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Evaluation of The First-Line Response by Adding a Proteosome Inhibitor to The Standard Treatment with Thalidomide and Dexamethasone in Patients with Multiple Myeloma from The National Institute of Cancerlogy of Mexico.

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Background

Multiple myeloma (MM) is a clonal proliferation of plasma cells with heterogeneous cytogenetic characteristics [1]. It corresponds to 1% of all types of cancer and 10% of all hematological neoplasms [2]. In the United States, 32,000 new cases are diagnosed each year and about 13,000 patients die from the disease [3]. The incidence is 4/100,000 people per year. The median age of presentation is 65 years and it is more common in Americans and Africans, with a higher incidence in men compared to women [4]. When MM is suspected, patients should be evaluated for the presence of M protein using a combination of tests, including the determination of serum-free light chains (FLCs) [5]. Once the diagnosis is made, the M protein should preferably be monitored using the FLC serum free light chain method, monthly if possible, and every 3-4 months when therapy is discontinued. Follow-up with FLCs is very useful even in patients who lack measurable M protein, as long as the proportion of free light chains involved is abnormal with a ratio (involved/uninvolved) ≥ 100mg/L6,7. It has been proposed that the greater the response of the disease at the start of treatment, the patient may have a better prognosis. According to the IMWG, strict complete response is defined as a proportion of normal free light chains and the absence of clonal plasma cells in the bone marrow by immunohistochemistry or immunofluorescence [7].

The use of thalidomide and dexamethasone has been the mainstay of treatment for more than 30 years, however, there are currently more effective substances. One of the drugs with the best results is the proteasome inhibitor bortezomib [8]. A higher response rate (35%) has been shown with the use of Bortezomib, thalidomide, and dexamethasone vs thalidomide, dexamethasone (14%) [9], bone marrow transplant after obtaining the best response to the disease is desirable in most of the patients who meet criteria.

Theoretical Framework Plasma cell disorders or plasma cell dyscrasias are a group of related monoclonal neoplasms that arise from common B-lineage progenitors. These include multiple myeloma (MM), Waldeström's macroglobulinemia, primary amyloidosis (PA), solitary plasmacytoma, and heavy chain diseases (Figure A).[10]

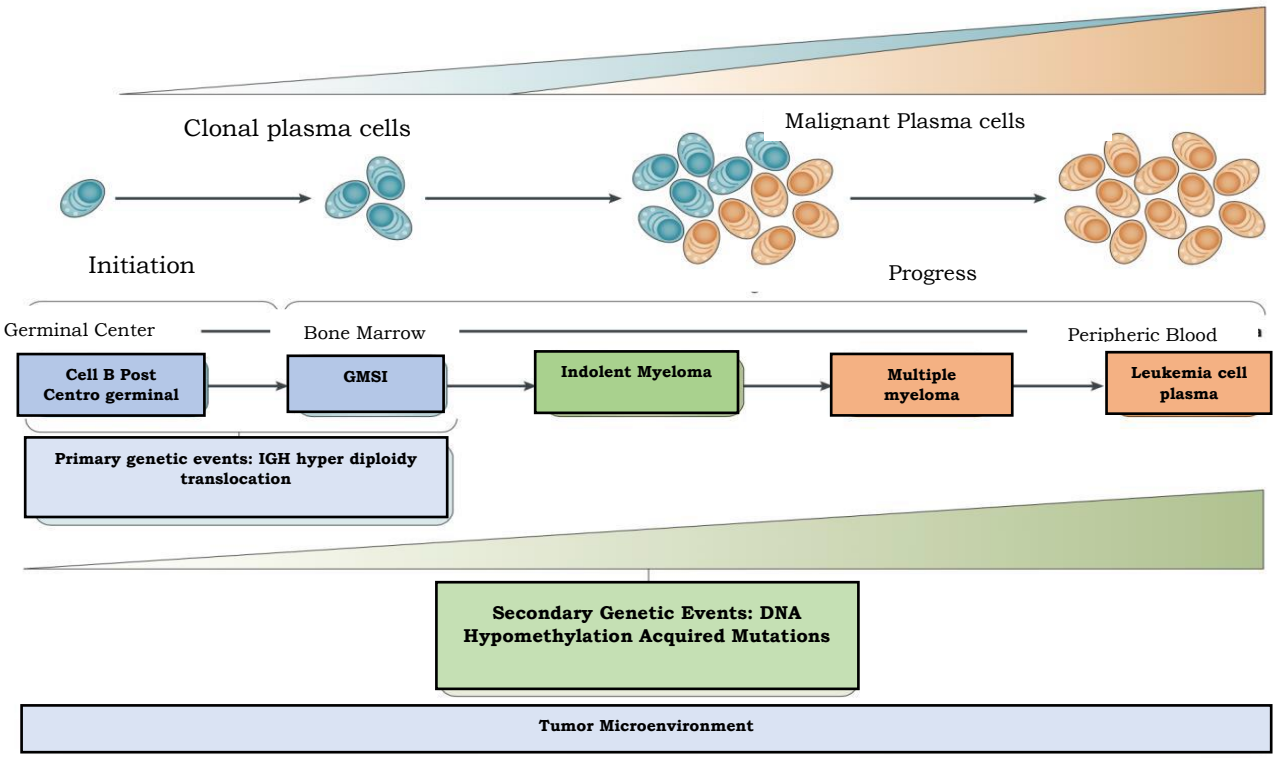


Figure A. Clonal evolution of plasma cell dyscrasias

Mature B lymphocytes destined to elaborate IgG present on their surface immunoglobulin molecules of the isotypes of heavy chains M or G, isotypes that have identical idiotypes (variable regions) for each clone. Under normal conditions, the maturation of antibody-secreting plasma cells is stimulated by exposure to the antigen for which the surface immunoglobulin has specificity; in plasma cell neoplasms, control of this process is lost [11].

The clinical manifestations of all plasma cell disorders are related to the expansion of neoplastic cells, with the secretion of cellular products (molecules or 8 subunits of immunoglobulins and lymphokines), and to some extent, with the host response to the tumor [10,11].

Epidemiology of Multiple Myeloma

MM represents 1% of all cancers and 13% of hematologic cancers. It is considered the second most common hematologic malignancy in the United States. It evolves from monoclonal gammopathy of undetermined significance (MGUS) at a rate of 1% per year. 3% of the population over 50 years of age are carriers of MGUS. The annual incidence of MM, adjusted for age according to the population of the year 2000 of the United States of North America, is 4.3 per 100,000 and in Eastern countries, it is 5.6 cases per 100,000 people. It is more frequent in the black race and in men, with a male: female ratio of

1.3:112. The median age at diagnosis is approximately 70 years (69 years for men and 71 years for women); 37% of patients are under 65 years of age and 37% are 75 years of age or older. Less than 5% of patients are under 40 years of age [12].

In Mexico, in a study that included 66 patients with MM, a prevalence lower than that reported internationally was identified, representing 7.7% of hematological neoplasms. Likewise, the average age at diagnosis was 66 years, and only 6% presented with non-secretory MM13. In 2015, 2,569 patients with MM were treated in the Mexican health system (outpatients and hospitalized patients), which corresponds to a prevalence rate of 2.12 x 100,000 inhabitants. In the same period, 2,039 patients with MM were hospitalized, with an average number of hospitalizations per patient-year of 1.36. A total of 1,169 patients with MM died in 2015, which corresponds to a mortality rate of 0.97 x100,000 inhabitants (Table 1). MM incidence rates during 2015 were on average 13% higher in men than in women. Both men and women had a unimodal distribution; the highest occurred in people 60 years of age or older (5.2 times the overall average rate) followed by adults between 50 and 59 years of age (3.3 times the overall average rate). From the age of 50, exponential growth was observed. Those under 20 years of age experienced the lowest incidence rates of MM during the study period. The absolute number of patients diagnosed with MM in Mexico during 2015 was 1,407, which corresponds to a rate of 1.16 x 100,000 inhabitants-year. The MM incidence rate ratio between men and women was 1.18. Patients aged 60 years or older were the ones who mostly used the health system due to MM during the study period (Table 2).[14]

Table 1. Multiple myeloma. Patients attended (prevalent), hospitalized patients and specific deaths in Mexico in 2015.

	Female	Male
Cases acquitted		
Prevalent cases	1,253	1,316
Inpatients	973	1,066
Hospitalizations	2,766	
Deaths	1,169	
Rates		
Prevalent cases*	2.12	
Inpatients•	2.65	
Hospitalizations	1.36	
Mortality	0.97	

**Patients served x 100,000 inhabitants-year.*

†Hospitalized patient's x 100,000 population-years.

‡*Average hospitalizations per patient-year.*

§*Specific deaths per 100,000 inhabitants-year.*

	Age Group						Total
Patients	<20 years	20-29 years	30-39 years	40-49 years	50-59 years	≥ 60 years	
Absolute Cases	28	25	102	402	768	1,244	2,569
Attended Percentage (%)	1.10	0.97	3.96	15.65	29.91	48.41	100
Hospitalized Absolute Cases	20	18	82	327	526	1,066	2,039
percentage (%)	0.99	0.88	4.01	16.05	25.79	52.29	100
Incidents Absolute cases	23	17	61	176	409	721	1,407
Incident rates*	0.05	0.08	0.34	1.16	3.77	5.97	1.16

Table 2. Multiple myeloma. Cases treated (prevalent), hospitalized and incidents according to age group in Mexico in 2015.

*Incident cases x 100,000 inhabitants-year.

Clinical Manifestations of Multiple Myeloma

They are a direct consequence of plasma cell infiltration of the bone marrow, monoclonal protein production in serum and urine, and immune deficiency. Symptoms can be nonspecific and diverse. In a retrospective analysis of 1,027 patients diagnosed with MM, they presented with the following initial symptoms [15]:

Bone pain was the most common symptom (58%), considered mild in 29%, moderate in 20%, and severe in 9% of patients. It persisted for less than 6 months in 73% of recorded events. The presence of fatigue related to anemia was recorded in 32%, lasting less than 12 months in 96%, and was more frequent in those patients with hemoglobin <9.9 g/dL

Weight loss in up to 24% of patients, of which half lost more than 9 kilograms. Paresthesias in 5% of patients. Disease-related fever in less than 1% of patients. Of these signs and symptoms, the most relevant are the following:

Extramedullary plasmacytomas: they are observed in 7% of patients with MM at the time of diagnosis, and in some cases, a worse prognosis of the disease has been observed. A percentage of approximately 6% of patients with MM may present plasmacytomas during the course of the disease12.

Anemia: It is the second most common clinical feature in patients with MM, occurring in 40 to 73% of patients at initial diagnosis. It is partially related to direct infiltration and cell replacement in the bone marrow. The hemoglobin level correlates directly with the percentage of MM cells in the S phase; which suggests that the medullary microenvironment that allows the proliferation of the MM inhibits erythropoiesis (alpha tumor necrosis factor and interleukin 1)[16],[17],[18].

Monoclonal proteins: They are the pathogenic cornerstone of the disease, 97% of patients have them, either an intact immunoglobulin, the production of free light chains, or, sporadically, free heavy chains. These can be detected by immunoelectrophoresis or immunofixation in serum or urine, visible as a band (Figure B).[16],[19]

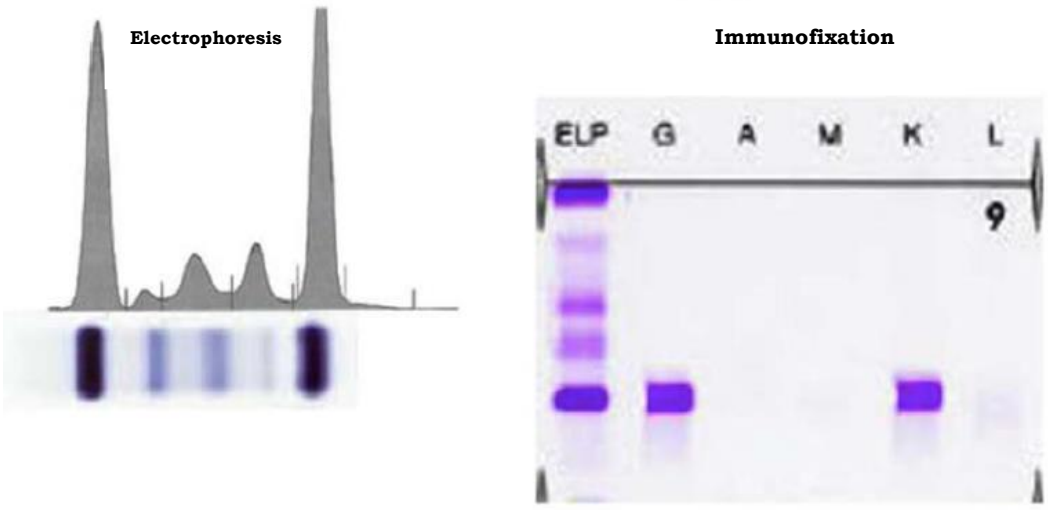


Figure B. Electrophoresis and serum immunofixation in a patient with IgG Kappa multiple myeloma.

A bone disease of myeloma: Present in two-thirds of patients, mainly in lumbar or coastal locations. It is a devastating complication characterized by destructive (osteolytic) lesions that lead to bone pain with loss of bone mineral matrix and pathological fractures. They are the main cause of disability in patients with MM. They are due to abnormal production of mediators including RANk ligand (RANKL), osteoprotegerin, and Wingless (Wnt), as well as increased bone resorption and occupying lesions (plasmacytomas). There are multiple methods to visualize bone alterations including magnetic resonance imaging, tomography, and positron emission tomography. [20,16,21]

Renal failure: Approximately 25% of patients with MM have creatinine levels > 2 mg/dL. Patients with light chain or IgD proteinuria have higher rates of renal failure. The pathological lesion of the myeloma kidney consists of monoclonal light chains that are deposited in the tubules, in the form of dense lamellar cylinders. Light chains are filtered by the glomerulus, reabsorbed, and catabolized in the proximal tubules of the nephron. In patients with MM, this system is exceeded, generating the formation

of cylinders, which are subsequently deposited, generating a disease that is more tubular than glomerular. Initial support with hydration, cessation of nephrotoxic drugs, limitation of contrast imaging studies, timely treatment of infections, and use of bisphosphonates are important strategies in the initial management to achieve recovery of renal function.[22,23,24]

Hypercalcemia: Occurs in 30 to 40% of patients. Patients complain of fatigue, constipation, polyuria, nausea, or confusion. Calcium can precipitate in the kidneys and aggravate kidney failure. The origin of hypercalcemia in MM is multifactorial and includes severe osteolysis mediated by pro-inflammatory cytokines, direct induction of bone resorption by M protein, as well as the potential production of parathyroid hormone-related peptide (PTHrP).[11.25].

Neurological symptoms: These are frequent symptoms that arise as a result of secondary extrinsic compression by plasmacytomas or bone fragments of the spinal cord or spinal nerves. Radicular pain secondary to compressive radiculopathy is the most common neurological disorder in patients with MM. Additionally, patients may present symptoms secondary to treatment. The final effect depends on the location and extension involved and ranges from weakness, pain, paralysis of the limbs, to fecal or urinary incontinence. Peripheral neuropathy associated with amyloidosis is observed. Sporadically, MM cells can invade the central nervous system, causing meningitis, papilledema, and cerebral vascular events. These patients have a dismal prognosis, occurring in patients with high disease burden and those with leukemic transformation.[26,27]

Amyloidosis: Result of the extramedullary deposit of insoluble fibrillar proteins, 20% of patients diagnosed with amyloidosis have multiple myeloma. In contrast, approximately 3% of patients with MM have amyloidosis. It manifests as carpal tunnel syndrome or generalized edema due to nephrotic syndrome. Other less frequent clinical manifestations are nail dystrophy, cardiomyopathy, macroglossia, and periocular hyperpigmentation/purpura.[28,29].

Infections: Mostly due to antibody deficiency/associated hypogammaglobulinemia. This gives patients a reduced capacity for humoral response to infections. In a study that included 771 infectious episodes in patients with MM, a bi-modal peak in the distribution of bacterial and viral infections were observed, with the duration of glucocorticoid therapy and intensive chemotherapy being important factors for its development. Additionally, the associated depletion of immunity generates secondary antibody deficiency. The main isolated microorganisms are Gram-negative bacilli in approximately 60% and encapsulated microorganisms such as S. Pneumoniae and H. Influenzae in 25%30,31.

Hemorrhage: As a complication of MM, it can be present in a third of patients, it is related to uremia, hyperviscosity, and interference in the function of coagulation factors. Bleeding occurs in 15% of IgG MM and 30% of IgA MM due to accompanying platelet dysfunction or acquired coagulopathy. Immunoglobulins or portions of these can interfere with the aggregation of fibrin monomers or serve as specific inhibitors of thrombin, von Willebrand factor, or factor VIII.[32]

Thrombosis: Patients with MM are at increased risk of arterial and venous thrombosis, however, the pathogenesis of this is not fully elucidated. There is a probable role of procoagulant factors such as acquired resistance to activated protein C, as well as the systemic inflammation that accompanies MM. It is important to emphasize that these patients have a multifactorial risk that includes age, immobility, surgeries, as well as other MM-specific factors that may contribute to this risk, increased in patients treated with immunomodulators with thalidomide-type angiogenic activity.[32,33]

Diagnosis of Multiple Myeloma

As part of the initial approach in patients with suspected MM, a complete clinical history, complete blood count with differential count, urea nitrogen, creatinine, serum electrolytes, calcium, phosphorus, uric acid, lactic dehydrogenase, alkaline phosphatase, electrophoresis should be performed. protein levels in serum and urine with immunofixation, immunoglobulin levels, determination of β2 microglobulin, C-reactive protein, light chains in serum and urine, targeted radiological bone screening, bone marrow aspiration, and biopsy, with the possibility of including baseline flow cytometry. In case of severe low back pain, MRI of the spine or positron emission tomography (PET-CT) should be performed.[10,21.]

As an operational definition, various diagnostic criteria have been used to try to classify patients with established multiple myeloma, that is, those who require initiation of treatment, against those with indolent myeloma or only monoclonal gammopathy of undetermined significance (MGUS) or monoclonal gammopathy of undetermined significance (MGUS). kidney (GMSR). These have required multiple revisions, since the advent of new therapies in MM has made it possible to improve the prognosis of patients and their survival, thus modifying the definitions of MM that benefit from the initiation of therapy. The latest operational definition of MM was published by the International Myeloma Working Group, and allowed the validation of several biomarkers that were associated with the virtually inevitable development of CRAB disorders (hypercalcemia, kidney damage, anemia, and bone damage). These defining criteria for myeloma are summarized in Table 3.[34]

Multiple Myeloma Definition (IMWG)
Bone marrow clonal plasma cells ≥10% or bone or extramedullary plasmacytoma confirmed by biopsy, and The presence of one or more of the myeloma-defining events
Myeloma defining events: • • Evidence of target organ damage attributable to plasma cell dyscrasia: o Hypercalcemia: serum calcium >1mg/dL above the upper limit of normal or >11mg/dL • or Renal insufficiency: Creatinine clearance <40 ml/min or serum creatinine >2mg/dL • or Anemia: hemoglobin >20 g/L below the lower limit of normal or <100 g/L • or Bone lesions: one or more osteolytic lesions in plain radiography, tomography, or PET-CT • • Any of the following positive biomarkers: o Clonal plasma cells ≥60% • or Involved CLL rate: non-involved ≥100 • or >1 focal lesion on MRI studies

Table 3. Diagnostic criteria for multiple myeloma.

Multiple Myeloma Staging

The prognosis of patients with MM depends on several factors, including those that depend on the patient, such as age, ECOG, and the presence of co-morbidities; of the disease, such as the type of monoclonal immunoglobulin produced, the presence of free light chains, and the tumor burden; and the interaction of both.21 The first system for staging patients with MM was developed by doctors Durie and Salmon in 1975, which correlated parameters such as the presence of anemia and amount of monoclonal protein with tumor burden (Table 4); however, the system has limitations regarding the categorization of bone lesions. The Durie-Salmon system relates the number of myeloma cells to the extent of bone disease, hemoglobin, calcium levels, and serum and urine monoclonal immunoglobulin levels.[36]

Stage	Criteria
I	• • Hemoglobin level > 10 g/dL • • Normal blood calcium level or < 10.5 mg/dL • • Bone radiograph and normal bone structure or only solitary bone plasmacytoma • • Low levels of M component production (IgG < 5 g/dL; IgA < 3 g/dL) • • Bence-Jones proteinuria < 4 g/24 h

II	Does not meet criteria for I or III
III	• Meet one of the following: • • Hemoglobin level < 8.5 g/dL • Serum calcium level > 12 mg/dL • Advanced lytic bone lesions • High levels of M component production (IgG > 7 g/dL; IgA > 5g/dL) • • • Bence Jones proteinuria > 12 g/24 h •
Subclassification (A/B)	A: normal kidney function (Cr < 2.0 mg/dL) B: abnormal kidney function (Cr > 2.0 mg/dL)

Table 4. Durie-Salmon Staging System; Cr: serum creatinine.

Although this staging system has some prognostic value, the biology of MM reflects new markers of cell kinetics, signaling, cytogenetic aberrations, and apoptosis that have diminished the significance of tumor mass as a predictor of survival. The combination of β2-microglobulin (β 2MG) and serum albumin levels from the new international staging system (ISS) provides the simplest and most reproducible staging method, which allows for classifying the disease and determining its extent (Table 5). The ISS was developed by the Southwest Oncology Group in collaboration with investigators from 17 institutions with data from 11,171 patients. He divided the patients into 3 groups, with survival results of 62, 44, and 29 months for stages I, II, and III; respectively. β2-Microglobulin is thought to correlate with tumor mass and kidney function, and low albumin reflects the effect of IL-6 that occurs in the bone marrow microenvironment with MM, however, this system has a limitation of not including genetic abnormalities.

Stage	**Criteria**
I	β2M < 3,5 mg/l + ALB ≥ 3,5 g/dl
II	β2M < 3,5 mg/l + ALB < 3,5 g/dl o β2M = 3,5–5,5 mg/l
3	β2M > 5,5 mg/l

Table 5. MM Staging System by ISS (International Score System); β2M: beta-2-microglobulin, ALB: serum albumin

The revised ISS-R model included more than 4,000 patients, with clinical, biochemical, and cytogenetic information for its development, demonstrating clear superiority over Durie-Salmon or ISS staging, categorizing the latter as high risk in case of presenting (17p) and/or (4;14) and/or t(14;16), see Table 6.

ISS- Revised	
Stage	Criteria
I	ISS stage I + standard cytogenetic risk + normal DHL
II	Does not meet for R-ISS stage I or III
III	ISS stage III + high cytogenetic risk or elevated LDH

Table 6. R-IPSS prognostic index. DHL: lactic dehydrogenase; ISS: International Scoring System.

Pathogenesis of Multiple Myeloma

B cell development occurs initially in the bone marrow (BM) and subsequently in the lymphoid tissues. Terminal differentiation of B cells occurs in the bone marrow, hematopoietic progenitor cells differentiate into a pro B cell, the first identifiable cell of the B lineage. The cell undergoes rearrangements in Ig heavy chains and becomes a pro B cell. B; subsequent rearrangement of the light chains allows the cell to express surface IgM and becomes an immature B cell. This cell leaves the BM and enters the peripheral blood, where it begins to express IgD and is called a virgin B cell. Subsequently, it remains in the G0 phase of the cell cycle; it enters lymphoid tissue, where it is exposed to antigen-presenting cells, activated, and differentiates into the short-lived, low-affinity plasma cell or memory B cell. Memory B cells travel from the extrafollicular area of the lymph node to the primary follicle, where they are confronted with antigens presented by follicular dendritic cells, resulting in the development of a secondary immune response. At this stage, the primary follicles change to secondary and contain germinal centers. Upon activation by antigen, memory B cells differentiate into centroblasts, resulting in immunoglobulin isotype switching, to generate high-affinity antibodies; these then progress to centrocytes, with reexpression of surface immunoglobulins. Centrocytes with high-affinity antibodies differentiate into either memory B cells or plasmablasts. The plasmablasts return to the bone marrow where they differentiate into plasma cells. Plasma cells live for about a month.[38]

Role of Light Chains in Multiple Myeloma

The presence of an altered ratio of kappa/lambda free light chains (FLC) was demonstrated by the Mayo Clinic group, who observed in a prospective cohort of 790 patients with MM the prognostic value of an abnormal ratio, since these patients had a lower average overall survival than those with normal rates (30 vs 39 months), likewise, by incorporating the CLL rate to the ISS score, they increased its prognostic performance39. In the same way, a British study that included 483 patients with MM concluded that the serum concentration of FLC was a better indicator of response to therapy than the concentration of

immunoglobulin involved (IgG, IgA), and in a different population, it was shown that an FLC concentration greater than 100 mg/L at the end of treatment was related to a poor prognosis.[39]

According to the IMGW guidelines, current assays for the measurement of kappa and lambda FLC should be used in three well-established clinical conditions during the diagnosis and follow-up of patients with MM and related plasma cell dyscrasias:

1. During case screening to assist in the diagnostic process, in combination with protein electrophoresis and immunofixation, it increases sensitivity and obviates the need for 24-hour urine collection; except for light chain amyloidosis.

2. Baseline FLC is a key prognostic factor in virtually any plasma cell dyscrasia.

3. The quantitative FLC assay allows objective monitoring of patients with oligosecretory MM, including those with secondary amyloidosis or oligosecretory MM; demonstrating superior value for follow-up compared to protein electrophoresis and immunofixation.[40,41]

Cast nephropathy is the most common cause of multiple myeloma-induced kidney injury, and its presence has been correlated with serum-free light chains, suggesting a direct pathogenic role.42 In a British study that included 77 patients with MM and kidney failure treated with high-flow hemodialysis, 86.7% had cast nephropathy in the renal biopsy and the factor that predicted independence from renal replacement therapy was the rate of reduction of free light chains (FLC) at 12 and 21 days of treatment. started hemodialysis. In contrast, attempts to reduce serum FLC by plasmapheresis in patients with MM-induced kidney injury have not been successful, although one of these studies corroborated the association of decreased creatinine and dialysis independence with reduced FLC serum.[44,42]

Controversies About the Prognostic Role of Light Chain Test in The Clinical Outcome of Multiple Myeloma

The variability of prognosis among patients with multiple myeloma has prompted multiple groups to search for factors that can predict therapeutic response, disease relapse, and overall survival in these patients. In addition to the prognostic scores already described, most patients with MM have increased levels of serum-free kappa or lambda chains, or abnormal kappa/lambda ratios. These have served as modalities both in the diagnosis and in the follow-up of patients with MM, especially considering their short half-life that allows rapid changes in therapeutic response to be measured.[45,46] There are several studies that indicate a prognostic role in the normalization of the ratio of kappa/lamba light chains:

In a study by Kumar SK et al. which included 840 patients with newly diagnosed multiple myeloma, those with anemia (36% vs 28%), kidney injury (21% vs 9%), ISS stage III (39% vs 27%) or isolated light chain disease (44% vs 20%) had an early response to chemotherapy, however, this was not related to

differences in disease-free survival or overall survival47. In a Japanese study that included 126 patients with multiple myeloma, 52 patients (41%) had normalization of the kappa/lambda free light chain ratio. These patients demonstrated superior progression-free survival (PFS) and overall survival (OS) compared with patients who maintained abnormal rates (3-year OS of 94% vs 48%, respectively). This favorable effect was not influenced by the initial serum concentration of free light chains48. Dr. Barloguie's group demonstrated that patients with elevated FLC at diagnosis (>75 mg/dL; 33% of patients) had a greater response to induction (37% vs 20% complete response), however, they presented a PFS (73% vs 90%) and OS at 24 months lower (76% vs 91%). Additionally, the presence of elevated serum FLC was related to isolated light chain disease, kidney injury at diagnosis, elevated beta-2-microglobulin, and bone marrow plasmacytosis greater than 30%.49 A Greek study that included 94 patients with a rate of FLC found that patients with a low rate of FLC had a higher 5-year OS than those with a high rate of abnormal FLC (82% vs 30%), suggesting their independent prognostic value.[50]

In contrast, a retrospective study by the Spanish Multiple Myeloma Group (GEM) analyzed 309 post-autologous transplant patients and found no difference in the risk of progression in patients with an abnormal CLL rate at diagnosis, although the persistence of the abnormal rate it was associated with worse PFS and OS51. Taken together, these results indicate an adverse prognostic value in patients who fail to normalize the kappa/lambda FLC rate, as well as lower disease-free survival and overall survival in these patients. However, these results seem to be partially dependent on ethnicity and the use of transplantation as consolidation, since the Spanish group did not report these differences, which highlights the need for a study on the Hispanic population. Finally, the role of an abnormally high rate of CLL in the progression of indolent MM is currently being studied, since a study by Dr. Rajkumar's group at the Mayo Clinic found a 72% probability of progression in patients with a rate greater than or equal to equal to 100, suggesting a potential pathogenic role [52].

Multiple Myeloma Treatment

For more than four decades, the standard treatment for MM was the combination of melphalan and prednisone (MP), with which favorable responses are obtained in 40 to 60% of cases; however, patients relapse shortly thereafter, and the median duration of overall survival is 3 years. New treatments for MM have been developed in recent years, with the introduction of targeted therapy, immunotherapy (daratumumab), and treatment with cell therapy/CAR-T cells. These emerging treatments have been found to be highly active against myeloma cells. [10,53]

Thalidomide

This drug induces responses due to its multiple mechanisms of action: a) antiangiogenic effect; b) it blocks the secretion of some MM cell growth factors (IL-6, vascular endothelial growth factor); c) effect on the adhesion molecules that regulate the contact between the stroma and the MM cells.[21,53]

Bortezomib

Bortezomib is a derivative of boronic acid and is the first clinically used proteasome inhibitor that has potent cytotoxic and cell growth inhibition effects. The multicatalytic pathway of the proteasome is responsible for the orderly degradation of eukaryotic cellular proteins. Proteosome inhibition leads to cell apoptosis with increased susceptibility of neoplastic cells.[21,53]

Hematopoietic Progenitor Cell Transplantation

It is a modality that allows prolonged times of remission of the disease. The two major problems with autologous transplantation in MM are the impossibility of eradicating the malignant cells of the MM, even with conditioning regimens that include high doses of chemotherapy, radiotherapy, or both. Today autologous transplant is still a useful tool in the treatment of patients with MM, however, recent studies have tried to prove the usefulness and role of targeted therapies as first-line over transplant.54

ASSESSMENT OF RESPONSE TO TREATMENT The treatment of multiple myeloma has radically changed the survival of patients, thanks to the introduction of new drugs that have improved response rates to treatment, as well as the depth of response. Because of this, refining treatment response categories are relevant. The latest consensus in this regard, published by the International Myeloma Working Group (IMWG) was held in 2016, including recent modalities for a better classification of them (Table 7)[7].

IMWG Criteria for The Assessment of Response and Minimal Residual Disease	
Sustained EMR-negative	EMR negative medullary (NGS) and confirmed image for at least one year apart
EMR-negative by flow cytometry	Absence of immunophenotypically aberrant clonal plasma cells in bone marrow aspiration according to EuroFlow
EMR-negative by sequencing	Absence of clonal plasma cells by NGS in bone marrow using the LymphoSIGHT platform or validated equivalents
EMR-negative by image plus	Negative EMR defined by NGS + disappearance of catchment areas in baseline PET-CT study or uptake less than the mediastinal pool
IMWG Standard Response Criteria	

Deep complete response	Complete response + normalization of CLL rate and absence of plasma cells by immunohistochemistry in bone marrow
Full response	Negative serum and urine immunofixation, and Disappearance of plasmocytomas in soft tissues, and <5% plasma cells in bone marrow aspiration
Very good partial response	M protein serine or urinary detectable by immunofixation but not electrophoresis, or ≥90 reduction M serum protein more Urinary protein M <100 mg in 24 hours
Partial response	≥50% reduction of serum protein M plus reduction of urinary protein M in ≥90% or <200 mg per 24 h
Minimum response	≥25% but ≤49% in serum M protein reduction and 50-89% urinary M protein reduction.
Stable disease	Not recommended to measure response to treatment, measure time to progression
Progressive disease	Any of the following: 25% increase in the lowest confirmed value of: Serum M protein (absolute increase ≥0.5 g/dL); Increase in serum M protein ≥1 g/dL if the lowest was ≥5 g/dL; Urinary protein M with absolute increase ≥200 mg/24 h; In patients without non-measurable protein, a difference in the rate of CLL involved/not involved with an increase greater than 10mg/dL In patients without measurable serum/urinary M protein or CLL rate, plasma cells in bone marrow with an increase ≥10%; Appearance of new lesions or increase ≥50% of the nadir; Incremement ≥50% in circulating plasma cells (minimum 200 cells/uL)

Table 7. Criteria for response to treatment in MM according to the IMWG; MRD: Minimal residual disease; NGS: next-generation sequencing.

Approach

At the National Cancer Institute of Mexico (INCan) an average of 66 new patients diagnosed with MM are treated per year. Current treatments are very varied, one of the first line schemes in INCAN is the combination of Bortezomib, thalidomide, and dexamethasone. The evaluation of the response to this treatment is essential to determine if it continues with the same regimen or requires a change of line, with the aim of achieving the best response to the disease and, where appropriate, early bone marrow transplantation. This directly impacts the overall survival and quality of life of patients.

Hypothesis

Patients with multiple myeloma from the National Cancer Institute of Mexico treated with a first-line treatment scheme with bortezomib, thalidomide, and dexamethasone obtained a higher response rate compared to patients who received only thalidomide-dexamethasone.

Methodology

• For the maneuver control by the investigator: Observational.

• Because of the relationship between the occurrence of the event and data collection: Retrospective.

• By measuring the phenomenon over time: Transversal

• For information management: Analytical.

• By type of study: Cases and controls

• Universe of the study: INCan patients diagnosed with multiple myeloma

• Period of time: 32 months

Objectives

Primary Objective:

To evaluate the response to treatment in patients with multiple myeloma who received first-line treatment with proteasome inhibitor, thalidomide, and dexamethasone using the criteria of the International Myeloma Working Group.

Secondary objectives:

• Compare the response obtained with respect to patients who received only thalidomide and dexamethasone.

• Describe the functional status of the patient at the time of diagnosis.

• Describe the number of cycles and doses applied.

• Describe the utility of measuring free kappa and lambda light chains as a method of monitoring responses

• Describe overall survival and disease-free survival.

• Describe the associated comorbidities and their effect on the evolution of treatment.

• Describe adherence to treatment.

• Describe the side effects and causes for suspension and/or abandonment of treatment if they occur.

• Describe the associated comorbidities and their effect on the evolution of treatment.

Study Overview

Patients with a diagnosis of multiple myeloma who were admitted to the INCan in the period January 2017 - to August 2019 who received first-line treatment with proteasome inhibitors, thalidomide, and dexamethasone will be identified. The background, clinical and biochemical data will be collected, as well as cabinet studies carried out. The number of cycles and doses of chemotherapy received will be determined.

The response will be evaluated at 3,6,9,12 months of treatment, as well as the clinical evolution and secondary effects.

Once the results are obtained, an analysis of the data will be carried out to determine the percentage of strict complete response, complete response, very good partial response, partial response, stable disease, and disease progression. In addition to the analysis of overall survival and disease-free survival. Adherence to treatment and the factors associated with it will be analyzed. Once the results are obtained, they will be compared with the data of the patients who received only thalidomide and dexamethasone and this will be compared with the international literature, analyzing the causes of consistency and/or discrepancy.

Statistic Analysis

The descriptive analysis of the variables will be carried out through means of central tendency and standard deviations for quantitative variables with normal distribution. Median and interquartile range analysis will be performed for quantitative variables with non-normal distribution. Proportions will be reported for qualitative variables.

For univariate analysis, the Student's t-test or Mann-Whitney's U test will be used for quantitative variables according to their distribution and Chi-square for qualitative variables. For this work, the SPSS version 22 program will be used as an analysis tool.

Inclusion Criteria

Adult patients who were admitted to the INCan in the period January 2017-August 2019 with a diagnosis of multiple myeloma received first-line treatment with a scheme based on bortezomib, thalidomide, and dexamethasone.

Exclusion Criteria

Patients who for various reasons could not access the established first-line treatment received an alternative regimen during the study period.

Patients who abandoned treatment.

List Of Variables to Use

Independent variables:

- Age (years) (discrete quantitative), sex (nominal qualitative).
- Comorbidities (ordinal qualitative) evolution time (continuous quantitative).
- Medications are previously taken (Qualitative ordinal).
- Results of laboratory and cabinet studies: Free light chains in serum kappa, lambda (quantitative continuous), protein electrophoresis (quantitative continuous), immunofixation in serum and urine (quantitative discrete), Bence Jones Protein (qualitative continuous), PET CT (qualitative ordinal).
- Histopathological study report of bone biopsy (qualitative ordinal)
- Bone marrow cytogenetic study report (qualitative ordinal).
- Immunophenotype report in bone marrow (qualitative ordinal).
- Number of cycles applied (discrete quantitative)
- Adverse reactions to treatment according to the Common Terminology Criteria for Adverse Events (CTCAE) (qualitative ordinal).

Dependent Variables:

• Response to treatment according to the criteria of the International Myeloma Working Group: strict complete response, complete response, very good partial response, partial response, stable disease, progression (polytomous qualitative).

• Overall survival and disease-free survival (continuous quantitative).

Resources Financing and Feasibility

Human Resources

This protocol will be prepared by the authors and their multidisciplinary team, who will be in charge of data collection in Excel spreadsheets. As well as the analysis of the results, the writing of the discussion, conclusions, writing of the final project, who will also coordinate the design of the protocol.

Material resources

- Physical: Electronic medical records from the INCan's Incanet program.
- Computer equipment, Excel spreadsheet, and statistical programs (SPSS version 20) Property of José Carlos Olvera Santamaría.
- Economic: To carry out this study, no external financing is required.

Feasibility

Given the population diagnosed with multiple myeloma that is admitted and receives treatment at the INCan, it is feasible to have patients who meet the characteristics mentioned in this protocol.

Ethical Aspects

The performance of this study does not contravene the "Declaration of Helsinki of the World Medical Association" of 1964, which establishes the ethical principles for medical research in human beings. This research, in accordance with the "General Health Law" of Mexico and its "Regulations of the General Health Law in Health Research", in Title 2, Chapter 1, Article 17, Section II, is considered as “less than minimal risk research”, since data from the clinical file will be reviewed, without putting the health of the patients at risk, for which reason the omission of the use of informed consent is requested.

Results

29 cases were obtained that met the inclusion criteria, of which 18 (62%) were men and 11 (38%) women. Table 8.

The mean age in women was 58 years (42-78), in men, it was 50 years (17-69).

The most frequent type of myeloma in descending order was Kappa light chains with 8 cases (24%), IgG lambda with 7 cases (24%), IgA kappa with 6 cases (20.6%), IgA lambda with 4 cases (13.7%), IgG Kappa 2 cases (6.8%), lambda light chains 2 cases (6.8%), Table 8.

The most frequent type of myeloma according to the patient's sex was lambda IgG for men with 6 cases (20.6% p=0.005) and Kappa light chains for women with 4 cases (13.7% p=0.05). All types of myeloma according to distribution by sex were statistically significant ($p \leq 0.05$). Table 8.

Regarding the CRAB criteria, 11% of patients with calcium alterations were found, 14.5% with primary glomerular filtration ≤ 40 ml/min, 40% with anemia (Hb <10gr/dL) and 62% with lytic lesions ($p< 0.05$).). Table 8.

Mean B2 microglobulin was 6.7mg/L; however, a significant increase was observed in men (8.4mg/L vs women 3.9mg/L p=0.036). Table 8.

Albumin levels remained close to the lower limit (3.6gr/dL p=0.39); contrary to this, the value of globulins shows a clear difference between men (9.7gr/dL) and women (3.6gr/dL) ($p<0.001$). On the other hand, this does not seem to affect the values of the monoclonal peak globally (3.16gr/dL) although men present higher values (4.2gr/dl) compared to women (1.76gr/dl) (p= 0.080). . Table 8.

High-risk cytogenetic alterations (del(17p), t(4;14), t(14;16) were found in 20.5% of the total number of patients studied. When disaggregating by sex, a significant increase in high-risk alterations for men (17.2%) vs. women 3.4%) (p= 0.003). This closely correlates with the staging according to the International Staging System (ISS) in which a higher percentage of patients in stage III (41.2%) is observed; in turn, the percentage of men in stage III is higher than that of women in the same stage 34.4% vs 6.8% p= 0.0042). Table 8.

The patients received a daily treatment scheme based on thalidomide and dexamethasone, in addition to 1 monthly dose of cyclophosphamide, to which a proteasome inhibitor was added, either Bortezomib (69%) or carfilzomib (31%), these percentages were not statistically significant. The sex distribution of each proteasome inhibitor is described in Table 8.

Figure 1 shows the distribution of treatment according to the type of myeloma and the proteasome inhibitor used, statistically, significant differences were obtained: However, in the univariate analysis, these differences did not show to be factors that influenced the response to treatment or the overall survival.

In the initial evaluation at 3 months of treatment, 6 (21%) patients obtained ROSC, 7 (24%) CR, 15 (52%) VGPR patients and 1 (3%) patient obtained PR, these results were statistically significant between them (p=0.003). In the univariate analysis, the response obtained at 3 months was shown to be a factor that influences the final response (12 months) and overall survival (p=0.012) Table 9, Table 10.

The analysis of the response in the first 3 months according to the treatment used of the 6 patients who obtained ROSC were all treated with bortezomib, no patient treated with carfilzomib obtained ROSC in the first 3 months. 7 patients obtained CR, of which 4 were treated with bortezomib and 3 with

carfilzomib. 15 patients obtained VGPR of which 9 were treated with bortezomib and 6 with carfilzomib. 1 patient obtained PR treated with bortezomib. In the univariate analysis of the proteasome inhibitor, the response obtained did not show an effect (p=0.539).

In the evaluation at 6 months of treatment, 8 (27.5%) patients achieved ROSC; of whom, 7 were treated with bortezomib and 1 with carfilzomib, 5 (17%) CR patients (2 with bortezomib and 3 carfilzomib), 14 (48%) VGPR patients (10 bortezomib and 4 carfilzomib), 2 (7%) RP patients (1 bortezomib and 1 carfilzomib); (p=0.0012). Table 9.

Regarding the follow-up 6 months after the initial response, of the 6 patients with initial ROSC, 5 continued with ROSC and 1 patient with VGPR. Of the 7 patients with initial CR, 3 achieved ROSC, and 4 continued with CR. Of the 15 patients with VGPR at baseline, 13 continued with the same status, 1 with PR, and 1 achieved CR. Table 11.

At 9-month follow-up, 9 patients obtained ROSC (7 bortezomib and 2 carfilzomib, 9 patients obtained CR (5 bortezomib and 4 carfilzomib), 9 patients obtained VGPR (7 bortezomib and 2 carfilzomib), 1 patient obtained PR (bortezomib, 1 patient with PR who received bortezomib progressed to progressive disease (p=0.010) Table 9. In the univariate model, the response at 9 months was associated with overall survival Table 10. In the follow-up of the initial response at 9 months of treatment, regarding the patients with initial ROSC, 5 continued in the same status and 1 patient decreased their response to VGPR. Of the patients with initial CR, 1 patient achieved ROSC, 5 patients continued in CR, and 1 patient decreased their response to VGPR. Of the 15 patients with VGPR at baseline, 7 continued with the same status, 3 patients obtained ROSC, 4 patients obtained CR, and 1 patient decreased to PR. 1 patient who achieved PR at baseline progressed to progressive disease. Table 11. At 12-month follow-up, 7 (24%) patients obtained ROSC (6 bortezomib, 1 carfilzomib); 11(38%) patients obtained CR (6 bortezomib, 5 carfilzomib): 6 (20.6%) patients obtained VGPR (4 bortezomib, 2 carfilzomib); 2 (7%) patients obtained PR (1 bortezomib, 1 carfilzomib); 3 (10%) patients had progressive disease (bortezomib); (p=0.067). Table 9.

Regarding the follow-up of the initial response; At 12 months of treatment, the following evolution was obtained: of the patients with ROSC, 5 patients continued with the same status and 1 patient with progressive disease; Of the patients with initial CR, 1 patient achieved ROSC, 5 patients continued with the same status, and 1 patient progressed to progressive disease; Of the patients with initial VGPR, 6 patients continued with the same status, 1 patient achieved ROSC, 6 patients obtained CR, 1 patient decreased to PR, and 1 patient had progressive disease. The only patient with initial PR continued in the same status at 12 months of follow-up. Table 11. The univariate model analysis of overall survival depending on the type of response obtained (ROS, CR, VGPR, PR, EP) and evaluation period (3,6,9,12 months) shows an association between all types of response except RP and EP in all evaluation periods. Table 10.

The analysis of the initial response at 3 months and the final response at 12 months shows that the 6 patients with initial ROSC remain stable with a slight increase at the end of follow-up p=0.07; an increase is also observed in patients with CR, increasing from 7 at the beginning to 11 at the end p= 0.043. Patients with VGPR decrease from 16 at the beginning to 6 at the end of follow-up p=0.03. 1 patient presented initial PR; however, at the end of follow-up, 2 patients had said disease status p= 0.08. 1 patient presented PE in the initial response, an increase to 3 patients with PE is observed at 12 months p=0.023. Table 11. Figure 1.

Regarding the proteasome inhibitor used according to the type of myeloma, 20 patients received treatment with bortezomib of which 2 patients presented IgG Kappa, 3 patients IgG lambda, 5 patients IgA kappa, 3 patients IgA lambda, 6 patients Kappa light chains, and 1 patient Lambda light chains. 9 patients received treatment with carfilzomib of which 4 patients presented IgG Lambda, 1 patient IgA Kappa, 1 patient IgA lambda, 2 patients Kappa light chains, and 1 patient Lambda light chains. Table 12.

Overall survival (OS) was 29.9 months (95% CI 24.8 – 35.1 months), subgroup analysis showed a lower OS for men at 25.8 months (95% CI 18.6-32.9) compared to women at 34.9 months (95% CI). % 28.4-41.3), in the Kaplan-Meier analysis no statistically significant difference was observed, Table 13. Figure 3.

Finally, the treatment received with a proteasome inhibitor (carfilzomib vs. bortezomib) did not show a statistically significant difference in overall survival (OS), the patients who received bortezomib had a survival of 30.29 months (95% CI 24.4-30.09, the OS of the patients who received carfilzomib was 20.37 months CI (95% 16.05-24.69). The Kaplan-Meier curve analysis shows no difference in behavior (p=0.731). Figure 2, Table 14

Característica	Total	Hombre	Mujer	Valor P
Sexo	29	18 (62%)	11 (38%)	0.265
Edad (años)	54	50 (17-69)	58 (42-78)	0.071
% Cel plasmáticas MO	43%	54 (30 - 90)	32 (9 - 70)	0.061
Tipo de mieloma				
IgG Kappa	6.80%	2 (6.8%)	0	**0.005**
IgG Lambda	24%	6 (20.6%)	1 (3.4%)	**0.005**
IgA Kappa	20.60%	5 (17.2%)	1 (3.4%)	**0.008**
IgA Lambda	13.70%	1 (3.4%)	3 (10.3%)	**0.04**
Kappa	27.50%	4 (13.7%)	4 (13.7%)	**0.05**
Lambda	6.80%	0	2 (6.8%)	**0.05**
CRAB				
C (Calcio > 11mg / dL)	11%	11%	0%	< **0.001**
R (FGP <40ml/min)	14.5%	5.50%	9%	< **0.001**
A (Hb < 10gr/dL)	40%	22%	18%	**0.003**
B (lesiones líticas)	62%	44%	18%	**0.039**
B2 microglobulina (mg/L)	6.7 1.5-43)	8.4 (1.5 - 43)	3.9 (1.7-8.9)	**0.036**
Albúmina (gr/dL)	3.68 (2.8-4.7)	3.6 (3.1-4.7)	3.6 (2.8-4-2)	0.39
Globulinas (gr/dL)	7.4 (2.1 - 76)	9.7 (2.5 - 76)	3.6 (2.1-7.4)	< **0.001**
Proteína M (gr/dL)	3.16 (0 - 22.7)	4.2 (0-15 - 22.7)	1.76 (0 - 5.6)	0.080
Citogenética alto riesgo: del(17p), t(4;14), t(14;16)	6 (20.6%)	5 (17.2%)	1 (3.4%)	**0.003**
ISS al inicio de tx.				
I	6 (20.5%)	2 (6.8%)	4 (13.7%)	0.188
II	11 (37.8%)	6 (20.6%)	5 (17.2%	0.07
III	12 (41.2%)	10 (34.4%)	2 (6.8%)	**0.042**
Inhibidor de proteosoma				
Carfilzomib	9 (31%)	6(20.6%	3 (10.3%)	0.402
Bortezomib	20 (69%)	12 (41.3%)	8 (27.5%)	0.308

Table 8. Demographic variables and characteristics of the disease

RCE	RC		VGPR	RP	EP	Valor p
3Months	6	7	15	1	0	0.003
6Months	8	5	14	2	0	0.012
9Months	9	9	9	1	1	0.010
12Months	7	11	6	2	3	0.067

Table 9. Evaluation of the type of response obtained

3 Months	6 Months	9 Months	12 Months
RCE	0.001	0.001	< 0.001	0.001
RC	0.009	0.007	0.002	< 0.001
VGPR	< 0.001	<0.001	< 0.001	0.008
RP	NS	0.134	NS	0.134
EP	NS	NS	NS	0.009

Table 10. Univariate model for overall survival according to the type of response obtained in the evaluation period

3 Months	6 Months	9 Months	12 Months	
RCE	6 RCE	5 RCE / 1 VGPR	5 RCE / 1 VGPR	5 RCE / 1 EP
RC	7 RC	4 RC / 3 RCE	5 RC / 1 RCE / 1 VGPR	5 RC / 1 RCE /1 EP
VGPR	15 VGPR	13 VGPR/ 1 RC / 1 RP	7 VGPR / 3 RCE / 4 RC/ 1 RP	6 VGPR / 1 RCE / 6 RC / 1 RP / 1 EP
RP	1 RP	1 RP	1 EP	1 RP

Table 11. Evolution of the initial response

Bortezomib		Carfilzomib	%	Valor p
IgG Kappa	2	0	2	6.80%	0.24
IgG Lambda	3	4	7	24%	< 0.001
IgA Kappa	5	1	6	20.60%	0.001
IgA Lambda	3	1	4	13.70%	0.15
Kappa	6	2	8	27.50%	< 0.001
Lambda	1	1	2	6.80%	0.205

Table 12. Proteasome inhibitor by myeloma type

IC 95%			
Time (Months)		Lower Limit	Upper Limit
Global	29.9	24.8	35.1
Man	25.8	18.6	32.9
Women	34.9	28.4	41.3

Table 13. Overall survival (OS)

Inhibitor of proteosome	**Survival months**	**IC 95%**
Lower limit		Upper limit
BORTEZOMIB	30.29	24.4 36.09
CARFILZOMIB	20.37	16.05 24.69

Table 14. Proteasome inhibitor survival

Feature	**Value p**
Calcium	0.003
Renal	0.009
Anemia	0.17
Bone (Lytic Lesions)	0.037
ISS II-III	0.037
IgA Kappa	0.004
Globulins	0.03
> 50% MO Plasma Cells	0.038
Man	0.0.17

Table 15. Variables associated with lower overall survival

Figure 1. Follow-up of the Initial Response

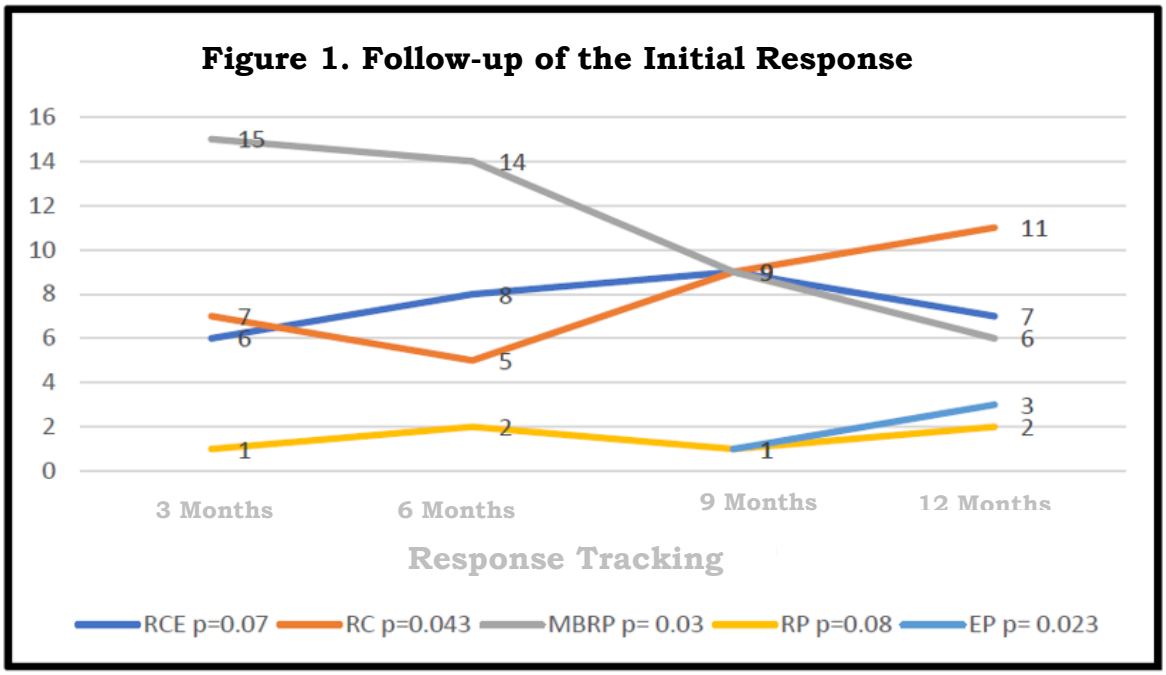


Figure 2. survival according to the proteasome Inhibitor Received

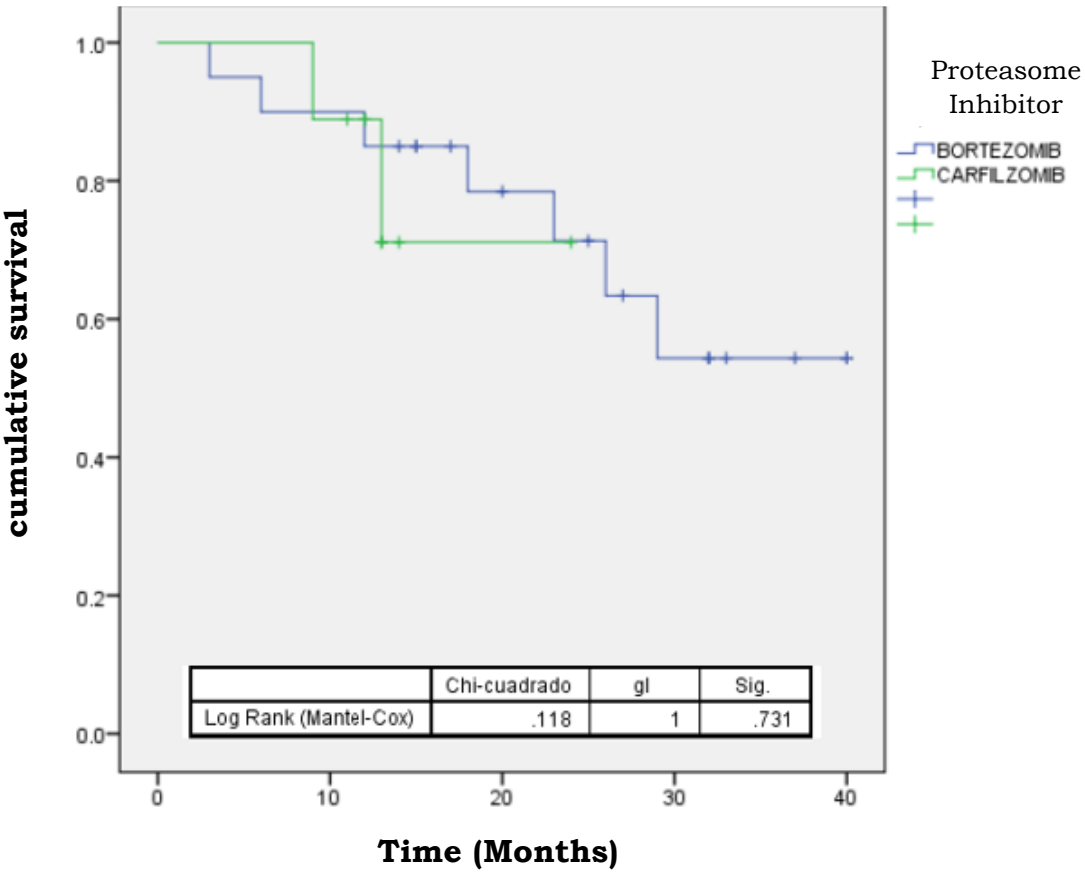
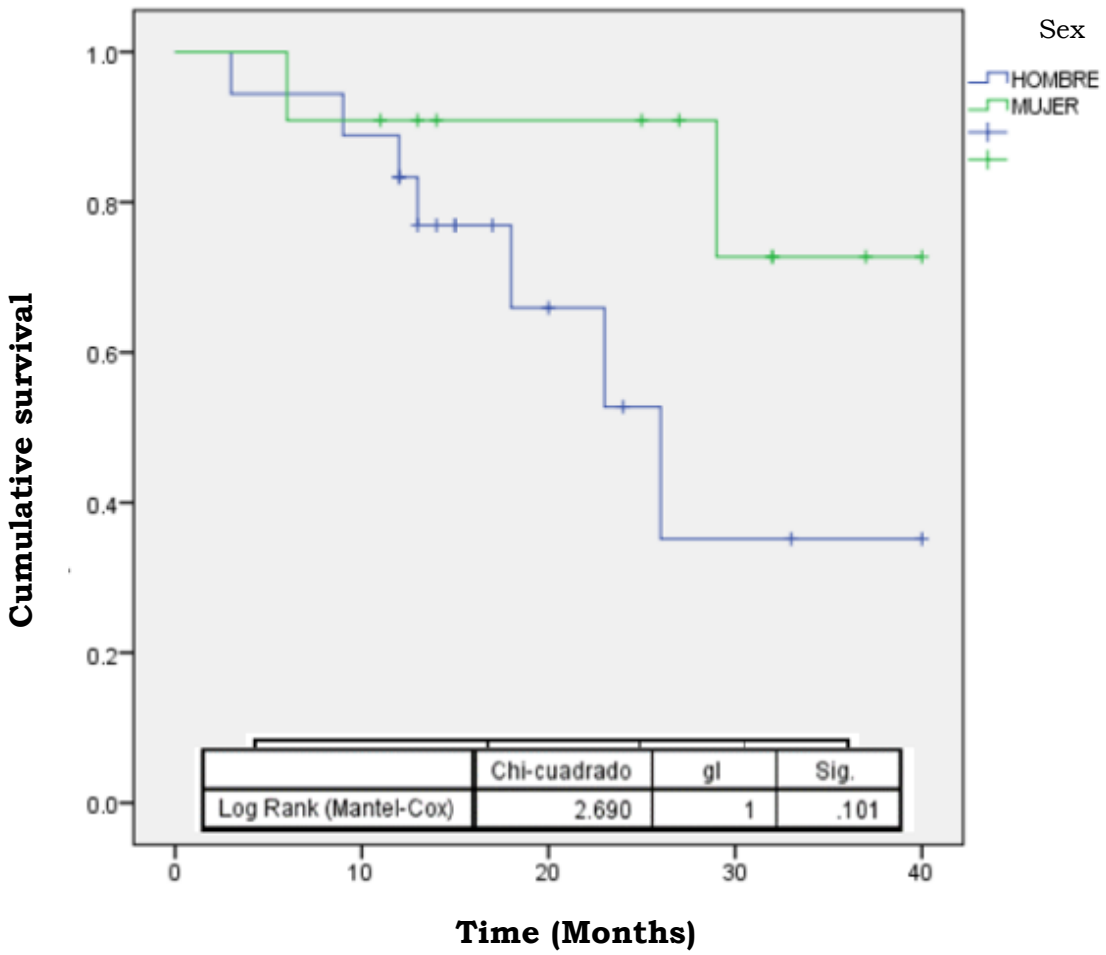


Figure 3. Global survival by sex



Discussion

The literature reports a higher prevalence of myeloma in men vs. women (1.1:1),55 In our study, a higher proportion of male vs. female patients was observed, which was not statistically significant, despite the fact that the subgroup of male patients corresponds to 62%. (p=0.265); Since the patients studied were only those who met the inclusion criteria, this must be taken into account when interpreting the results. In our study, the male gender was associated with lower overall survival (p=0.17); on the other hand, the male gender is associated with other variables that confer a poorer prognosis, Table 8, Table 15.

The general mean age at diagnosis was 54 years, in the analysis by sex, men have a lower age at diagnosis than women 50 vs 58 years (p=0.071), this is close to what has been published in the literature where the reported mean is 58 years.[56].

The percentage of plasma cells at diagnosis was 43% slightly higher than the average reported in the literature; however, an increase in this percentage is observed in men compared to the average number of plasma cells in women (54% vs 32% p=0.061), it has been suggested that patients with a percentage greater than 50% of cells plasma cells in bone marrow have lower overall survival.57 In a study of 389 patients, it was observed that 81% had >10% plasma cells in BM (39.5% ± 23.4%), this was related to an increase in creatinine levels, total proteins, and a decrease in albumin58. In our study, no difference was observed in relation to the percentage of plasma cells and albumin values (mean 3.6 mg/dL) in both women and men; however, we found that in the group of men the mean plasma cell count is 54%, and this was also associated with lower overall survival Table 8, Table 15.

In the case of renal function, women presented a lower rate of FGP, and paradoxically, women present a lower percentage of plasma cells at diagnosis Table 8.

The most frequent type of myeloma was Kappa light chains (27% p=0.05); furthermore, it is also the main type of myeloma seen in women. In men, the most frequent myeloma was IgG lambda (20.6% p=0.05). It is likely that since it is not a random sample, the results are not compatible with the international literature that reports IgG kappa myeloma as the most frequent with 50%-65% of cases.55 In the case of IgA myeloma, we found a total percentage of 34.3%; furthermore, IgA myeloma was associated with lower overall survival Table 8. In the IgA kappa subgroup in our study, we found a frequency of 20.6% (p=0.008); on the other hand, in the case of free light chain myeloma we found a total frequency of 34.3% with 27.5% for kappa chains and 6.8% for lambda chains (p=0.05), this differs from the international literature where 20% is described for both IgA myeloma and light chain myeloma.[55]

CRAB criteria with >10% plasma cells are recognized as myeloma-defining events2. In our study we found significant alterations (p<0.05) in calcium 11%, kidney failure 14.5%, anemia 40%, lytic lesions 62%. The results are very similar to those reported in a study conducted with 1,027 patients at the Mayo Clinic, where alterations compatible with CRAB criteria were reported in the following percentages: calcium 13%, creatinine 19%, anemia 35%, lytic lesions 66%.15 has suggested that the presence of lytic lesions and hypercalcaemia confers a decrease in survival, while patients with renal failure and anemia did not show differences in survival.59 We observed that the differences in CRAB criteria for men and women are statistically significant Table 8. On the other hand, in the linear model we observed that all the CRAB criteria were related to lower overall survival, higher tumor load and severity of the disease, Table 15.

In the analysis of B2 microglobulin, a mean of 8.4 mg/L was reported in men vs 3.9 mg/L in women. It is known that patients with multiple myeloma and/or kidney failure have high levels of B2 microglobulin; however, values above 7mg/L have been related to a high tumor burden and a deleterious impact on survival.60 We can observe in our study that men have higher levels of B2 microglobulin compared to women ($p<0.036$), we did not find a direct association between B2 microglobulin levels with decreased survival.

The mean albumin for men and women was 3.6 gr/dL, in the univariate and bivariate models we found no associations with decreased survival. It has been reported that levels below 3.5 gr/dL are more frequent in patients with advanced age, poor functional status, and low hemoglobin levels, was also identified as a pretreatment prognostic factor, in general, the low level of albumin reflects more severe disease.[61]

We can observe in our study that the mean of globulins for men and women was 7.4 gr/dL. In the analysis by patient sex, we identified higher globulin levels in men compared to women, 9.7 gr/dL vs. 3.6 gr/dL, respectively ($p<0.001$). High globulin levels have been associated with hyperviscosity syndrome, mainly in Waldenstrom's macroglobulinemia (30%) and in multiple myeloma (2%-6%). The main type of immunoglobulin associated with hyperviscosity is IgA62; In a study with a small cohort, a mean of 4.98 gr/dL (2.3-11.6) was observed, this does not seem to negatively affect the response to treatment or overall survival.63 We can observe in our study that there is an evident increase in globulin levels probably related to higher percentages of patients with IgA (34.3%), in addition, we also observed that the higher globulin load in men is related to more aggressive disease and higher tumor burden and decreased overall survival, Table 8, Table fifteen.

The monoclonal peak, also called M protein, had a general mean of 3.16 gr/dL; In the analysis by sex of the patients, a greater elevation is again observed in men compared to women (4.2gr/dL vs 1.76 gr/dL), this was not statistically significant ($p = 0.313$). Approximately 40% of patients with symptomatic multiple myeloma have M protein levels less than 3 g/dL.64 On the other hand, it is evident that the greater increase in plasma levels of M protein in men is associated with greater tumor burden and severity. disease in this group of patients.

Cytogenetic alterations that confer adverse outcomes have been reported to include t(4;14), t(14;16),t(14:20, aneuploidy, del(13), del(17p), gain(1q21), and these they are found in 25% of patients with multiple myeloma.65,66 We took for this study the translocations considered high risk in the Revised International Staging System for Multiple Myeloma {t(4;14), t(14;16) , del(17p)}.37 We found a general average of 20.6% of high-risk cytogenetic alterations, in the analysis of patients by sex, men presented a higher percentage compared to women, which was statistically significant (17.2% vs 3.4 % $p=0.003$), this coincides with what is reported in the international literature We can observe that high-risk cytogenetic alterations occur mainly in the subgroup of men who also have high levels of other

biochemical characteristics associated with greater tumor burden and severity of disease (B2 microglobulin, plasma cells in OM, lytic lesions). In a recently published study, it was observed that t(4;14), t(14;16), and some others were associated with B2microglobulin levels > 5.5 mg/L and more than 50% of plasma cells in MO, in addition to t (4;14) was associated with higher serum monoclonal peak; on the other hand, this same study associated better responses with proteasome inhibitors to translocations that include the immunoglobulin heavy chain (IgH).67 We can consider that the cytogenetic alterations found in this study clearly correlate with a greater aggressiveness of the disease in the male subgroup; however, we did not find a decrease in overall survival associated with high-risk cytogenetic alterations.

The ISS was published in 2005 based on B2-microglobulin and albumin levels, 25% of patients were classified as stage I, 35% as stage II, and 40% as stage III; stage III patients have a much shorter survival (29 months) vs stages I and II (62 and 44 months, respectively).68 We report a frequency of ISS in stage I of 20.5%, stage II at 37.8%, and stage III at 41.2 % also corresponding to albumin and B2microglobulin levels. When we analyze the subgroups by patient sex, we again observe that the percentage of men in stage III at diagnosis is significantly higher than women (34.4% vs. 6.8%, respectively, p= 0.042). It is interesting to observe that the mean albumin level remains the same in both groups; however, the mean of B2 microglobulin is significantly higher in men than in women (p= 0.036), which has already been explained in previous paragraphs. Therefore, we can conclude that according to the international literature, men have a more advanced stage at diagnosis that is associated with a higher tumor burden, more aggressive disease, and lower overall survival compared to women, Table 8, Table 15.

Currently recommended first-line treatment regimens include 3 drugs, in the NCCN guideline the combination of bortezomib, lenalidomide, dexamethasone (category 1) is recommended as first-line for transplant candidates and non-candidates;69 other regimens with bortezomib, cyclophosphamide and dexamethasone have shown benefit for patients with acute renal failure and those who do not have access to lenalidomide. The use of carfilzomib, cyclophosphamide, and dexamethasone is also recommended for patients with kidney failure and/or neuropathy.69 In our setting, access to lenalidomide and bortezomib is limited due to high cost; therefore, therapy with bortezomib and/or carfilzomib, thalidomide, and dexamethasone in addition to monthly cyclophosphamide is of choice for most patients.[69]

In this study, an overall response rate of 100% was observed after 3 cycles of treatment, 21% obtained ROSC, 24% CR, 52% VGPR, 3% PR. At 12-month follow-up, 24 patients obtained ROSC, 11% CR, 20% VGPR, 7% PR, 3% EP. This agrees with the international literature; In a study conducted in 66 patients with bortezomib, lenalidomide, and dexamethasone, an overall response rate of 100% was obtained with 29% CR, 11% near complete response (nCR), 27% VGPR, and 22% PR.[56]

In the study EVOLUTION in 2008, at the 4th cycle of treatment with bortezomib, dexamethasone and cyclophosphamide (VDC) a rate of ROSC 0%, CR 3%, VGPR 13%, PR 63% was found. In the same study, the best response at the end of 6 cycles was ROSC 9%, CR 22%, VGPR 41%, PR 75%, EP 3%.70 The regimen with bortezomib, lenalidomide and dexamethasone (VRD) vs lenalidomide, dexamethasone RD showed PFS of 43 months vs 30 months and an overall survival rate of 75 months vs 64 months, respectively; CR rate was 15%, MB PR 27.8%, PR 38%, EE 15.7%, progressive disease 2.8%. This led to the treatment of first choice being VRD.70 These results agree with those obtained in this study at the end of the 12-month follow-up With the introduction of new treatments including proteasome inhibitors (PIs) and immunomodulators (IMDs), the overall survival of patients with multiple myeloma has improved in the last 15 years.71 Evidence has grown around the idea that a profound response early confers a greater benefit to patients with MM.72 One of the current objectives to obtain a prolonged response is to obtain a rapid decrease in the monoclonal peak at the 4th. Treatment cycle eligible and ineligible patients for transplantation.[72]

In our study, it was observed that after 6 months of treatment, the rate of patients with VGPR decreases from 52% to 48%, in contrast to patients with CR, which decreases from 24% to 17%. This suggests that patients with an early profound response will not necessarily achieve better overall results.

It is possible that a rapid reduction in tumor burden indicates that there is a population of cells that are sensitive to therapy, however, this can also generate resistant plasma cell clones with poor late results, which is consistent with reports in the literature. In a recent study at the Mayo Clinic, patients with high cytogenetic risk as well as those with ISS III were more likely to have a rapid response, it was found that patients who had early responses (≤ 3 months) experienced inferior results compared to those obtaining gradual or partial responses before 3 months (OS 126 vs 30 months).[47]

We observed that most of the patients who died obtained VGPR after 3 months of treatment; however, in the univariate, multivariate and linear regression analysis it was not significant ($p<0.05$). When the types of response obtained in the evaluation periods (3, 6, 9, and 12 months) and their association with overall survival were analyzed, it was observed that patients with ROSC, CR, and VGPR had higher overall survival Table 10.

It is important to note that the group of male patients has lower overall survival than women. However, this was not statistically significant ($p=0.101$). Table 13, Figure 3. Due to the fact that it is not a random sample, it must be taken into account for the analysis of the results; On the other hand, it is evident that the group of men has more poor prognostic factors. In addition, patients at the National Cancer Institute of Mexico present in advanced stages of the disease. In the multivariate model, the characteristics associated with lower overall survival were: CRAB criteria, ISS II-III, IgA Kappa myeloma, elevated globulins, > 50% of plasma cells in BM, and male sex. Table 15.

Regarding the analysis of survival by type of proteasome inhibitor, no statistically significant differences were observed between patients who received carfilzomib and/or bortezomib Table 14, Figure 2. This is consistent with current treatment regimens where both types of proteasome are part of the treatment of first choice.[69]

Conclusion

Patients with multiple myeloma at the National Cancer Institute present in more advanced stages of the disease, which confers a poor prognosis.

Male patients have clinical and biochemical characteristics that are associated with a higher tumor burden and severity of the disease; In addition, they have lower overall survival.

The best responses obtained in the first cycles of treatment do not determine better survival.

In this study, treatment with the proteasome inhibitors carfilzomib vs. bortezomib is not superior to one another. Prospective studies comparing first-line proteasome inhibitors are required in Mexico to adopt the best treatment for our population.

It is necessary to carry out actions to recruit patients in the early stages of the disease and improve access to new drug treatments that have shown greater efficacy in order to improve the survival rate of patients with multiple myeloma.

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