 5. Risk stratification according to IPSSWM 2019

Risk stratification according to IPSSMW 2009			
Risk group	Low	Intermediate	High
Risk factors ^a	0-1 (except for age)	Age or 2	≥ 3
OS at 5 years	87%	68%	36%

^aRisk factors: age ≥ 65 years, Hb ≤ 11.5 g/dL, platelets ≤ 100 × 10⁹/L, B2M > 3 mg/dL and IgM > 70 g/L.

Diagnosis

WM diagnosis is based on the histopathological confirmation of BM infiltration by a lymphoplasmacytic lymphoma (presence of small lymphocytes with plasma cells and lymphoplasmacytes) and the detection of an IgM monoclonal component in serum, which must always be confirmed by immunofixation¹⁰. Dutcher's bodies (IgM-containing intranuclear vacuoles) are frequently observed. The lymphoplasmacytic monoclonal population in BM, must express CD19, CD20, CD22, and CD79a in lymphocytes by immunophenotype or immunohistochemistry; CD38 for the plasmacytic component; in addition to the accumulation of B cells with phenotype CD22 (+ dim), CD25 +, CD27 +, and IgM +, which differentiates it from other lymphomas by its negative expression of CD5, CD10, CD11c, or CD103/23. The rest of the diagnostic evaluation is summarized in table 3.

Once recommended tests for a WM diagnose are performed, the disease stage must be classified based on the following criteria (Table 4).

Clinical manifestations

Manifestations may be divided into two large groups: target organ involvement, and IgM paraprotein related symptoms. Target organ involvement include: B symptoms (fever, weight loss, fatigue, and nocturnal diaphoresis), lymphadenopathy, hepatomegaly, and/or BM infiltration. Related symptoms to IgM paraprotein include: systemic amyloidosis, cryoglobulinemia, peripheral neuropathy (20-25% of cases), and symptoms related to hyperviscosity (visual changes, neurological, and cardiovascular compromise, normally occurring when levels are above 30-40 g/dL)²⁴.

Risk stratification and prognostic factors

A multivariate analysis performed on 1511 patients registered in the RFS from January 2000 to December

2014 showed that age, symptoms B, elevated DHL, and hemoglobin (Hb) levels < 11.5 g/dl were factors of poor prognosis. The serum immunoglobulin M level had no prognostic significance; likewise, the sex of the individual did not present prognostic significance.

International Prognostic Scoring System (IPSS) described for WM¹⁰, includes five variables impacting negatively in the prognosis: anemia, thrombocytopenia, beta-2-microglobulin levels, IgM serum concentration, and age (Table 5).

IPSS did not include the HDL serum level and low levels of albumin which have adverse prognostic relevance.

Treatment

Asymptomatic patients (watch-and-wait)

There is not a standardized treatment for the asymptomatic disease. In WMA patients a follow-up with a 3-4 months frequency are recommended, in case of stable disease, the follow up may be extended up to every 6 months. Within the evaluation the following points should be considered: careful physical examination, including fundoscopy (preferably assessed by an ophthalmologist) to assess retinal vein congestion, bleeding or exudates, and papilledema.

Criteria for treatment initiation

Treatment must be initiated in those patients with IgM levels > 60 g/L, constitutive symptoms, symptomatic hepatosplenomegaly or lymphadenopathies, either symptomatic or bulky (> 5 cm), hyperviscosity syndrome, severe neuropathy, systemic amyloidosis or symptomatic cryoglobulinemia²⁵, Hb ≤ 10 mg/dL, and platelets < 100 × 10⁹ ²⁵.

Symptomatic patients

In WM, there is not a standard treatment, the lack of randomized trials between regimes make it difficult to provide recommendations with a evidence level. Treatment options are largely based on the long-term experience and the experts' opinion. Multiagent immunochemotherapy should be preferred over rituximab as monotherapy, since it has shown PR rates of 80% versus rituximab, where response rates are < 50%.

Hyperviscosity is an infrequent manifestation of WM; the most common presentation is nose or gums bleeding. The level of viscosity should always be measured in patients with suspicion of hyperviscosity syndrome, and the therapy of choice is the plasma exchange. A single plasma exchange may normalize viscosity and allow chemotherapy to successfully reduce the tumor mass. An inconvenience of rituximab monotherapy is the slow response time and the transient IgM increase or "flare," which takes place within the 1st and 4th months of treatment in 10-15% of the cases, with a risk of exacerbating neuropathy and the symptomatology associated to hyperviscosity. Besides, caution is required to differentiate an IgM flare from a lack of response²⁶.

Regimes of combined treatment with rituximab have shown a fast reduction of the IgM levels, being used in patients with hepatosplenomegaly or BM significant infiltration and requiring a fast cytoreduction.

The combination of rituximab with cyclophosphamide and dexamethasone showed efficacy in a prospective trial of 72 naive patients, resulting in an ORR of 83%; the progression-free survival (PFS) and OS at 2 years of 67 and 81%, respectively²⁷. In the trial update, the mean time to relapse was 35 months; in relation with the risk groups, the OS at 8 years was 100, 55, and 27% for the groups of low, intermediate, and high risk, respectively²⁸.

In a randomized trial of 64 patients, the use of CHOP versus R-CHOP was compared, where the latter resulted in a higher OR (91% vs. 60%) and PFS at 2 years (78% vs. 47%). Fludarabine has shown a significant response in combination with rituximab (FR), as well as in combination with the latter and cyclophosphamide (Fludarabine, cyclophosphamide, and rituximab [FCR]). FR showed an overall response rate (ORR) and PFS at 2 years of 96.3 and 67%, respectively^{29,30}. FCR reached an ORR and OS at 3 years of 76 and 96%, respectively³¹. The regimes associated to fludarabine are recommended in relapsed/refractory patients due to prolonged cytopenia and the risk

of second neoplasms (10-15%). The combined use of rituximab and bendamustine (BR) showed better results versus R-CHOP in a Phase III clinical trial³², reaching a higher PFS (69.5 months vs. 28.1 months; $p < 0.001$) with a better safety profile.

The use of PI, as in MM, has shown a significant response in patients with WM. In a Phase II trial³³ with 26 patients, the combined use of bortezomib and rituximab reached a minor or better response in 88%, with an IgM decrease in 100% of the patients; the median PFS was not reached, with an estimated OS of 96% at 1 year. The scheme with rituximab and dexamethasone (BRD) has proven efficacy in two studies, reaching an ORR of 90-96%, PFS 40-80%, and an OS of 80-100%. However, the most frequent toxicity was neuropathy, requiring the withdrawal of bortezomib in 8-61% of the patients^{34,35}.

In a Phase III trial in previously treated patients, the use of carfilzomib resulted in an 87.1% ORR, with a lower frequency of neuropathy (3.2%) and to be $\geq$ Grade III. Carfilzomib, as from 20 mg/m² and a scale of 36 mg/m², was received on days 1, 2, 8, and 9 of each cycle; rituximab and dexamethasone on days 2 and 9 of each cycle, and a maintenance treatment every 8 weeks for eight cycles. As overall response, the rate in 31 patients was 87%; 36% reached $\geq$ very good partial response (VGPR) with a mean response time of 2.1 months without peripheral neuropathy > Grade 1. This combination has also been used to treat the relapsed disease³⁶ (Figure 1).

Relapse of refractory disease

The use of rituximab has shown efficacy in relapsed or refractory patients. In a Phase II trial²³ 72 patients were included (34 previously treated), reaching a similar response on treated and untreated patients (51.4 years 52.9%, respectively). The combination of rituximab plus fludarabine or brentuximab has shown better responses with an ORR of 83.3 and 93.8%, respectively³⁹. In a retrospective study³⁰, the scheme FCR showed an ORR and OS at 3 years of 77.2 and 89%, respectively.

PIs have proven efficacy in different trials, initially in studies with bortezomib as monotherapy. In a small study of 10 patients³¹, where they reached an overall response and a major response of 80 and 60%, respectively. In two other studies with a larger population³⁹, bortezomib as monotherapy resulted in overall responses and major responses of 78-85 and 44-48%, respectively. In both studies, the time to reach a response

Figure 1. Dx: diagnosis; WM: waldenström's macroglobulinemia; BMT: bone marrow transplant; HVS: hyperviscosity syndrome; benda-R: bendamustine + rituximab; BDR: bortezomib + dexamethasone + rituximab; CaRD: carfilzomib-lenalidomide-dexamethasone; CDR: carfilzomib-daratumumab-lenalidomide; R: rituximab.

Adapted from Gertz MA.2018²⁶

Figure 2. IgG: immunoglobulin G; Hb: hemoglobin; tto: treatment; CPH: hematopoietic progenitor cells; Cfa: cyclophosphamide.

Adapted from Gertz MA.2018.²⁶

was fast (1.4 and 1.5 months) and variable duration of response, with a mean progression of 6.6 months in one study³⁹ and PFS of 16 months in the other³³. In a more recent, Phase II trial²² bortezomib was evaluated as monotherapy, and in those cases with the lack of response dexamethasone were added to the scheme (20 mg/day for 2 days); the ORR was 43.2%, OS at 2 years 84% and a median PFS of 15.3 months, without differences between the groups in which dexamethasone was or not added.

The combined use of bortezomib with other treatment schemes has improved the depth of the response and PFS. In a prospective study³⁵, BDR showed efficacy, with an ORR and major response of 96 and 83%, respectively; the time to reach a response was fast (1.4 months). In the follow-up of this study⁴⁰, the OR and the major response were 96 and 91%, respectively, with a mean progression of 52 months. However, the most relevant toxicity was bortezomib related neuropathy, requiring the suspension in up to 60% of the patients. Regarding a way to improve neurotoxicity, Ghobrial et al., administered different dose schemes in two similar trials, reaching an ORR and a major response of 81-88 and 51-65%, respectively; peripheral neuropathy was present in 41% grades 1-2 and only 5% grade ≥ 3 ³⁷.

The use of carfilzomib with a low risk of peripheral neuropathy, but a higher risk of cardiotoxicity, has been evaluated in a series of cases ($p = 7$) in combination with dexamethasone in relapsed patients, reaching an overall response and a major response of 100 and 86%, respectively.

The mTOR inhibitor, everolimus, has been used to treat WM in a trial with 60 patients who were treated in relapse or refractory with an ORR of 50% and a clinical benefit rate of 73%. The median response time for patients reaching a PR was 2 months. Median PFS was 21%. Unfortunately, toxicities grade ≥ 3 were observed in 67% of the patients. Everolimus has also been combined with bortezomib and rituximab in a Phase 1-2 trial where six cycles were administered, followed by maintenance with everolimus; 57% of the patients had previous use of bortezomib and 98% of rituximab; however, the OS at 1 year was 89%, the PR rate was 53%, and the median PFS was 21 months³⁸ (Figure 2).

Maintenance

Castillo et al. recruited 182 patients with three treatment schemes: Benda-R, Borte Dexa R, Ciclo, and

Table 6. Response criteria from the International workshop on WM

Response criteria from the international workshop on WM		
Response	Abbreviation	Criteria
Complete response	CR	Normal IgM, disappearance of abnormal protein by immunofixation, adeno and visceromegaly resolution, asymptomatic
Very good partial response	VGPR	Serum IgM decrease $> 90\%$ or size of adeno and visceromegaly reduction. Without new symptoms
Partial response	PR	Serum IgM reduction $> 50\%$ or adeno and visceromegaly reduction. Without new symptoms
Minor response	MR	Serum IgM reduction of $\geq 25\%$ but $< 50\%$. Without new symptoms
Stable disease	SD	IgM $< 25\%$ reduction and $< 25\%$ increase or adenomegaly
Disease progression	PD	IgM increase of $\geq 25\%$ or symptomatology or complication caused by MW

Modified from Blood, 2015.

Dexa-R, followed or not by maintenance with rituximab for symptomatic patients. Patients achieving a longer disease-free survival were those treated with BDR, followed by maintenance with rituximab for $p < 0.001$.

After the treatment administration, the grade of response achieved with the treatment must be assessed, based on criteria described in the following table 6.

Module 3

Myeloma overview

Clinical manifestations

Clinical manifestations of MM may be divided in two:

Those which are secondary to the disease activity and part of the CRAB acronym, and those that are a consequence of a high tumor load, as those related to hyperviscosity or plasmacytomas.

Most patients with a MM final diagnosis arrive to the hematologist after a long way through many different specialties, and after the study of complications such as pathologic fractures, renal failure, and anemia related symptoms. The early reference of these patients to our offices depends on the experience and knowledge of the first contact physician, who must bear in mind the clinical manifestations of the disease to suspect this.

Most frequent data are: anemia (73%), bone pain (52%), fatigue (32%), creatinine increase (48%), hypercalcemia (28%), and weight loss (24%), fever was only present in 0.7% of the cases¹.

Diagnostic criteria

Diagnostic criteria for MGUS, asymptomatic MM, and other gammopathies will be covered specifically in the corresponding section; here, we will only focus on the criteria for MM.

Gammopathies are diseases of complex biology that requires a series of studies to integrate the different diagnoses. The initial diagnostic approach for myeloma should be done based on a clinical suspicion and supported on the following lab and clinical tests.

Clinical component: anemic syndrome, bone pain, lethargy, headache, or any other sign of hyperviscosity syndrome.

- Biochemical component: complete blood count, glucose, creatinine, blood urea nitrogen, globulins, albumin, total proteins, lactic dehydrogenase, alanine aminotransferase, aspartate aminotransferase, uric acid, beta-2 microglobulin, serum calcium; 24 h urine creatinine clearance.
- Assessment of serum immunoglobulins levels.
 - Detection and assessment of the monoclonal component by electrophoresis in serum and/or urine.
 - Immunofixation to determine restrictions of light chains restrictions.
 - Morphological component: BM aspirate and biopsy.
 - Imaging component: metastatic bone series, CAT, and IMR.

Once all the tests are done there would be the possibility to integrate any of the gammopathies diagnoses, specifically for MM, according to the IMWG 2014 review (Table 1).

Staging and prognosis

The first step to stage a disease is to differentiate prognostic from predictive factors. The former refer to factors which provide information about how the disease will evolve; while the latter provide guidance on how feasible is that the disease respond to a given therapeutic intervention². Having clarified this, the clinical and biological factors must be differentiated.

Conventionally, MM had been staged based on the Durie-Salmon classification, which considers clinical

Table 1. International Myeloma Working Group Criteria

Both criteria must be met
<p>Clonal plasma cells > 10% or bone biopsy with involvement or extramedullary plasmacytoma.</p> <p>– One or more of the following defining events:</p> <ul style="list-style-type: none"> • Evidence of target organ damage which may be attributed to a proliferative disorder of plasma cells, specifically: <ul style="list-style-type: none"> • Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL); • Renal failure: creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L; • Anemia: hemoglobin decreases of > 2 g/dL below the lower limit of normal, or hemoglobin < 10 g/dL; • Bone lesions: one or more osteolytic lesions by X-ray, CT, PET-CT; • Clonal plasma cells in bone marrow > 60%; • Alteration in the FLC ratio > 100; • > 1 lytic lesion by IRM (5 mm at least).

Based on the monoclonal component found, the frequency order is: IgG 52%, IgA 21%, light chains 16%, IgD 2%, biclonal 2%, IgM 0.5%, non-secreting 6.5%
Modified from Kyle et al.

Table 2. International Prognostic Index

International prognostic index		
Stage	Criteria	Overall survival
I	Beta-2 microglobulin < 3.5 and serum albumin > 3.5 g/dL	62 months
II	None I or III	44 months
III	Beta-2 microglobulin > 5.5	29 months

Adapted from Moreau et al., 2017.

and biochemical factors, segmenting the disease into three categories (low, intermediate, and high risk) based on the presence of lytic lesions, monoclonal component, Hb, and serum calcium (table to be defined); besides, subdividing the patients into two groups according to their renal function. This system is no longer used due to its low utility and applicability with new imaging techniques³.

Nowadays, the most used is the International System (ISS), which requires two easily accessible biochemical markers and stages de disease in three categories based on beta-2 microglobulin and albumin⁴ (Table 2).

The use of biochemical, molecular, and genetic prognostic factors has changed radically our understanding of myeloma, and therefore, also the way we approach it from diverse points of view.

The reviewed ISS is a system that considers the ISS traditional factors and adds cytogenetic factors⁵.

Table 3. Cytogenetic abnormalities and clinical course

Cytogenetic abnormalities and clinical course	
Cytogenetic abnormality	Determination of the clinical stage
	Multiple myeloma
Trisomies	Good prognosis, standard risk, OS 7-10 years
t(11:14)(q13;q32)	Good prognosis, standard risk, OS 7-10 years
t(6:14)(p21;q32)	Good prognosis, standard risk, OS 7-10 years
t(4:14)(p16;q32)	Intermediate risk, OS 5 years
t(14:16)(q32;q23)	High risk, OS 3 years, relates to a high degree of free light chains and initial renal failure
t(14:20)(q32;q11)	High risk, OS 3 years
Gain (1q21)	Intermediate risk, OS 5 years
Del(17p)	High risk, OS 3 years
Normal	Good prognosis, OS 7-10 years

Modified from Rajkumar, 2016.

Table 5. Revised International Staging system

Cytogenetic risk stratification of the mayo clinic	
Risk group	% of <i>de novo</i> patients with the alteration
Standard risk	75%
Trisomies	
t(11:14)	
t(6:14)	10%
Intermediate risk	
t(4:14)	
Gain (1q)	15%
High risk	
t(14:16)	
t(14:20)	
Del(17p)	

Modified from de Dimitros et al., 2018.

Table 4. International Staging System (ISS)

Stage	Overall survival at 5 years	Progression-free survival at 5 years
ISS-R I	82%	55%
ISS-R II	62%	36%
ISS-R III	40%	24%
Revised international staging system		
Stage		
Stage I		
All the following criteria:		
– Serum albumin $\geq$ 3.5 mg/dL;		
– Serum beta-2 microglobulin < 3.5 mg/dL;		
– No high-risk cytogenetic alterations;		
– Normal serum lactate dehydrogenase		
Stage II		
– Does not meet criteria for Stages I or III		
Stage III		
Both criteria:		
– Serum beta-2 microglobulin > 5.5 mg/dL;		
– High-risk cytogenetic alterations [t (4:14) or Del17p] or elevated LDH		

Modified from Rajkumar, 2016

was only a matter of time to prove their use for myeloma. Initially, karyotype was the tool used for this purpose and was followed by *in situ* hybridization (fluorescence *in situ* hybridization). The panel of alterations must contain, at least, those contained in table 3.

Translocations related to chromosome 14 [t (4:14), t (11:14), t (6:14), t(14:16), and t(14:20)] result in fusion products related the immunoglobulin heavy chain, which in turn stimulate a series of oncogenes that increase the proliferative capacity of the altered clone. The deletion of the short arm of chromosome 17 (Del17p) is related to the loss of the TP53 suppressor gene³.

As mentioned before, a combination of clinical, biochemical, and cytogenetic factors increases the predictive capacity and overall prognosis of these factors, giving place to the ISS revised scheme (Table 4), which is independent from the patient's age and the therapy received previously, providing a better prognostic information with respect to the ISS. The Mayo Clinic has also developed a cytogenetic staging scale that guides us on the prognosis of the newly diagnosed patients (Table 5).

Cytogenetic risk

With the arrival of new technologies, cytogenetic alterations became more relevant in the determination of a prognosis of this disease, those techniques have already proven their usefulness for other hemopathies; hence, it

Module 4

Treatment

MM treatment has radically changed in the past 10 years. The inclusion of new agents and combinations has allowed physicians to design treatments according

to each patient's characteristics and needs; however, the large amount of generated information requires a precise and objective analysis to make decisions in each case. There are several international guidelines which have been developed and updated during the last decade, containing very valuable information, since they provide objective guidance for clinicians in their daily work for a MM patient.

Objectively, we have divided the different therapeutic options by grouping the patients based on: age, physical status, cytogenetic risk, and treatment lines received, to facilitate the making of decisions.

First-line treatment for patients younger than 65 years, good physical performance (fit) and/or candidates for HSC transplantation, standard risk

This group of patients represents a large proportion in medical centers where the diagnostic approach protocol is carried out, while there is a low percentage in reference centers. First-line treatment for these patients must be directed to reach the best possible response before the hematopoietic stem cell transplant (HSCT), this is done through the combination of agents with different mechanisms of action to ensure the coverage of diverse pathological points of the disease, to generate a deep response.

Several studies have shown that a combination of three drugs with different mechanisms of action reaches this goal. In a meta-analysis published by the Brazilian group, in which the treatments available in the scientific literature were stratified, from 2006 to 2016, grouping them into those based in anthracyclines, PI, and IMiD, it was found that those with better response rates were those including IMiD and PIs, and in the last place, those based on anthracyclines. Safety profiles by chosen combination may guide each treatment according to each patient's comorbidities¹.

European and American guidelines reproduce the indication of combining three drugs for this specific group, including regimes with PI, IMiD, and chemotherapy combinations, issuing special considerations for specific groups which will be discussed in other sections. Based on these recommendations, the following guidelines are determined:

- In patients younger than 65, good performance status, and candidates to HSCT, treatment should be initiated with three-drug schemes, including at least one PI/IMiD, possible combinations are summarized in figure 1 and 2.

- After four cycles the disease response should be determined, following the criteria mentioned in the "Response criteria" section.
- Follow guidelines presented in section "HSC autologous transplantation" to request its inclusion in the waiting list for the transplantation program.
- Residual minimal disease has an added value for clinicians in the decision-making regarding the number of cycles de patient must receive.

Follow-up in these patients will be done according to guidelines presented in the "Response criteria and follow-up" section.

At present, there are studies that have analyzed the efficacy of thalidomide containing schemes versus those with cyclophosphamide, showing higher complete response (CR) and strict CR (sCR) rates for the schemes including thalidomide. However, the high incidence of neurologic and thrombotic adverse events when compared to cyclophosphamide, must be considered before indicating it². Special regimes should also be considered for this group of patients, such as those with PI contraindications, in which schemes such as lenalidomide-dexamethasone may be used with good response rates compared to traditionally used schemes, such as melphalan or thalidomide. Schemes used by international consensus for patients requiring intensive chemotherapy (plasma cells leukemia or extramedullary disease) recommend VTD-PACE as an option (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide), however, and due to the high toxicity related to treatment with this scheme, the case of the patient should be discussed and assessed thoroughly before deciding in favor of this therapeutic option³.

Patients over 65 years or in poor physical condition, not candidates for HSCT

Frailty scales have made it possible to unify criteria for the selection of patients who are not transplant candidates. The use of new agents and combinations should be considered in this group of patients, since they have shown an increase in survival, with deeper responses and a better quality of life.

For this reason, in patients who are not HSCT candidates, because of their age or a bad performance status, the following should be considered:

- Use combinations including a PI and an IMiD for at least eight cycles of the selected scheme, the possible combinations are summarized in figure 3.
- Perform disease assessments following guidelines in section "Response criteria."

Figure 1. Modified from Shaji Kumar. Ideal treatment scheme for multiple myeloma patients, according to the transplantation eligibility.

Figure 2. Treatment algorithm for transplant eligible patients.

Adapted from Dingli, et al., 2017⁴.

- After finishing the minimum cycles according to the chosen scheme, continue with the maintenance.

In the same way, as in those candidates for HSCT, the use of alternative schemes can be considered in special cases, such as intolerance to IMiDs or PIs, previous neuropathy, or contraindication by any of the other consultation support services (e.g., heart disease, severe kidney disease, and dementia). In these cases, the use of two-drug regimens will be considered, according to the profile of each patient (Table 1 and 2).

Second-line treatment and progression in candidates and non-candidates to HSCT

Managing relapses in these patients involve a deeper analysis of the disease, the patient, and the response to previous treatment or treatments. This is the section

where factors related to poor prognosis take on greater importance, since they will determine, to a certain extent, which therapy we should choose for our patient. It is worth mentioning that a basic goal of the relapse treatment is to achieve the best possible response, whether or not the patient is a transplant candidate.

Choosing a treatment regimen for a relapse is complicated, since many factors must be assessed, such as: time to relapse, response and depth of response reached with the previous therapy, relapse aggressiveness, and physical performance. For this reason, the selection of a rescue scheme in relapsed patients is crucial since it will impact on the progression-free period, considering that the duration of the responses in subsequent remissions will be less than the first response achieved⁴.

Progression should be treated as soon as identified; table 3 shows the criteria requiring treatment for the patient.

Figure 3. Treatment algorithm for non-eligible transplant patients.
Adapted from Dingli, et al., 2017⁴.

Table 1. Routes of administration, dosage, adverse events, and special considerations for proteasome inhibitors

	Bortezomib	Carfilzomib	Ixazomib
Route of administration	SC	IV	PO
Doses and schemes	1.3 mg/m ² on days 1, 4, 8, and 11 28 days cycles	20/27 mg/m ² on days 1, 2, 8, 9, 15, 16, or 20/70 mg/m ² weekly for 3 weeks 28 days cycles	4 mg on days 1, 8, and 15 28 days cycles
Adverse events to be followed	<ul style="list-style-type: none"> – Peripheral neuropathy – Hypotension – Cardiotoxicity – Lung toxicity – GI toxicity – Thrombocytopenia – Neutropenia 	<ul style="list-style-type: none"> – Cardiac failure – Renal failure – Lung toxicity and dyspnea – Hypertension – Venous thrombosis – Bleeding – Thrombocytopenia – Liver toxicity 	<ul style="list-style-type: none"> – Thrombocytopenia – GI toxicity – Peripheral neuropathy – Rash – Liver toxicity
Management considerations	Monitor platelet count, safe in RI	Watch cardiac and renal function	Reduce dose in case of renal failure

Table 2. Routes of administration, doses, adverse events, and special considerations of IMiD

	Lenalidomide	Pomalidomide	Thalidomide
Route of administration	PO	PO	PO
Doses and schemes	25 mg/day for 21 days and 1 week off (induction) 10 mg/day for maintenance	4 mg/day 21 days and 1 week off	200 mg daily
Adverse events to be followed	<ul style="list-style-type: none"> – Venous thromboembolism – Thrombocytopenia – Neutropenia – Fatigue – <i>Rash</i> – Poor HSC mobilization – Second neoplasms 	<ul style="list-style-type: none"> – Venous thromboembolism – Neutropenia – Fatigue – Liver toxicity – <i>Rash</i> 	<ul style="list-style-type: none"> – Venous thromboembolism – Constipation – Peripheral neuropathy – Orthostatic hypotension – <i>Rash</i> – Bradycardia – Somnolence
Management considerations	Watch the renal function (dose adjustment in treatment with lenalidomide). Prophylaxis for thrombosis according to individual risk factors or myeloma related factors. ASA (81-325 mg/day) or LMWH (enoxaparin 40 mg/day) o warfarin (INR: 2-3).		

Table 3. IMGW criteria for MM progression

IMGW criteria for MM progression		
Non-aggressive relapse		Aggressive relapse
Biochemical	Clinical	Adverse cytogenetic abnormalities: t(4:14), del (17p)
M protein increase	Mild symptoms and mild M protein increase	B2MG elevation or albumin decrease, extramedullary disease, LDH increase
Asymptomatic	Relevant organic involvement	Short duration of achieved response
		Aggressive clinical presentation
		Circulating PCs
		Change of the immunoglobulin clone or isotype or light chain

Modified from Sonneveld et al. 2017.

Table 4. Clinical trials with schemes based on lenalidomide for patients with relapsed/refractory MM

Treatment	Response rates %	RC %	PFS meses	SG meses
ENDEAVOR Kd vs. Vd Dimopoulos, et al., 2016 ⁷	77 vs. 63	13 vs. 6	18.7 vs. 9.4 HR: 0.53	NA vs. 24.3 HR: 0.79
CASTOR DVd vs. Vd Palumbo, et al., 2016 ⁹	84 vs. 63	29 vs. 10	16.7 vs. 7.1 HR: 0.31	NA HR: 0.63

RC : PFS: progression-free survival; SG: global survival RC: HR: hazard ratio; NA: not Apply; Kd: Carfilzomib-Dexametasona ; Vd: Bortezomib-Dexametasona ; DVd: Daratumumab-Bortezomib-Dexametasona .
Modified from: Stewart AK.⁷, Palumbo A et al.⁹

Table 5. Clinical trials with schemes based on lenalidomide for patients with relapsed/refractory MM

Treatment	Response rates %	PFS months	SG months
Pom/Dex (n = 302) Richardson, et al., 2014 ¹⁰	31 vs. 10	4.0 vs. 1.9	12.7 vs. 8.1
Bortezomib + Pom/Dex (n = 559) Richardson, et al., 2019 ¹¹	82 vs. 50	11 vs. 7	NA
Carfilzomib + Pom/Dex (n = 57) Shah, et al., 2015 ¹²	62	10.3	NA (1 año: 67%)
Daratumumab + Pom/Dex (n = 103) Chari, et al., 2017 ¹³	60	8.8	17.5
Ixazomib + Pom/Dex (n = 32) Krishnan, et al., 2018 ¹⁴	48-58		

PFS: progression-free survival; SG: global survival; NA:; Pom/Dex: Pomalidomida/Dexametasona.
Modified from Richardson PG et al.^{11,12}, Shah JJ. et al.¹³, Chari A et al.¹⁴, Krishnan, et al. 2018¹⁵

It is adequate to consider the following to start a treatment:

1. Characteristics of the patient in relapse: the physical performance of the patient must be taken into account, as well as his eligibility for a HSCT. In frail and elderly patients, the schemes will target not only the best possible response but also the least possible toxicity (ref relapse blood). The usable combinations for this group of patients can be those that include PI, IMiD, and alkylating agents, such as melphalan. The IWMG suggests that schemes with known toxicity are to be used with less possible impact (ref IWMG relapse). In patients in good condition their wishes and needs in other areas of life should be taken into account, that is, if the patient is able to go to receive their established intravenous therapy or he/she prefers or needs an oral scheme, always bearing in mind the achievement of the deepest response.
2. Disease characteristics: known risk factors for relapse and poor response to treatment are relevant. Alterations such as del17p could have been absent at the time of diagnosis and could be identified in the evaluation of progression, in the same way; there are patients with standard risk at diagnosis who relapse with high-risk characteristics. (Ref 17 IWMG relapse) It was until recently that value was given to these factors for decision-making; in this way, the use of more aggressive schemes is currently preferred, for those who tolerate it, when one of these data is present; the combination of three drugs, including second generation PIs and second generation IMiDs, is preferred over retreatment with the previous scheme based on the observation of

Figure 4. Schemes recommended for relapsed/refractory patients.
Modified from Stewart AK.⁷, Palumbo A et al.⁹

several phase two studies, in which regimens based on carfilzomib, lenalidomide, or other novel agents were administered to patients with these characteristics.

3. Characteristics of the previous response: retreatment with the previous scheme can be considered as long as the previous response had been a partial response with a duration of at least 18 months, or a free treatment interval of 6-9 months, taking into consideration adverse effects and toxicities secondary to treatment. If the progression occurred during treatment or with duration of < 6 months, the patient should be considered as a high-risk patient and treated according to such group. (ref IWMG relapse) In those cases, where a deep response is not achieved during retreatment, one of the agents used can be titrated before deciding on a complete combination change.
4. Transplant eligibility: those patients who have not undergone HSCT should be treated in seek of a deep response to be brought to this procedure, based on a combination of three drugs. In general, a second treatment scheme and a second transplant are considered in those who have

previously undergone one, and who have had a progression-free survival (PFS) of 18-24 months or more. If patients have not received a consolidation scheme after the first transplantation, it should be considered after the second transplant⁵.

Third and further lines

As treatment lines increase, the chances of response decrease by an average of 5% for each scheme.

Schemes for the third line or later should take into account the same characteristics that were taken in the previous relapse, considering the physical performance of the patient at the second- or third-line of treatment, since they may have had significant deterioration and probably need the support from other areas such as geriatrics, pain management, and palliative care.

Most patients in these circumstances are receiving maintenance therapy at the time of relapse, either based on PIs or IMiDs; therefore, the recommendation for them is the initiation of combinations that include at least one drug that has not been previously used.

Table 1. Response evaluation tests at the induction¹

Test	Monthly	Quarterly	Biannual
Complete blood count	+	+	+
Biochemistry, including calcium, creatinine, total proteins: albumin, globulin	+	+	+
Lactate dehydrogenase	+	+	+
Serum proteins electrophoresis		+	+
24 h urine collection for protein electrophoresis		+	+
Immunoglobulins quantification (Nephelometry)		+	+
Serum and urine immunofixation		+	+
Serum light chains measurement		+	+
Bone radiologic study including spine, pelvis, and skull			+
Bone marrow aspirate and/or biopsy; morphology and immunophenotype			+
Cytogenetic of bone marrow plasma cells (metaphase karyotype and fluorescence <i>in situ</i> hybridization) * biannual *			
Bone scan, CAT, or magnetic resonance if clinically indicated, as in the case of plasmacytoma at diagnosis.			+
PET CT			+ whenever possible

FISH: fluorescent in situ hybridization; CT: computed tomography; MRI: magnetic resonance; PET-CT: positron emission tomography-computed tomography.
Adapted from Rajkumar, et al., 2014¹

Second-generation PI Carfilzomib has shown a good safety and efficacy profile, in a Phase II trial, in patients relapsed or refractory to bortezomib and/or lenalidomide, with ORRs of 50% and OS at 12 months of 60%, with an acceptable safety profiles, at least for patients with a good performance status⁶ (Table 4).

Daratumumab, a monoclonal antibody, was initially used in relapsed patients with multiple prior treatment lines in combination with dexamethasone, with ORRs of up to 26%. After that, it has shown improvement of such response rates when combined with bortezomib or lenalidomide plus dexamethasone, with ORRs of up to 93%. The safety profile of this drug is acceptable, despite the high rate of infusion related reactions, of reactions related to the infusion, which are manageable; it is considered a good option in cases of OI or IMiD refractoriness (ref castor and pollux)^{8,9}.

Pomalidomide, a third-generation IMiD, indicated in lenalidomide refractory patients, has shown to be effective, both in patients with a good performance status, and in frail patients¹⁰. The dosage turns this into a good option for patients who may not or do not want to be submitted to the administration of intravenous or subcutaneous drugs (Table 5)¹⁰.

In Figure 4 are summarized therapeutic schemes for relapse/refractory patients.

Treatment	Response rates %	CR %	PFS Months	OS Months
ASPIRE KRd vs Rd ⁶	87 vs 67	32 vs 9	26.3 vs 16.6 HR: 0.69	48.3 vs 40.4 HR: 0.79
TOURMALINE IxaRd vs Rd ⁹	78 vs 72	14 vs 7	20.6 vs 14.7 HR: 0.74	NA
POLLUX DRd vs Rd ¹⁰	93 vs 76	57 vs 23	44.5 vs 17.5 HR: 0.44	NA vs NA HR: 0.63

Module 5

Response criteria in MM

Disease evaluation is key at the time of establishing the diagnosis, at the third cycle, and at the end of the protocol, with evidence of the prognostic value shown by the PETHEMA-GEM group. Ideally, for such evaluation, the studies included in the following table 1 should be performed, comparatively with the Baseline.

Table 2 summarized International IMWG criteria for response.

It is worth mentioning that any response must be maintained by 6 months at least. A monthly disease follow-up during therapy is suggested, along with the performance of a complete blood count, calcium, and total proteins. The quantification of monoclonal proteins in serum and urine must be performed

Table 2. Treatment response criteria. Multiple myeloma international group

sCR Strict complete response	CR + normal light chains and absence of clonal cells in flow cytometry or immunohistochemistry in BM
CR Complete response	Negative immunofixation in serum and urine, disappearance of plasmacytomas and < 5% BMPC.
VGPR Very Good Partial Response	Monoclonal component detectable in serum and urine by immunofixation, but not in electrophoresis, or reduction of < 90% in the serum component with monoclonal urine component lower than 100 mg/24 h.
PR Partial response	Reduction of the serum monoclonal component of $\geq 50\%$, urine $\geq 90\%$, and/or < 200 mg/24 h, as well as a 50% or higher reduction of the plasmacytomas diameter.
SD Stable disease	Patients not meeting criteria for CR, VGCR, PR, or progressive disease.
Progression	Requires one or more of the following CRAB criteria <ul style="list-style-type: none"> – 1-25% increase versus baseline in: <ul style="list-style-type: none"> • Serum monoclonal component (absolute increase must be ≥ 0.5 g/dl) and/or • Urinary monoclonal component (the absolute increase should be ≥ 200 mg/24 h) and/or • Only in patients without measurable serum and/or urine monoclonal protein: difference between FLC (absolute increase must be > 10%) – Medullary plasmacytosis: the increase must be >10% – Development of new bone lesions or plasmacytomas, or size increase of bone lesions or existing plasmacytomas. – Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l), which is attributable to the plasmacytoma proliferative disorder itself.
Clinical relapse	Requires one or more of the following: Direct indicators of increase of the disease and/or organic (CRAB findings). These are used until progression: <ul style="list-style-type: none"> – Development of new plasmacytomas or bone lesions. – Increased size of existing plasmacytomas or bone lesions. An increase larger than 50% (and at least 1 cm) by serial measurements. – Hypercalcemia (> 11.5 mg/dl or 2.65mmol/l) – Hb decrease > 2 g/dl – Increased creatinine concentration > 2 mg/dl.
Relapse after complete response	One or more of the following: <ul style="list-style-type: none"> – Reappearance of the monoclonal component in urine and/or serum measured by immunofixation or electrophoresis. – Development of medullary plasmacytosis > 5% – Appearance of other signs of progression: new plasmacytomas, osteolytic lesions, or hypercalcemia.

Modified from Munshi et al.²

systematically every 3 months. In patients with heavy chains myeloma the follow-up will be done by electrophoresis in urine and/or serum².

It is possible to issue recommendations for specific myeloma forms. In patients with heavy chains of IgA isotype with an M spike in serum, electrophoretic migration in the beta region, other serum proteins may confound the precise evaluation of the monoclonal component. In those cases, a total IgA by nephelometry has been a useful tool for the quantitative follow-up. Appearance of specific antibodies against IgA-kappa and IgA-lambda may also be used to distinguish between monoclonal and polyclonal IgA, which allows a more precise

assessment. When a patient only has a monoclonal light chain with serum monoclonal protein, but the IFE is negative for IgG, IgA or IgM, the possibility of a monoclonal IgD must be considered. IgD serum quantification and electrophoresis in 24 h urine in patients with IgD myeloma are required. In cases of oligosecretory myeloma, the serum M component below 10 g/l and a urine component below 200 mg/24 h have been established as diagnostic criteria^{3,4}.

In patients with suspicion of relapse treatment should be initiated, only if there are certain clinical or biochemical criteria for relapse.

Table 1. Common phenotype of normal plasma cells

Marker	Expression
CD38	++
CD138	+
CD19	+
CD45	+
CD56	–
cylgκ/cylgλ	Polyclonal
β2microglobulin	+
CD81	+
CD117	–
CD27	+
CD28	–

+: positive expression, ++: intense positive expression, –: negative expression.

Module 6

Usefulness of the flow cytometry in the MM diagnosis

Due to the subjectivity of the morphology and its impossibility to demonstrate clonality, the evolution of flow cytometry has positioned itself in the comprehensive clinical management of MM and other plasma cells alterations both, in a sensitive and specific way, with the aim of characterizing plasma cells, differentiating normal phenotypes (Table 1) from aberrant ones through antibodies panels that have been standardized, allowing the comparison among different diagnostic centers, unifying the information given to

Table 2. EuroFlow panel for plasma cells diagnosis²

Tubes	Markers and fluorochromes							
	PacB	PacO	FITC	PE	PerCP Cy 5.5	PECy7	APC	APC-H7
Tube 1 Diagnosis and clonality	CD45	CD138	CD38	CD56	β2micro	CD19	cylgκ	cylgκ
Tube 2 Prognosis	CD45	CD138	CD38	CD28	CD27	CD19	CD117	CD81

PacO: pacific orange, PacB: pacific blue, PE: phycoerythrin, PECy7: phycoerythrin cyanin 7, PerCPCy5.5: peridinin chlorophyll–protein–cyanin5.5, APC: allophycocyanin, FITC: fluorescein isothiocyanate; APC-H7: allophycocyanin H7.

Table 3. EuroFlow panel for MRD monitoring³

Tubes	Markers and fluorochromes							
	BV421	BV510	FITC	PE	PerCP Cy 5.5	PECy7	APC	APC-H7
Tube 1	CD138	CD27	CD38*	CD56	CD45	CD19	CD117	CD81
Tube 2	CD138	CD27	CD38*	CD56	CD45	CD19	cylgκ	cylgκ

BV421: brilliant violet 421, BV510: brilliant violet 510, PE: phycoerythrin, PECy7, phycocyanin cyanin 7, PerCPCy5.5, peridinin chlorophyll–protein–cyanin5.5, APC, allophycocyanin, FITC, fluorescein isothiocyanate, APC-H7, allophycocyanin H7. *Optional change to CD38-multiepitope in patients with anti-CD38 therapy.

Table 4. Usefulness of plasma cells' markers²

TUBE	Antigen	Plasma cells identification	Aberrant markers	Clonality identification
Common markers	CD38	X	C	
	CD138	X	C	
	CD19	X	C	
	CD45	X		
Tube 1	cylgλ		C	X
	cylgκ		P	X
	CD56		P	
	β2 Micro			
Tube 2	CD27		P	
	CD28		P	
	CD117		P	
	CD81		P	

C: common aberrant markers, P: prognostic markers.

the treating physician¹. The only standardized strategy is that designed by the EuroFlow consortium, which published the panels for diagnosis and prognosis (Table 2), and the monitoring of the minimal residual disease (MRD) (Table 3).

To differentiate the phenotypic alterations in aberrant plasma cells, it is essential to know the antigenic use it defines, which is described in table 4.

Specifications recommended by the NCCN of 2019 to perform a new generation cytometry (NGF) in the MRD monitoring, are the following:

- 1) Sensitivity: 1 in 100,000 events (10^{-5}), acquisition of 10 million cells (10^7) at least.
- 2) The use of operating procedures standardized by EuroFlow for MRD in MM^{3,4}.

Regarding the monitoring specifications for the MRD in MM, according to the experts meeting in 2018, it is recommended to perform this in all patients reaching a CR or a VGPR, according to the International Workgroup of Myeloma (IWGM) criteria⁵.

Module 7

Hematopoietic stem cell transplantation in MM

MM is an incurable disease that makes up 10-13% of hematological neoplasms, the median age at diagnosis is 65-70 years. Thirty years after the work of Powles, Barlogie, and McElwain, it led to the beginning of the concept of high-dose therapy (HDT), followed by an autologous HSC transplantation (AHST). Transplantation remains the standard for the treatment of newly diagnosed MM (NDMM) in young and elderly patients with an adequate performance. The superiority of the procedure was initially approved by the Intergroupe Francophone du Myelome (IFM) and then confirmed by the UK Medical Research Council. Despite its significant and confirmed impact on event-free survival (EFS), several trials failed to show a significant impact on OS. Although it is considered a standard therapy, the procedure is still challenged by inevitable relapses that threaten prolonged remissions¹.

Early AHST has been shown to be superior to the latter option (in terms of relapse), even in the era of new agents. A meta-analysis, where 3829 patients with *de novo* MM who received high doses of chemotherapy with an early AHST compared to standard chemotherapy or late transplantation were analyzed, the results were favorable for early transplantation regarding progression-free survival with hazard ratio (HR) 0.73 (95% 0.56-0.94), although this difference

was not observed in OS with an HR 0.86 (95% confidence intervals [CI] 0.70-1.04)¹.

Transplant-related mortality (TRM) with AHST is very low (1-2%), median PFS is 50-56 months and the expected median SG is 8-10 years. Through a multivariate analysis it was observed that the sCR is an independent predictor for better survivals, HR 0.44 (95% 0.25-0.80)².

AHST indications in MM

AHST in MM remains the consolidation treatment of choice in eligible patients. Since the 90's, better ORRs have been shown, further deepening the RC rate by 15-20%. In addition, better rates of OS and PFS have been achieved in patients undergoing HSCT. In subsequent studies, the greatest benefit of transplantation has been observed in terms of PFS, being more inconsistent in demonstrating this same benefit in terms of SG (Figure 1).

This benefit had been demonstrated with induction schemes based on cytotoxic chemotherapy; however, there was not a clear benefit in the era of novel therapies (IMiDs, Pls, etc.) with which the best global outcomes were achieved¹. Phase III CT results have been published recently, which assessed the benefit of a HSCT in the current therapy scenario (RVD vs. RVD-HSCT), demonstrating a PFS benefit in patients undergoing a HSCT (50 vs. 36 months; $p < 0.001$) in all patient subgroups. Likewise, a better CR was observed (59% vs. 48%; $p = 0.03$) and MRD negativization (79% vs. 65%, $p < 0.001$), with no impact on 4-year OS or TRM³.

Eligibility

There is no consensus on an age limit beyond which a HSCT treatment is questionable, and, as such, this practice varies by institution and country.

Advanced age is no longer an exclusion criterion for determining transplant eligibility. In a Phase II trial, there was no difference in TRM in patients of 60-65 years versus 65-70 years, with a low TRM rate in the two cohorts ($< 1\%$)⁴.

A previous study, in which the median age of the patients was 72 years, concluded that elderly MM patients should not be excluded from transplantation, showing good results with melphalan 140 mg/m².

In a consensus made by the Mayo Clinic, they recommended that, in contrast to strict chronological age limits for eligibility for HSCT, the functional status and comorbidities should be considered for eligibility

Figure 1. Multiple myeloma treatment algorithm.

HSCT: hematopoietic stem cell transplantation; CT: computed tomography; FDG-PET / CT: positron emission tomography / tomography 18F-fluorodeoxyglucose computerized; MRI: magnetic resonance.

for HSCT. They further recommend that the depth of the induction chemotherapy should not dictate transplant eligibility. Both recommendations with a level of evidence III, grade of recommendation B⁵.

The indication of an AHSCT in *de novo* MM or in 1st relapse should be extended to any patient with partial or better response, regardless of the degree of depth reached during induction. It is not necessary to routinely evaluate the MRD; however, it is recommended to evaluate it on any patient who is in sCR before the transplantation to document the depth of the response, as the pre-transplant response has been shown to be a determinant for PFS in these patients⁵.

Comorbidity scales

Some authors recommend using comorbidity scales to assess a patient's eligibility for HSCT. The three most used scales are the HCT Comorbidity Index (HCT-CI), Charlson Comorbidity Index (CCI) and the Pretransplant Assessment of Mortality score; being the last the most used for allogeneic transplantation⁶ (Table 1).

Although there are no defined criteria for the indication of transplantation in the MM patient, there are

increasing studies that reflect that a complete remission should be an important goal for the patient when thinking about a transplant. The depth of response (ideally the spinal and extramedullary negative MRD) correlates with increased PFS and OS in all patient subgroups, including those with high cytogenetic risk.

In a consensus made by IMWG in 2016, it was recommended to initiate intensive chemotherapy (HDT) with a HSCT as the standard therapy for patients eligible for transplantation with NDMM. It contributes to improving the outcome in all prognostic groups. Dual HDT/HSCT combined with bortezomib may improve PFS in patients with t (4; 14) or del (17p), and in those with both abnormalities. Although the results of stratified randomized trials are not yet available, HDT plus double ASCT is recommended for patients with high-risk cytogenetics⁶.

Performing an early transplantation versus a late option has been analyzed in several studies. In times of conventional chemotherapy, the French Group reported, since 1998, the results of both arm, and they were comparable in terms of OS, however, early transplantation was superior in terms of quality of life by reducing the treatment associated toxicity, and

Table 1. Comparison of Charlson Comorbidity Index and Specific comorbidity index for hematopoietic cell transplantation

Comorbidity	Definition	CCI score	HCT-CI definitions	HCT-CI score
Lung disease				
Mild	Dyspnea in moderate activity	1	Dyspnea in moderate activity or DLco and/or FEV1 81-90%	0
Moderate	Dyspnea in light activity	1	Dyspnea in light activity DLco and/or FEV1 66-88%	2
Serious	Dyspnea at rest with oxygen	1	Dyspnea at rest or requires oxygen or DLco and/or FEV1 ≤ 65%	3
Cardiac disease				
General	Congestive heart failure	1-2	Coronary disease, congestive heart failure, IAM LVEF < 50%	1
Arrhythmia	N/A	0	Atrial fibrillation or flutter, sick sinus, ventricular arrhythmias	1 3
Valvular disease	Except mitral valve prolapse	0	Except mitral valve prolapse	
Liver disease				1
Mild	Chronic hepatitis or cirrhosis	1	Chronic hepatitis, bilirubin > 1.5 times or AST/ALT > 2.5 times	
Moderate to severe	Portal hypertension, esophageal varicose veins	3	Cirrhosis or fibrosis or bilirubin > 1.5 times or AST/ALT > 2.5 times	3
Renal disease				0
Mild	Creatinine 2-3 mg/dl	0	Creatinine 1.2-2 mg/dl	
Moderate to Severe	Creatinine >3, dialysis, kidney transplant	2	Cr > 2 mg/dl, dialysis or kidney transplant	2
Other neoplasms				1
Solid tumor	Treated in the last 5 years	2	Treated at any time in the patient's medical history	
Metastatic cancer	Present	6	Not included	N/A
Other comorbidities				
Diabetes	Treatment with insulin and/or oral hypoglycemics	1	Treatment with insulin and/or oral hypoglycemics	1
Cerebrovascular disease	Vascular event, transient ischemic attack	1	Vascular event, transient ischemic attack	1
Rheumatologic	SLE, RA, polymyositis, mixed connective tissue disease.	1	SLE, RA, polymyositis, mixed connective tissue disease	2
Peptic ulcer	Requires treatment	1	Requires treatment	2

increasing the time without symptoms and/or treatment. In more recent trials, transplantation benefit is evident due to the treatment response depth and an increase in PFS (79). Based on these data, it is safe to conclude that an A-HSCT significantly improves overall outcomes, both in first line, and in the rescue scenario; hence, it should continue to be part of the consolidation scheme in patients eligible for transplantation with NDMM (1st line)⁷.

In the era of conventional chemotherapy, tandem HSCT was a therapeutic option that improved global outcomes in terms of PFS and OS, even in patients who did not achieve pre-transplant CR¹. In the age of immunotherapy, the role of tandem transplantation needs to be reassessed. The results of the EMN02/HO95 (RVD) study have recently been published

where significant beneficial impact was shown in terms of CR, OS, and PFS in the tandem transplant arm, including in the subgroup of high cytogenetic risk. On the other hand, the StaMINA trial did not identify this same benefit¹.

Allogeneic HSCT in MM is controversial. Early studies failed to demonstrate a clinical benefit due to an increase in TRM. Subsequently, still in the era of induction schemes based on cytotoxic chemotherapy, tandem transplantation was proposed (autoHSCT followed by reduced intensity alloHSCT), achieving discordant results in the different studies, probably due to heterogeneity in the conditioning schemes, prophylaxis for GVHD and design of clinical trials. In the age of novel therapies, the role of allogeneic transplantation takes place in the scenario of the patient

with post-autoHSCT relapse and within the clinical trial scenario, especially due to the modest activity of grafting against tumor (GvT) in MM (JCO)⁷.

Mobilization

Autologous transplantation in MM faces the problem of reaching an adequate cell dose during the harvest period, since this is one of the diseases considered to be a poor mobilizer; the problem increases when there is the intention to harvest for tandem transplantation. The minimum number of peripheral blood stem cells (PBSC) required for an AHSCT is 2×10^6 CD34+/kg cells; harvests of $< 1 \times 10^6$ /kg associate to a late graft with high transfusion requirements and even permanent graft loss, while $3\text{--}5 \times 10^6$ CD34+/kg cells are ideal⁸.

There are two different strategies for mobilizing HSC from MO to SP, these are: (1) colony-stimulating factors (CSF), and (2) a sequence of chemotherapy followed by CSF.

Colony stimulants

For granulocyte CSF (G-CSF) mobilization, the only products approved are filgrastim and lenograstim. The recommended dose for filgrastim is 10 µg/kg/day SC for 5-7 consecutive days and lenograstim 10 µg/kg/day SC for 4-6 consecutive days. The use of biosimilar G-CSF has equivalent efficacy⁹. The use of pegfilgrastim of 6 and 12 mg SC, single dose, also has favorable evidence in harvest for auto-transplantation, in a meta-analysis pegfilgrastim versus filgrastim were compared, showing increased harvest of CD34 and an earlier harvest day for patients with pegfilgrastim. No difference was found for the number of apheresis performed or on the day of transplant grafting.

It is expected to achieve the ideal number of CD34+ in the first mobilization with the lowest toxicity, so the CD34 number in SP is monitored to select the 1st day of apheresis, being earlier with the use of pegfilgrastim, between days 3-5, and days 5-7 for filgrastim, and between days 10-13 post-chemotherapy for CT+ G-CSF. The ideal day to start the harvest is when it is expected to have >10 CD34+ cells/mcl¹⁰.

If the number of cells collected is inadequate, mobilization with G-CSF can continue for 1-2 days. However, if the collection target is not reached after the third leukapheresis, successful mobilization is unlikely.

The main advantages of CSF mobilization are: relatively low toxicity, predictable leukapheresis time, outpatient administration, and reduced costs

compared to chemo-mobilization. The main disadvantages are variable mobilization failure rates and lower CD34+ cell yields compared to chemo-mobilization. G-CSF mobilization can only be used in patients without additional chemotherapy, for example, in patients with stable remission of the underlying disease. It is estimated that around 20% of MM patients will not be able to achieve an adequate harvest under the G-CSF scheme¹¹.

Mobilization with chemotherapy

The use of chemotherapy in combination with G-CSF is the preferred form of mobilization for all patients who will need a greater decrease in tumor load and/or those with the need to collect a large number of HSC.

The most commonly used dose is cyclophosphamide (CY) 2-4 g/m² also called chemo-mobilization, which has been shown to provide higher number of CD34+ for harvesting. Higher doses of cyclophosphamide have been associated with prolonged neutropenia, antibiotic use, and transfusions.

Another scheme that has proven effectiveness is intermediate doses of cytarabine (ID-AraC) with doses of 1.6 g/m² + G-CSF as a first- or second-line mobilization scheme, which in a retrospective study proved to be more efficient than CY + G-CSF or G-CSF alone, with a median 1-day apheresis compared to two with G-CSF alone, with a median harvest of $20.2 (2.9\text{--}59.4) \times 10^6$ CD34 + /kg with ARA-C versus $5.9 (0\text{--}11) \times 10^6$ CD34+/kg ($p < 0.00001$). Toxicity was higher in the group receiving CT with Grade 3/4 neutropenia in 34% and Grade 3/4 thrombocytopenia in 75%¹¹.

Furthermore, there is high mobilization effectiveness with plerixafor, a CXCR4 antagonist, in combination with G-CSF, which has been shown to be able to harvest $>2 \times 10^6$ CD34/kg in the first collection (OR $\times 4.05$, 95% CI, 1.19-13.83, $p = 0.03$) and 5×10^6 /kg CD34+ in total harvest. (OR = 3.09, 95% CI, 1.04-9.23, $p = 0.04$)¹².

Predictors of suboptimal mobilization

The failure of mobilization is generally defined as the inability to obtain 2×10^6 CD34 + cells/kg in four apheresis sessions. Despite recent advances in PBSC collection strategies, the inability to obtain an adequate cellular dose continues to delay and exclude auto-HCT in suitable transplant candidates. Factors associated with inadequate HSC mobilization in MM patients include: thrombocytopenia, age > 60 years,

Figure 2. Mobilization Prognostic factors. Modified from Wallis et al. CSF-G: Colony stimulating factor; PB: Peripheral blood; CM: Chemomobilization.

extensive treatment course, prior radiation therapy, prior exposure to alkylating agents, and prolonged use of lenalidomide¹³ (Figure 2).

Conditioning

Conditioning scheme

In MM patients undergoing an AHSCT, the standard conditioning is melphalan 200 mg/m². Several studies have been conducted with the aim of finding the best conditioning scheme.

The IFM Group performed a Phase III, open, randomized study, in 2017 to compare melphalan 200 mg/m² versus bortezomib 1 mg/m² for 4 days + melphalan 200 for 1 day; no difference was found in responses, OS, or adverse events; however, the scheme has not been evaluated regarding MRD¹⁴.

In a Phase II study comparing busulfan 130 mg/m²/day for 4 days + melphalan 70 mg/m² for 2 days, an increase in PFS was observed, but with no difference in response rates¹⁵. In 2019, Bashir et al. compared busulfan 32 mg for 4 days + melphalan 140 mg/m² versus melphalan 200 mg/mm² in a Phase II study with

202 patients, in which an EFS of 64.7 versus 43.5 months, respectively (HR 0.53, 95% CI 0.30-0.91, p = 0.022). More non-hematological adverse events Grades 3 and 4 were reported, mainly diarrhea and mucositis, but lower incidence of hepatic veno-occlusive disease¹⁵.

Another scheme evaluated the use of bortezomib (1.3 mg/m² added to BUMEL) in a Phase II study. It showed a 75% VGPR or better, 55% CR at 3 months post-ASCT; however, it will be necessary to perform Phase III studies to be able to compare between V-BuMel and BuMel versus MEL200¹⁶.

The addition of bendamustine 200 m² for 2 days + melphalan 100 mg/m² for 2 days is being explored with promising results in response rates and PFS in the second transplant with unfavorable cytogenetics¹⁷(Figure 3).

Special cases

In the case of extramedullary disease, the use of BEAM as conditioning scheme (dexamethasone with carmustine, etoposide, cytarabine, and melphalan) has been evaluated in retrospective studies, which is typically used as conditioning in patients with lymphoma and may be effective¹⁸.

In patients with renal disease at diagnosis (GFR < 30 ml/min or Cr > 2 mg/dL), a retrospective study with melphalan 140 mg/m² versus Melphalan 200 mg/m² was less toxic with no difference in transplant associated mortality, PFS, OS 87 Badros. Patients over 70 years of age in good condition should not be excluded, because conditioning with melphalan 140 mg/m² is less toxic and equally effective as melphalan 200 mg/m²¹⁹.

So far, the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus confirmed that melphalan 200 mg/m² remains the standard conditioning therapy used outside a clinical trial. Participation in clinical trials with new agents such as conditioning schemes is suggested to continue the search for the best conditioning scheme. Evidence Level I, grade of recommendation A⁵.

Post-transplant maintenance

The aim should be to extend the duration of remission without impacting on the quality of life. Thalidomide produces 7-19% grade 3-4 PPN which leads to the drug suspension hence it is NOT an ideal medicine.

Figure 3. Induction therapy scheme. *If > 70 years or CrCl < 30 ml/min, consider Mel 140 mg/m². aHST: autologous hematopoietic progenitor cell transplantation; Mel: melphalan; CrCl: creatinine clearance. Adapted from Gonsalves et al., 2019⁶

Table 2. Post-transplant maintenance schemes

Maintenance	Treatment of Choice	
Lenalidomide (IA) Thalidomide (AI) Bortezomib (IB)	<ul style="list-style-type: none">– Lenalidomide has a better toxicity profile than thalidomide, which favors its long-term use.– Bortezomib is safer and more effective than thalidomide.– IMiDs alone could be suboptimal in high-risk patients and in patients with renal failure, who may benefit from bortezomib.– Ixazomib reduces the risk of progression or death compared to placebo.– Carfilzomib is safe and effective.	
	<p style="text-align: center;">Duration of therapy</p> <ul style="list-style-type: none">– Lenalidomide: at least 2 years or until tolerated.– Thalidomide: until tolerated.– Bortezomib: 2 years.– Ixazomib: weekly for 2 years.– Carfilzomib: weekly for 1 year. <ul style="list-style-type: none">– There are no randomized studies comparing lenalidomide for 2 years with lenalidomide until progression.– The use of long-term thalidomide is limited due to poor tolerance.– Bortezomib has been administered in clinical trials for up to 2 years.	

Modified from Gay et al.

Bortezomib (HOVON-65/GMMG-HD4 study) significantly reduces the risk of progression (p = 0.04) and death (p = 0.05) compared to thalidomide, but with similar PPN rate (5% vs. 8%). It is suggested that pre-transplant induction and maintenance with

bortezomib significantly reduces SV in patients with del (17p) and FRC.

Lenalidomide is less neurotoxic (four studies demonstrated benefit in maintenance PFS with lenalidomide vs. not giving it) (HR 0.46-0.5) and randomized

studies report an increase in OS (OS at 7 years 62% vs. 50%, HR 0.75 $p = 0.001$), except in patients with high cytogenetic risk, and improvement in PFS. The main toxicity Grade 3-4 is neutropenia (23 vs. 51%) and infections (6-13%), although the second neoplasms are higher (hematological 6.1% vs. 2.8% and solid tumors 7.3 vs. 4.2%)²⁰.

In the TOURMALINE-MM3 study, post-transplant maintenance with ixazomib against placebo was evaluated, a 28% reduction in the risk of progression or death was observed, PFS 26.5 months (95% CI 23.7-33.8) versus 21.3 months (18-24.7); HR 0.72, 95% CI 0.58-0.89²¹; P post-transplant maintenance.

Carfilzomib is safe as 1-year maintenance in NDMM (including patients over 75 years) and leads to a deeper response (50% CR at the end of maintenance, with PFS at 28.1 months and estimated OS at 36m of approximately 70% = 0.0023). There was no increase of second neoplasms with ixazomib: 12 (3%) patients, against 8 (3%) placebo patients; 108 (27%) out of 394 patients in the ixazomib group; and 51 (20%) out of 259 patients in the placebo group experienced adverse events. During treatment, one patient died in the ixazomib group and none in the placebo group²¹.

A summary of the characteristics of both schemes of conditioning is presented in Table 2.

Module 8

Pain and supportive treatments

MM is a disease which from the very early stages manifests with symptoms interfering with the quality of life.

It is important to mention that a MM patient will be affected on the physical, social, emotional, and spiritual spheres, so they require a transdisciplinary approach.

Usually, chemotherapy and radiotherapy may control some of the complications; however, additional treatments must be implemented to improve comfort and quality of life.

Among the main symptoms presented by patients, there is bone pain, neuropathy, anxiety, fatigue, and insomnia, among others¹.

Bone complications

Myeloma-related bone disease is a frequent complication that presents in different grades, from mild osteopenia; it is estimated to be present in 85% of

cases and may go to severe bone lesions which result in pathological fractures and their specific complications. This disease is due to the loss of balance of the osteoclasts-mediated bone resorption and bone formation that is the osteoblasts responsibility. It is known that myeloma cells stimulate osteoclasts due an increased release of ILs, macrophages-colonies stimulating factor, tumor necrosis factor (TNF)-alpha and beta, as well as other molecules, which in turn, stimulate osteoclasts to release several molecules which stimulate the replication of MM cells, closing thereby the vicious circle².

Finally, a lot of importance has been given to a signaling pathway that has proven to be involved in the bone disease of diverse neoplasm pathologies, including myeloma: the RANK-RANKL-OPG pathway. Osteoclasts are derived from hematopoietic precursors, RANKL, a TNF family protein of cytokines which regulates the replication, mobilization, and functioning of these cells, its opposite ligand, osteoprotegerin (OPG) secreted by stromal cells regulates RANKL in turn. An unbalance of the RANKL/OPG relation results in the inappropriate functioning of osteoclasts and altered bone resorption².

Bone disease lesions myeloma related are lytic, may be present in any bone, and are related to a high tumor activity. Conventionally, the diagnosis and determination of these lesions have been made with metastatic bone series, which, despite of being the less costly and available in most of the medical centers, have a big drawback, it is only sensitive to very advanced lesions, considering that among 30 and 50% of the bone may suffer destruction before being detected by this technique³. Low dose computerized tomography is, presently, one of the most widely used tests, its sensitivity and specificity, as well as the relative availability of the equipment needed to perform it, turn this test into one of the better diagnostic options for this complication⁴. Magnetic resonance and PET-CT are highly useful tests for the early detection of lytic lesions, with a high sensitivity, however, they are not available in most medical centers, and require a more complex preparation from the patient to be performed.

Treatment of MM-related bone disease

Treatment of MBD has been determined after the approval of agents used for bone complications in other neoplasms. The management cornerstone is bisphosphonates: pyrophosphate analogs which in

turn inhibit pyrophosphate synthase, inhibiting the proliferation and maturation of osteoclasts, inducing their apoptosis and preventing their fixation to bone. Clodronate, pamidronate, and zoledronic acid are the approved bisphosphonates currently approved for use in MM. Multiple Phase III trials have been carried out comparing activity and benefit of these drugs one-to-one. One of the most recent and large is the one performed by the Medical Research Council of the United Kingdom, called Myeloma IX trial, comparing the use of clodronate versus zoledronic acid, where the latter showed to be more efficacious in decreasing the number of fractures related to lytic lesions, as well as an improvement in the quality of life and even in the OS. Zoledronic acid dosing varies according the group consulted; however, the most commonly used is 4 mg IV every 4 weeks for 2 years⁵.

Bisphosphonates safety profile is acceptable, but there are two very relevant events to be considered primarily:

1. Osteonecrosis of the jaw (ONJ) may occur between 2% and 10% of patients with the use of bisphosphonates. This complication is characterized by the exposure of bone tissue in the oral cavity. Among the risk factors for developing ONJ are dental injuries before the use of the drug, poor dental hygiene, advanced age, and late evolution of myeloma. When this complication occurs, stomatology experts should be consulted, and before this, the patient should be guided to carry out adequate dental hygiene, avoid unnecessary dental procedures, and monitor the oral cavity; if an urgent surgical dental intervention is required, the use of the chosen bisphosphonate should be suspended for up to 90 days before the procedure. If the complication is already established, broad-spectrum antibiotic treatment should be initiated, and the experts should be consulted⁶.
2. Acute renal failure: It can be seen in up to 12% of patients with myeloma and the use of zoledronic acid, since it is eliminated in up to 40% through the kidneys. There are no studies of the use of this drug in patients with severe kidney failure; however, the recommendation is to decrease and adjust the dose of the drug in case of kidney failure.

The recently describe RANKL-OPG guidelines brought a new set of opportunities to find new therapeutic targets. One of the first developments focused on this area was denosumab, a human monoclonal antibody

that binds and inhibits RANKL irreversibly. Its efficacy was proven first in bone metastatic disease in solid tumors, to be directed to EORM later on, where it showed the non-inferiority versus zoledronic acid in the event free survival, defined as a pathological fracture or the need of palliative radiotherapy (EFS 22 vs. 23 months), as well as similar OS. Regarding safety, there was a slight increase in the frequency of osteonecrosis of the jaw in the denosumab group versus zoledronic acid, without statistical significance. The dosage of this monoclonal antibody is administered subcutaneously, with load doses on days 8 and 15 in the first cycle, followed by 120 mg every month, conferring it a good practical and safety profile². Some of the advantages of denosumab are:²

1. Monthly subcutaneous administration.
2. No accumulation in bone.
3. Half-life 26 days.
4. It is cleared by the reticuloendothelial system (it is not necessary to adjust the dose based on the renal function).

Disadvantages:

1. Hypocalcemia.
2. Necrosis of the jaw.

Table 1 summarized dose adjustment of zoledronic acid.

Radiotherapy is still an important tool, in special for the relief of the secondary symptomatology from pathological fractures. It is estimated that 38% of MM patients will receive palliative radiotherapy during their disease. Indications for this therapeutic option are: prevention and treatment of fractures that may not be corrected by surgical means, intense pain, vital organ involvement, extramedullary disease, and palliation of other symptomatology fracture-related. Fractionated doses between 10 and 30 Gy are used, with response rates of up to 76%, at least for pain palliation⁶.

Regardless of the option available in each site, it is important to consider the management of this complication due to its huge impact on the quality of life and the overall experience of the patient with the treatment provided for his neoplastic pathology.

PAIN MANAGEMENT

Cancer pain may be due to tumor progression (lymphatic and vascular obstruction, distention, edema, inflammation, and necrosis). Tumor bone infiltration is the most frequent cause of pain in the hematological patient. The mechanisms causing bone pain are explained by the production of prostaglandin E₂ (PGE₂)

Figure 1. WHO analgesic scheme.

NSAID: Nonsteroidal anti-inflammatory drugs; VAS: Visual analogical scale.

Table 1. Zoledronic acid dose

– Standard dose 4 mg.
– Not recommended if ClCr < 30 ml/minute.
– Patients with mild to moderate RF (ClCr 30-60 ml/minute) recommended dose:
• ClCr > 60 ml/min→4 mg
• ClCr 50-60 ml/min→3.5 mg
• ClCr 40-49 ml/min→3.3 mg
• ClCr 30-39 ml/min→3.0 mg

Table 2. Classification of analgesics

Weak	Strong
Nalbuphine	Sufentanil
Tapentadol	Fentanyl
Tramadol	Buprenorphine
Codein	Hydromorphone
D – propoxyphene	Oxycodone

that sensitizes nociceptors. Bone destruction leads to pathological fractures and perineural invasion. Among hematological diseases, MM has the highest incidence of bone pain, affecting up to 75% of patients².

To reduce bone pain, the most effective way is to control the underlying disease, but sometimes it is necessary to resort to the use of conventional analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant drugs (paracetamol, local anesthetics, steroids, antidepressants, neuromodulators, alpha 2 agonists, and among others). The treatment of pain can be systematized according to what is proposed in the analgesic ladder of the World Health Organization (WHO)³.

To understand pain treatment, it is important to know the classification.

According to its pathophysiology, it is classified as nociceptive (somatic) and neuropathic. Nociceptive pain is caused by the stimulation of Ad and C fibers

by a harmful stimulus on the body tissues; it is a physiological response to aggression. Somatic pain originates from injuries to the skin, muscle, bone, and joint capsules, it is usually well localized. Bone pain falls into this category. Neuropathic pain originates as a direct consequence of injury or disease affecting the central or peripheral nervous system⁴.

With the above, it is also important to mention the analgesia scheme proposed by the WHO (Figure 1).

To evaluate pain intensity there are different scales; however, the easiest is the verbal analogue scale (VAS) or any other unidimensional analog scale to assess pain.

The use of NSAIDs is limited to patients whose kidney function is > 60 ml/min and the recommendation is to use it in a maximum period of 7 consecutive days. For this reason, it is important to mention that the pharmacological management of bone pain in patients with MM is based on opioids.

Table 3. Analgesics used in Renal Failure and adjustment according to GF

Group and drugs	Glomerular filtration (GF) (ml/min/1.73 m ²)			Hemodialysis
	Mild (> 60)	Moderate (30-60)	Severe (< 30)	
Fentanyl	FENTANILO® EFFENTORA® ACTIQ® ABSTRAL® PECFENT® INSTANYL®			Safe with dose reduction Scarcely dialyzable Caution
Buprenorphine	TRANSTEC®			
Tramadol			10-30 ml/min: 200 mg/24 h > 10 ml/min: 50 mg/24 h	Eliminates minimal amounts of tramadol
Prolonged released tramadol				Eliminates minimal amounts of tramadol
Morphine		25% in GF 30-59 ml/min	50% GF 115-29 ml/min and 75% GF > 15 ml/min	Caution and dose adjustment Dialyzable
Prolonged released morphine				
Oxycodone oxycodone/naloxone	OXYCONTIN® TARGIN®		Need to adjust dose in RF Initiate with half (50%) the usual dose and titrate accordingly In case of sever RF, a strict medical surveillance is particularly necessary	
Hydromorphone	JURNISTA®		Need to adjust dose in moderate RF Initiate with a third to a half of the usual dose and adjust as necessary	Turns into a less active metabolite, which is easily eliminated by hemodialysis
Tapentadol retard	YANTIL® PALEXIA®		Not recommended in severe renal failure (GF < 30 ml/min)	
Codeine			Need to adjust dose in moderate RF Initiate with 75% of the usual dose and adjust as needed Not recommended in severe renal failure (GF < 30 ml/min)	
Gabapentin		50-79 ml/min: 600 mg/8 h	30-49 ml/min: 300 mg/8 h 15-29 ml/min: 300 mg/12 h < 15 ml/min: 300 mg/24 h	With caution
Pregabalin		> 60 ml/min: 300 mg/12 h	> 30-59 ml/min: 150 mg/12 h 15-30 ml/min: 150 mg/24 h < 15 ml/min: 75 mg/24 mg	With caution
Paracetamol			< 10 ml/min stagger dose every 8 h	
NSAID			Avoid unnecessary use in RF	
	Allowed		Caution	Contraindicated

This group of drugs may be classified according to their potency as follows as shown in table 2.

Morphine is considered the gold standard of opioids and their potency is determined according to it⁷.

It is suggested to initiate pain management with weak opioids and to adjust the dose, however, is pain is very intense treatment could start with a strong opioid to control pain and adjust the dose as necessary.

Figure 2. Objective of the psychological interventions according to the different phases of the disease.

Recommended initial doses for pain management are the following:

Nalbuphine: 10-20 mg every 3-6 h. Maximum dose 160 mg/24 h⁸.

Tapentadol: 50-100 mg every 6 h. Maximum dose 500-600 mg/24 h⁹.

Tramadol: 1-3 mg/kg. Initial dose 25 mg. Maintenance dose 50-100 mg every 6 h. Maximum dose 600 mg/24 h. Adjusted dose based on renal function: 200 mg/24 h maximum⁸.

Morphine: 10-15 mg/12 h (opioid naive patients) and 20-30 mg/12 h (patients previously exposed to opioids). Initial dose 5 mg/4 h. In patients with mild-to-moderate renal failure it is necessary to adjust the dose to 25-50% of the baseline dose¹⁰.

Oxycodone: 5 mg/4 h. (1 mg oxycodone= 2 mg morphine). It is safer to use in patients with renal failure¹¹.

Buprenorphine: 0.3-0.6 mg/6-8 h. Maximum dose 140 mcg/h (3,360 mcg/24 h).

Fentanyl: 0.04 mcg/kg as initial dose and 0.5-1 mcg/kg/h for maintenance⁹.

It is important to point out the dual action of opioids such as tramadol and tapentadol⁹.

Table 3 shows the dose adjustments for analgesics based on the renal function for a safe use in MM patients.

Once pharmacological pain management has begun, or if there is no favorable response or inadequate pharmacological resources, it is suggested to refer the patient to a palliative care clinic for transdisciplinary symptom management.

Neuropathic pain: origin, clinical manifestations, and treatment

MM is a disease with a very high symptom load and may condition the patient to present neuropathy and neuropathic pain, which presents different characteristics in the perception and reference by the patient versus bone pain.

Table 4. Mucositis according to WHO classification

Grade	Mucositis according to WHO
0	No lesion
1	Painless pink mucosa with abundant saliva
2	Erythema, small ulcers, swallowing are maintained
3	Extensive ulcers, edematous gums, thick saliva, swallowing of liquids, pain, and difficulty speaking
4	Very extensive ulcers, bleeding gums, infections, no production of saliva makes swallowing impossible, very severe pain

Characteristics of neuropathic pain include: paresthesia, dysesthesias, burning pain, impaired sensitivity to touch, muscle contraction, and skin disorders such as hyperesthesia, hypoesthesia, and paresthesia. Location: hands and feet. It is accompanied by alterations of the autonomic nervous system, muscular atrophy, loss of strength, atrophy of the distal muscles, orthostatic hypotension, bradycardia, and hypotension¹¹.

Neuropathic pain treatment in MM patients

There are several therapeutic guidelines to treat neuropathic pain, drugs commonly prescribed are: tricyclic antidepressants, serotonin reuptake inhibitors, anticonvulsants, and opioids¹¹.

First-line treatment.

– Tricyclic antidepressants.

Amitriptyline: 25-150 mg/24 h.

Nortriptyline: 25-150 mg/24 h.

– Selective norepinephrine and serotonin reuptake inhibitors.

Duloxetine: 30 mg/24 h-60 mg/12 h.

Venlafaxine: 375-225 mg/24 h.

– α_2 -d calcium channel blockers.

– Pregabalin in low doses, to reduce side effects such as drowsiness, dizziness, and nausea.

Initial doses of 25-75 mg every 24 h increasing the dose of 150 mg, 300 mg, up to a maximum dose of 600 mg/day divided into two doses.

- Gabapentin: the initial dose is 300 mg/d, increased by 300 mg every 3-7 days, up to doses of 900-3,600 mg/d at 8-h intervals. The most frequent, moderate, and normally well-tolerated side effects are drowsiness, dizziness, headache, and diarrhea.
- Lidocaine patch 5% (700 mg): place the patch on the affected area for 12 h, the maximum dose is three patches.

Second-line: opioids

- Tramadol has two mechanisms of action, binding to opioid receptors and inhibition of reuptake of norepinephrine and serotonin, this second effect is the most potent. Dose of 50-600 mg/24 h divided into three doses.
- Tapentadol: 50 mg twice a day, titrating up to a maximum dose of 250 mg twice a day, with a maximum dose of 700 mg a day. The standard dose is 50 mg every 6-8 h, with a maximum dose of 400 mg/d.
- Potent opioids: use oxycodone has good results in the treatment of neuropathic pain, initial dose 5-10 mg/12 h.
- Morphine sulfate: start with low doses of 15-30 mg in 24 h¹².

Supportive measures:

The following support measures are recommended:

In general, these patients have difficulty performing activities of daily living, so they benefit from rehabilitation exercises and physical therapy.

As support for the prevention of opioid-induced constipation: fiber and liquid intake, as well as laxatives, hydration, and drug adjustments¹.

Due to the great variety of causal and contributing factors in the pathogenesis of neuropathy, there is no satisfactory single treatment for this entity. Relief from this manifestation can be one of the most difficult problems faced by doctors and patients. Genetic differences in pain pathways seem to explain why different types of drugs that selectively inhibit specific pathways may be effective in some patients, but not in others.

Chemotherapy-induced neurotoxicity

Neurotoxicity is common in cancer patients, whether caused by the disease or the treatment. It frequently involves different structures of the nervous system, such as peripheral sensory nerves, that frequently are the most affected and produce pain. Pain intensity

depends on its type and accumulation, besides being dose-dependent. It is more frequent in patients with pre-existing neuropathy. Symptoms will depend on the fibers involved, however, the most common presents with alterations of temperature perception and pain, the condition is usually symmetrical, similar to the distribution of diabetic neuropathy, in glove and sock, and mainly affecting feet¹³.

Besides treatment previously mentioned, management of chemotherapy-induced neuropathy will benefit with the use of Vitamin E at doses of 200-400 mg every 12 h¹⁴.

Management of other MM symptoms

Unfortunately, there are more symptoms affecting MM patients. Within the early stages of the disease, the symptoms that most affect quality of life are pain and psycho-affective symptoms, such as anxiety and depression. In more advanced stages, extreme fatigue and mucositis have been reported, mainly in the case of management with melphalan and cyclophosphamide¹⁴.

Mucositis

Mucositis is defined as a side effect to chemotherapy or radiotherapy and it is characterized by:

- Erythematous areas.
- Ulcerative lesions of the oral mucosa causing pain and feeding limitations.
- This is one of the most common side effects in the cancer treatment, about 40% of the patients will develop mucositis, depending on the chemotherapy agent used¹⁸.

According to their classification, the following scale may be used as shown in table 4.

Non-pharmacological measures

Promote oral hygiene using non-abrasive agents: *Aloe vera*, honey, bicarbonate, and chamomile; these agents promote healing, slow the evolution of the lesion, prevent the progression of advanced stages, due to its properties for the production of saliva, anti-inflammatories, antioxidants, and antibiotics¹⁵.

Pharmacological therapy

Some of the drugs used against mucositis are: Mucosal protective drugs, benzydamine, calcium

phosphate, chlorhexidine, cryotherapy, growth factors, laser therapy, and oral hygiene¹.

Mouthwashes: cytoprotective drugs combined with local anesthetics and antihistamines; they form a protective plaque on the mucosa, increasing the secretion of prostaglandin E₂; and promote tissue repair with anti-inflammatory and analgesic properties¹⁶.

The following master formula is recommended:

- Lidocaine 1% 5 ml.
- Aluminum and magnesium hydroxide 30 ml.
- Diphenhydramine or chlorpheniramine syrup 30 ml¹⁶.

Benzylamine: decreases the severity of the injury and painful symptoms.

Calcium phosphate or chlorhexidine rinses: decrease injury and pain, thus improving food intake.

Cryotherapy: causes vasoconstriction reducing the size of the lesion, as well as reducing painful symptoms.

Fatigue

Similarly, to understand treatment of fatigue it is necessary to know its causes, which in MM turn out to be multifactorial and are usually associated to insomnia. Being fatigued and unable to sleep has a high impact on patients' quality of life and mood indexes¹⁶.

Fatigue is defined as a symptom that can be derived from the disease or its treatments, negatively impacting the quality of life of patients. The clinical manifestations of fatigue include low energy levels, feeling weak or lethargic, reduced concentration and memory impairment, abrupt mood changes, irritability and emotional lability, dizziness, disorientation, dyspnea, insomnia, altered libido, and loss of appetite¹⁶.

The origin of fatigue in the case of MM is multifactorial and among its causes there is anemia, renal failure disturbances, pain, associated infections, little food intake, metabolic alterations (due to the release of cytokines caused by the disease), mood disturbances, and hematological treatments. It is important to treat each of the causes to control this symptom to promote a better quality of life in this group of patients¹⁷.

Within the treatment for fatigue, we have pharmacological and non-pharmacological measures. Among the non-pharmacological measure, we can have the patient to rest during the day, with a limited schedule to avoid interference with the circadian cycle; blood transfusions to correct anemia, a topic that will be addressed in the section of prophylaxis and management of cytopenias, and maintaining adequate

hydration and nutrition, sometimes requiring food supplements. Among the pharmacological measures, we have the use of opioids and adjuvant drugs for pain control (previously described in the pain section) and antibiotics in case of infections (the schemes should be used according to the sensitivity and causing microorganism)¹⁸.

Insomnia

Insomnia is a symptom present in up to a third of hemato-oncology patients at some point in the disease. It is closely related to the presence of depression, anxiety, or uncontrolled physical symptoms. It can also appear on its own without being an expression of a psychiatric disorder, as a side effect of other treatments. Its treatment is based on correcting the cause when possible, on adequate sleep hygiene (placing clocks, calendars, keeping the room illuminated with natural light during the day and completely dark at night, establishing sleeping schedules, and routines) and in the use of benzodiazepine, non-benzodiazepine, or neuroleptic hypnotics, if a situation of dementia or delirium occurs. Sleep inducers such as melatonin may also be used occasionally¹⁸.

Valoración multidimensional en cuidados paliativos. In: Benítez del Rosario MA, Salinas Martín A, editores. Cuidados paliativos y atención primaria. Barcelona: Springer-Verlag Ibérica, 2000; p. 207-35.

Psychoaffective symptoms

Two important aspects must be considered in the appropriate management of psycho-affective symptoms: the pharmacological one, which will be addressed in this section; and the non-pharmacological, which will be addressed in the section on psycho-emotional approaches for patients and informal primary caregivers.

DEPRESSION

According to the WHO, it is a mood disorder characterized by the presence of sadness, loss of interest or pleasure, feelings of guilt, or lack of self-esteem, sleep or appetite disorders, feeling tired, and lack of concentration¹⁸.

There are clinical conditions usually associated with the presence of depressive symptoms in patients with MM, such as changes in calcium, sodium and

potassium levels, anemia, Vitamin B12 deficiency, pre-existing diseases, and the use of drugs: steroids, interferon, some antibiotics, chemotherapeutic agents (vincristine, vinblastine, asparaginase, intrathecal methotrexate, IL, amphotericin B, and tamoxifen) or appetite disturbances, feeling tired, and poor concentration.

Antidepressants are the indicated drugs to manage depressive episodes and their clinical manifestations. Antidepressant groups with more scientific evidence are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TADs)¹⁹.

Prophylaxis and management of cytopenias

Neutropenia

Neutropenia is a common adverse effect of many drugs used in hemato-oncology, as well as an initial manifestation of various diseases. The development of guidelines for the management of this complication is aimed at its prophylaxis and management in solid tumors and diseases that require intensive chemotherapy, such as acute leukemia; there are no specific guidelines for neutropenia in MM; therefore, we will adapt what is useful to us from the existing guidelines.

The initial step is to determine whether or not a patient requires prophylaxis with G-CSF in determining the risk of neutropenia. This determination is made based on the type of management and the characteristics of the patient. We will consider high-risk factors for neutropenia to aplasia causing chemotherapies (anthracyclines, antimetabolites, and the only scheme used in MM considered as high risk is DT-PACE), use of monoclonal antibodies, age over 60 years, poor physical status, active infections at the time of chemotherapy administration and those with liver or renal failure. This group of patients is considered to have a 20% risk of developing febrile neutropenia and requires prophylaxis with stimulating factors. Patients who do not fall into this category will be considered intermediate risk, with a 10% risk of developing febrile neutropenia, and the use of prophylaxis with stimulating factors will remain, at the decision of the treating physician.

The choice of the factor to be used (G-FEC vs. pegylated G-FEC) will fall on the availability of the treatment. FEC-G is one of the most widely used, the recommended dose is 5 mcgr/kg of body weight, 3-4

days after aplasiant chemotherapy or until neutropenia is resolved. The recommended dose of pegylated factors is 6 mg, a single dose 1 day after chemotherapy has ended. In the event of febrile neutropenia, the same stimulating factor used for prophylaxis should be used, considering that there is no accurate evidence that this intervention has any impact on mortality, especially if the dose was reduced during neutropenia, and the dose to be used will be the same as for prophylaxis, but accompanied by the appropriate antibiotic scheme for each case¹⁶.

Anemia

Anemia is, *per se*, a manifestation of MM and of some of the gammopathies studied, its surveillance is one of the key points for the follow-up of these patients, therefore, before deciding on the use of any stimulating factor, we must rule out that such cytopenia is not a manifestation of disease progression.

It is known that erythropoietin and its analogs increase the risk of thrombosis, a risk already elevated by the biology and treatment of the disease, so its use should be discussed and weighed against this risk in cases where it has been fully demonstrated that anemia is secondary to any of the therapeutic schemes used.

In this case, transfusion of RBC concentrates should be considered for the management of anemic syndrome, according to the guideline for clinical use of blood. In this way, all patients with Hb < 10 g and those with clinical data of tissue hypoxia (integumentary pallor, dizziness, and dyspnea of medium to small efforts) should be transfused RBC, the recommended dose will depend on each patient and presence of comorbidities, and special attention should be paid to those patients undergoing HSCT or post-transplant, in whom the indication is transfusion of irradiated RBCs¹⁸.

In case, the patient is highly dependent on RBC transfusions, the use of erythropoietin analogues as a treatment measure may be assessed, which has been shown to decrease transfusion dependence, but not positively impact the disease prognosis¹⁷.

Thrombocytopenia

Thrombocytopenia may also be an initial finding of the disease, less frequently than anemia. Administration of platelet concentrates or prophylactic platelet apheresis is indicated in the following cases: clinically stable patients with platelet counts < 10,000 platelets

secondary to chemotherapy, HSCT, or disease activity; patients with < 20,000 platelets with active infections, coagulation disorders, either secondary to treatment or disease, and with a history of massive bleeding. The dose of platelet concentrates to administer will be 5-8 PC every 24 h or one platelet apheresis every 24 h until the resolution of the risk factor for bleeding or the normalization of the platelet number. In the case of patients undergoing HSCT, leukoreduced platelet products should be administered¹⁹.

Psycho-emotional approaches in patients and primary and informal caregivers

From the biopsychosocial model, it is assumed that a disease comprises not only alterations at an organic level but also that there is a process of change and adaptation at the psychological, family, social, work, and spiritual level that considers the history of the patient's development, as well as its social, historical, political, and cultural context. Thus, the approach to MM implies the integration of disciplines complementary to medicine, such as psychology, which in the health field has been implementing interventions in the three levels of health care for several decades, ranging from prevention and health promotion to palliative care and well-dying care, with special emphasis on behavior, since this plays a fundamental role in the health-disease process²⁰.

First, it is necessary to consider that informing the diagnosis of MM to a patient implies giving bad news that cause an alteration of the meaning and expectations of the present and the future of the patient's life²¹. This diagnosis supposes that the disease acquires the quality of stressor, since it is perceived as a threat to the organism by the patient; therefore, response patterns are automatically generated based on the individual differences of each patient, such as coping styles and perception of resources available to deal with this threat^{22,23}.

These responses to stress can be observed through changes at the cognitive, emotional, physiological, and behavioral levels, and in the context of a diagnosis such as MM, there are a series of responses that can be expected due to the relevance of this situation in life, such as crying, anger, sadness, anxiety, fear, negative thoughts, social isolation, irritability, exacerbation of pain, increased dyspnea, and among others.

As such, the constant monitoring of the patient and his family by the health team is an extremely important task, since MM acquires the character of chronic stressor, this can generate maladaptive responses and

evolve to pathological states. Thus, the support the patient receives, whether from his family, friends, and medical team, acquires a fundamental role in the course of the disease, since it allows the patient to develop adaptive response patterns and to have the necessary resources to face effectively the demands of the disease, and thus, a better adjustment to the situation²⁴.

Despite the fact that therapeutic advances in the treatment of MM have achieved an increase in PFS and OS rates, the effects of the disease and the toxicity produced by treatment, plus a greater intensity of symptoms and negative effects typical of the natural history of the disease still translate into a lower quality of life for the patient. Therefore, one of the greatest challenges at present is to achieve a balance between the burden of the symptoms of the disease and those derived from treatments while maintaining the functionality and quality of life of the patient²⁵.

In view of the foregoing, there is currently recognition of the need for psychological care in patients with hematological cancers such as MM, because it is itself a risk factor for the development of mental health problems²⁶. Psychological needs do not have a specific course of behavior, on the contrary, they can appear at the time of diagnosis, during the treatment and in the last days of life, so the evaluation performed by the health personnel represents a key factor in the recognition and care of these needs²⁷.

From the scope of palliative medicine, these psychosocial needs acquire special relevance in the care of patients and their relatives, for these reason psychological interventions are aimed at²⁸:

- Symptoms management such as pain, nausea, vomit, insomnia, and dyspnea;
- Psychoeducation about the disease, symptoms, treatments, and adverse effects;
- Management of emotional state in problems such as depression or anxiety;
- Development of protective and self-care behaviors such as adherence to treatment and physical activity;
- Attention to sexual problems;
- Strengthening of self-esteem, spirituality and sense of life;
- Management of grief and early grief;
- Improvement in interpersonal relationships and optimization of family resources;
- Maintenance of life values, hope, and dignity.

In this way, one of the present challenges for psychology as a discipline has been the adaptation of

interventions to adjust them to frailty conditions in which palliative medicine works²⁹.

Multifactors get special relevance in MM care, since it must be addressed from different aspects, from the physical to the psycho-emotional to provide quality care to the patient throughout the disease.

It is important to consider the psychologic structure and personality of the patient; as well as the presence of previous psychopathologies, and the direct experience with the disease may influence on the patient's emotional response.

Hence, it becomes necessary to count on a psychological attention protocol to allow the intervention with the patients from the initial phase and to be able to accompany them during their disease.

Associated factors to emotional disturbances in MM patients

- MM multifactors gain special relevance during treatment, since it must be approached from different angles, starting with physical to psychoemotional aspects to provide the patient with quality care during their disease;
- Persistent anxiety from the onset and during the disease, with limited resources to face it;
- Limited support networks, increasing the threat perception and physiological responses before stress;
- Low adherence to medical treatments, which results in the lack of control of the physical and psychological symptoms;
- Poor communication with the medical team, making difficult a therapeutical alliance with the medical team.

Diagnostic phase

In the diagnostic phase, the intervention of the psychologist is aimed at detecting the needs and deficits of the patient and his family, as well as providing communication skills to the patient and his family to establish common goals and treatment objectives with the medical team, in addition to maintain a level of information appropriate to the patient's personal needs³⁰.

In addition, the psychologist intervenes by providing functional tools to the patient to provide the perception of control over the disease, such as promoting the integration of the patient's coping styles that allow them to maintain their daily functionality and start

training with stress management, anxiety, and other psychological symptoms that may occur due to notification of the diagnosis of the disease. Likewise, it is important to support informal primary caregivers and family members in solving problems related to the new health situation of their patient.

Treatment phase

At this stage, it is important to support the patient in the knowledge of the disease, as well as in the symptoms associated with it and the treatments proposed by the medical team through psychoeducation sessions, where relevant, clear, and effective information are provided. Likewise, an open space should be provided for the resolution of doubts with the medical team, achieving a therapeutic alliance with the health team that will lead to adherence to treatments³¹.

In addition to the above, to approach to physical symptoms associated with the disease (anticipatory nausea, pain, etc.) and the expected emotional reactions (anxiety, depression, loss of sense of life, etc.) from psychology, through interventions based on evidence such as cognitive behavioral therapy, relaxation techniques, cognitive restructuring techniques, mindfulness, or meaning-focused therapy facilitate adaptation to disease during the treatment process³².

It is equally relevant to promote the creation of effective social support networks in this phase, since they will be of utmost importance to directly affect treatment adherence and the prevention of primary caregiver syndrome³³.

Disease-free interval phase

The intervention of the psychologist at this stage becomes relevant, since the patient may present emotional alterations related to the previous experiences with the disease and the fear that they will appear again. This can also be reflected in constant attention to the bodies' reactions, which can create hypochondriacal attitudes, drift, and problems such as anxiety and depression.

Transplantation phase

Literature reports that before admission for a transplantation, 40% of patients present anxiety, which may disappear during follow-up, however, depression persists as the predominant symptom associated with

prolonged hospital stays, as well as physical symptoms that can be presented. Similarly, isolation is an important part of the factors that promote depressive symptoms.

It is important to note that entering a transplantation unit can lead to various emotions such as anguish, fear, confusion, hope, and uncertainty, and there will be an important psychological adjustment. One of the moments reported as most distressing for patients and families who undergo a transplant is the signing of the informed consent, which describes all the details of the procedure and the possible consequences for the patient³⁴.

Here, the role of the psychologist is to explore the conflicts that arise in each phase of the transplantation to carry out a detailed intervention aimed at the patient and his family, such as hospitalization in isolation, which can last up to several months. The psychological intervention will be aimed at adapting the patient to these treatment conditions, in addition to developing and enhancing resources and strategies that favor adherence to it and carrying out interventions from the cognitive behavioral approach.

Recurrence phase

The emotional impact can be much stronger than the diagnosis, and various symptoms that are difficult to control for the psychology team can appear. This stage is aimed at providing containment and emotional validation, helping to prevent and detect mental health problems, providing support strategies for adaptation to this disease state, supporting the doctor/patient relationship to create strengthened alliances, as well as opening channels for communication for the expression and resolution of doubts regarding this new stage.

Palliative phase

This phase is particularly relevant to accompany the patient and the family before the irreparable loss of health, and the limitations that come along. To be with the family and support these new needs, as well as the mobilization of resources to manage adverse emotions such as rage, sadness, complaints, repercussions in self-sufficiency, and among others; hence, it is important to be able to detect the patients specific needs and prioritize those more relevant.

In this final stage of the disease, physical and emotional symptoms, cognition, spiritual, and psychological needs become more relevant; therefore, attention must be paid to emotions management, communication between doctor/family and patient, decision-making, and attention of the primary caregiver.

In this sense, it is important to prevent caregiver overload, promoting self-care and healthy habits, as well as promoting family planning and organization in patient care.

Likewise, one of the psychologist's interventions is focused on accompanying the family in the preparation of grief, through various clinical interventions (family reunions, psychoeducation, and therapy tailored to the needs of the relative) that can promote active communication and conflict resolution with the patient.

Spirituality

Spirituality is generally recognized as encompassing experiential aspects, either related to participation in religious practices or to the recognition of a general feeling of peace and connectivity. Spirituality is a resource to transcend the suffering that accompanies loss and to promote acceptance in the process of dying.

Spiritual care is based on the bio-psycho-social-spiritual care model, and on an integral perspective of the person, recognizing, and enhancing the resources of patients and facilitating healing by transcending suffering. Patients accept that professionals care about their spiritual needs and want to be supported in the dying process.

It is important to validate the spiritual needs of the patient which may be oral or written. There are several instruments to evaluate spiritual belief systems, the integration of a spiritual community, medical attention implications, end of life events planning, and among others. The approach of the spiritual aspects has implications in improving the quality of life, and a higher probability to receive attention at the end of the life³⁵

Module 9

Thromboprophylaxis and hemostasia in MM

It is well known that cancer is a risk factor for thrombosis, with an increased risk of 4-7 times in comparison with the general population. MM increases 9

Table 1. DVT risk factors in multiple myeloma patients

Patient related	Disease related	Treatment related
AGE	Monoclonal component related	IMiD
BMI > 30	Hiperviscosity	High dose dexamethasone
Family history of DVT	Fibrin mesh disorders	Polychemotherapy
Immobilization	Lupus anticoagulant	Doxorubicin
Comorbidities	Antithrombin inhibition, PC and S	Central catheter
Recent surgery	Related to the hypercoagulability component	
Central catheter	Increase of FT, f fibrinogen, VWF, and FVIII	
Acute infection	Decrease of PC, S, and APT	
Hospitalization	Increase of PAI 1	

Table 2. Risk factors for thrombosis

Risk factor
Individual factors
– Obesity (BMI > 30)
– Pacemaker
– Prior thrombosis
– Related diseases
• DM
• SBP
• Renal disease
• Infection
• Bedridden patient
– Surgery
– EPO use
– Coagulopathies
Myeloma related factors
– Myeloma in itself
– Hiperviscosity
Therapy related factors
I. IMiD in combination with dexamethasone high dose, doxorubicin, or combined CT.

Modified from NCCN 2019.

times the risk of thrombosis because this a malignancy, and therefore phenomena of the pathophysiology of the disease, treatment and patient's own factors, with an estimated thrombosis incidence in myeloma of 8-22/1000 persons/year¹.

The risk of deep venous thrombosis is higher in the first 3-6 chemotherapy cycles in newly diagnosed patients, in comparison with arterial thrombosis which increases in the year after the diagnosis².

The pathophysiology of thrombosis in MM depends on factors inherent to the disease, the patient, and the treatment used.

The factors related to the disease are divided into:

A. Monoclonal component: includes the production of paraprotein factors which cause excessive blood viscosity, resulting in an alteration of the fibrin structure, and the delay of fibrinolysis, as well as the production of pro-coagulant antibodies of the lupus anticoagulant type.

B. Hypercoagulability: increased Factor VIII, VWF and fibrinogen, decreased Protein C and S, increased PAI-1.

The most significant characteristics of the patient considered to be at risk are: age, older than 60 years; overweight; cardiac, renal, pulmonary, and metabolic comorbidities; a history of surgery < 6 weeks before diagnosis; infection; central venous accesses; and coagulopathies (Table 1)¹.

Treatment is the third element that comes into play when defining the risk of thrombosis in myeloma patients. It is well known that the use of chemotherapy and high-dose steroids, such as dexamethasone at doses higher than 480 mg/cycle, should be taken into account when deciding whether to give treatment or not.

IMiD deserve special attention, this group of drugs has been shown to increase thrombotic events in varying degrees, this is due to increased expression of tissue factor, VEGF, resistance to activated protein C, and among others (reference TO). Clear examples are thalidomide, which is frequently reported with thrombotic events of 2-4% used as monotherapy, and up to 17% in combination with chemotherapy and steroids¹.

In other studies, the combined use of thalidomide and dexamethasone reported up to 26% of thrombosis, while the combination with anthracycline confers

Figure 1. Thrombotic Risk.

MM: multiple myeloma; DX: diagnostic; FR: risk factor; ASA: acetylsalicylic acid; LMWH: low molecular weight heparin.

Table 3. Anticoagulant treatment in multiple myeloma

Treatment	Days	Duration
LMWH 1 mg/kg every 12 h	21 days initially, followed by a change to VKA, DAC, or LMWH (prophylactic dose)	4-6 months*
VKK	INR 2-3	4-6 months*
DAC	No evidence	4-6 months*

*Individualized by each patient's risk.

a risk of 35%. In the case of lenalidomide, the reports are similar.

There are several international guidelines for the use of thromboprophylaxis in malignant diseases, but in most of these, there is a special consideration for MM due to the high frequency of thrombosis and the risk implied by its characteristics. There are no specific risk predictor models for these patients, but efforts have been made taking into account the number of risk factors available at the time of diagnosis, to guide the clinician regarding which medicine to the use for prophylaxis (Table 2).

The decision to use aspirin versus heparins or coumarins will be made based on the number of factors present at the time of assessment and the absence of contraindications to their use. Aspirin is the most frequently used prophylactic medication. Acetylsalicylic acid has been shown to be effective in preventing thrombotic events in sub-analyses of several treatment studies; however, the

information obtained from these studies is not robust enough to be considered high-quality sources for this recommendation, since in most of them patients with a high risk of thrombosis have been eliminated³.

IMWG and NCCN guidelines accept that the use of ASA as monotherapy may be useful for low-risk patients (one individual factor or related to myeloma), but not for those initiating an IMiD plus chemotherapy³.

Low-molecular-weight heparin and coumarins have shown similar efficacy in the prevention of thrombosis in a comparative study between these drugs and ASA⁴. In case of coumarins, the INR to follow is between 2 and 3, the advantage of an oral administration and the existence of an antidote, as well as studies specifically aimed at demonstrating its efficacy in patients with MM make them an excellent option; however, its monitoring and management are complex and may have repercussions on patient adherence. Low-molecular-weight heparins decrease the frequency of thrombus in the same way as coumarins, their great disadvantage is the route of administration, and their advantage is their relative safety and little interaction with other medications or foods; however, the fact of being injected also impacts negatively on the adherence to it.

For several years now, there has been an extensive discussion regarding the role of direct anticoagulants in myeloma and cancer in general. While less recent guidelines, such as the IMWG, did not recommend these drugs due to the lack of

appropriate studies to demonstrate their safety, more recent guidelines open up the possibility of their use, especially in those patients who have contraindications to traditional ACs, those who do not wish to receive the latter or those who are resistant to them. In the area in which we can find more information about it is in the treatment of proven thrombosis.

Direct anticoagulants have shown superiority over aspirin in the management after the acute phase of thrombosis, the phase in which the indication is still LMW heparin. Although, the oral administration and not requiring monitoring are attractive conditions for its use, there are some objections that we must consider. Patients with myeloma and cancer in general have alterations in the gastrointestinal absorption of medications due to chemotherapy, secondary nausea, the use of multiple drugs and other alterations. In addition to the lack of knowledge of the interactions that may exist between ACDs and the medications used for myeloma management, their routine use may be questionable⁵.

There is a special group in which DAC may be the first-choice treatment (frail patients or long distances to sample collection).

NCCN, IMWG, and ESMO have established management algorithms according to the patient risk, considering those with an individual factor or one of those related to myeloma previously described as low risk and high risk for those with two or more, or those with prior history of VTE (NCCN). Having categorized the thrombotic risk and ruled out the risk of bleeding (presence of thrombocytopenia, renal failure, liver failure, hemophilia, or HAS) in our patients, measures to be taken include the following:

In case patients with renal failure with GFR < 30 ml, dose adjustments, or switching to another type of heparin should be considered (Figure 1).

Surgical procedures tend to be common events in cancer patients, as well as prolonged hospitalizations due to drug toxicity or other complications. During hospitalization periods the use of prophylactic full dose low-molecular-weight heparin (LMWH) is recommended. In case a surgical procedure is needed, LMWHs are also the choice over other agents⁶.

With respect to management of established thrombosis in these patients, it will depend on the site, grade and severity of the thrombosis; besides, international guidelines should be followed and tailored for each thrombosis type, and if possible, involve a thrombosis and coagulation expert.

In Table 3 are summarized some of the interventions recommended by local and international guidelines.

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Classification of monoclonal gammopathies

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Module 2

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy) syndrome, Castleman disease and Waldenström Macroglobulinemia (WM)

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Module 3

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Module 4

Treatment

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