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Research Article

OUTCOMES AND EVOLUTION IN THE TREATMENT OF MULTIPLE MYELOMA IN THE LAST 20 YEARS EXPERIENCE OF A MEXICAN INSTITUTION

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ABSTRACT

Objective: Analyze the effectiveness of four therapeutic programs in patients with Multiple Myeloma (MM), seen in the last 20 years in a single hospital.
Patients and Methods: Retrospective and comparative. With symptomatic MM patients de novo, treated from January-1995to December-2014. Characteristics of the MM and the impact to organs were studied. Treatment: melphalan-prednisone (MM01), polichemotherapy-interferon (MM02), melphalan-prednisone-thalidomide (MM03) and bortezomib-cyclophosphamide (or doxorubicin) - dexamethasone (MM04).
Results: 237 patients. No difference in gender. Age: median 58 years; mode 50. No-secretory: 25%; Type G 54%; kappa chains 91%; plasmoblastss 26% (average); plasmacytomes in 23%. With 27% of kidney failure; hyperviscosity 4%.Without predominance in any therapeutic arm (p> 0.09). Distribution of treatments: MM01 39 (17%); MM0263 (27%); MM03 85 (37%); MM04 44 (19%); 6 eliminated by early death (3%). Remissions (complete or partial): MM01 87%; MM02 73%; MM03 92%; MM04 85%. The average of (PFS) progression-free survival (months): MM01 24; MM02 38; 86 MM03; MM04 63. 81 patients received another treatment, by failure or progression. Variables with negative prognostic value (p< 0.03): Salmon-Durie, ISS, existence of plasmacytoms, hypoalbuminemia, and amount of plasmoblasts.
Conclusion: The age of presentation is unusually low. The PFS is comparable to other studies. The scale of Salmon-Durie is as useful as the ISS.

INTRODUCTION

Multiple myeloma (MM) is a clonal alteration of plasma cells which proliferate and accumulate in the bone marrow; lead to cytopenias, bone destruction and, in most cases, the production of a monoclonal protein (Fonseca *et al*., 2007). Apparently, the first patients with this disease were described by S Solly in 1844. T Watson and H Bence Jones in 1845 were those related clinical findings with alterations in the urine that led to the identification of the protein B Jones. Von Rustizky used, first, the term multiple myeloma 1873 (Diaz-Maqueo, 2006). For a long time there were no therapeutic resources that could significantly alter the natural course of the disease. But, recently have been appearing. It should be noted that the progress is seen in multiple directions. The existence of new drugs must be integrated with new strategies that facilitate the action of innovativedrugs. Thus, from the point of view of diagnosis it has been highlighted the importance of orienting to own data of the disease and not centrally in their consequences (Rajkumar, 2016).

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This allows more opportune diagnosis. Although Durie and Salmon staging remain in effect, the prognostic criteria of the International Staging System (ISS), and then others, have been very useful to choose treatments (Greipp *et al*., 2005). The existence of several effective drugs for MM, has made necessary to have prognostic data, applicable in different populations, which allow selecting between various drugs and get a reasonable balance between tolerance and effectiveness. There are already molecular and cytogenetic classifications with very accurate forecasting approaches that contribute to better possible treatment indication (Kumar *et al*., 2012; Bergsagel *et al*., 2013). In the last decade of the past century, the autologous transplantation (ABMT) begun to be used, preceded by high-dose chemotherapy. Initially it was the usual treatment for young patients. Now the indication has been extended at least until age 65. The effectiveness of the ABMT has not been improved by the transplant itself, but by induction regimens that include more effective drugs (Thalidomide, Lenalidomide, Bortezomib) (Cavo *et al*., 2011) which allow to reachbetter remissions, before moving to the ABMT. Another major change is the use of these drugs in stages postransplant (Ludwig *et al*., 2012). Melphalan, first drug routinely used for the MM, has had a long stay, since 1962, as the main antimyelomadrug; now is the regularly drug occupied as conditioning agent in the

ABMT. But the major therapeutic advances are due to the introduction of thalidomide, bortezomib, lenalidomide, carfilzomib and others.
Alone or in combination has allowed greater efficacy and reduced side effects. And it is frecuent to include two old drugs in this combinations, which had been revalued: dexamethasone and cyclophosphamide. Until 2000, patients had a median overall survival of 2.5 years. Now, until 2010, it is of 6 years (Kumar *et al*., 2012). This is a result of new drugs and new strategies that include the use of ABMT. The purpose of this study is to relate the experience of a hospital (CMN "20 de Noviembre" ISSSTE) in the therapeutic management of MM, over the past 20 years. It involves considering treatments based on melphalan, various alkylating agents, thalidomide and bortezomib. Evaluate and compare these drugs is necessary and important for several points of view, technical-medical centrally but there are other implications, particularly economic. Previously a review has been made of the fate of MM patients managed with ABMT (Alvarado Ibarra *et al*., 2015). Here they will be analyzed only those who did not received it.

MATERIALS ANDMETHODS

The study is retrospective, comparative and longitudinal. Patients older than 16 years treated at the hematology from January 1995 to December 2014 were included. The patients were considered for antimyelomatreatment effectiveness, from the end of the first month after inclusion to any program. The data were taken from the clinical records and database of the Hematology Service. The diagnosis of multiple myeloma was set according to the following criteria:

Majorcriteria

- Plasmocytoma (biopsy)
- Monoclonal immunoglobulin
- Abnormal plasma cells (clonal) in bone marrow.
- Serum light chains (SLC), abnormal ratio (normal: 0.26 to 2.0).

Minor criteria

- Corrected Ca with albumin > 11.5 mg / dl
- Creatinine> 2.0 mg / dl.
- Hemoglobin <10 g / dl
- Osteolytic lesions.

Diagnosis

A major criterion and more than one minor. Exclusion criteria were inability to initiate anti-myeloma specific treatment for any reason and the lack of complete file. Elimination criteria were inability to initiate or continue treatment by decision of the patient or family and the existence of comorbidities incompatibles with antimyeloma therapy. The following variables were recorded: age, sex, blood count, blood chemistry, serum calcium (corrected with albumin), serum albumin, immunoglobulins, SLC, Bence-Jones, B2 microglobulin, lactate dehydrogenase (LDH), C reactive protein (CRP), karyotype, radiographs of the skull, spine and long bones. Stage according to Durie-Salmon criteria and International Prognostic Index (ISS) (Greipp *et al*., 2005) was calculated. They were consigned the treatments used in first and second line, its immediate result, time to progression-free survival (PFS), deaths and their cause and overall survival (OS).

The treatments were

MM01

- Melphalan, 0.25 mg / kg / day, orally (days 1 to 4) every four weeks (18 cycles)
- Prednisone 60 mg / m2SC / day, orally (days 1 to 4) every four weeks (18 cycles).

MM02

First month

- Week 1: Vincristine IV, 1 mg / day (day 1). IV cyclophosphamide 500 mg/m^2BS (day 1).Melphalan orally, 0.25 / kg / day (days 1 to 4).Prednisone orally, 60 mg / day (day 1 to 4).
- Week 3: alpha-interferon SC, 5,000,000 / day (days 1 to 3)

Second month

- Week 1: Vincristine same. BCNU IV, 50 mg/m^2BS(day 1).Epirubicin IV, 40 mg/m^2BS / day (day 1). Prednisone same.
- Week 3 equal.

Continue the sequence until completing 18 months.

MM03

- Melphalan 0.25 mg / kg / day, Orally, in fast, (days 1-4) every four weeks (18 cycles)
- Prednisone 60 mg / m2SC / day (day 1 to 4) every four weeks (18 cycles)
- Thalidomide 100 mg / day (continuous). If the patient can not tolerate, at least 50 mg, quit the program.

MM04

- Bortezomib: 1.3 mg/m^2BS, IV, days 1, 4, 8, 11, 22, 25, 29, 32, cycles 1 to 4. Continue with the same dose, days 1, 8, 22, 29, cycles5 to12.
- Cyclophosphamide: 300 mg/m^2BS, IV on days 1, 11, 22 and 29, cycles 1 to 4. Continue with the same dose, days 1 and 22, 12 or 5 cycles:
- Doxorubicin 30 mg/m^2BS IV, 1 and 22, cycles 1 to 4. Continue with the same dose, day 1of each cycle, cycles 5 to 12.
- Dexamethasone 40 mg IV, after application of Bortezomib.

Definition of Terms

Response: The magnitude of response to treatment was assessed according to criteria of the International Myeloma Working Group, 2003 (IMWG), as follows:

- Complete Remission (CR): No serum light chains (SLC) or urinary (ULC); without plasmacytomas; with less than 5% plasma cells in bone marrow. Responses with normal SLC relation and the absence of clonal plasma cells were included.

- Partial Remission (PR): More than 49% reduction in component M; more than 89% reduction of ULC; more than 49% decrease in the difference between SLC affected, more than 49% reduction in plasma cells in bone marrow; more than 49% reduction in plasmacytomas. Responses over 90% of component M and less than 100 mg / 24 hours ULC were included.
- Progression Reappearance of manifestations of disease or lack of response (failure).

Statistic analysis:

Frequencies are expressed in percentages, medians, means and real limits. Comparisons of numerical variables were performed using ANOVA or chi^2 for nominal. Survival analyzes were performed using the Kaplan and comparisons with logrank. Association tests with Kruskal-Wallis and chi^2. The confidence intervals (CI) were calculated at 95%**.**

RESULTS

237 patients were included. The basic findings income, are in Table 1. The gender distribution was 116 for women and 121 for men. The median age was 58 years and mode of 50. The youngest patient was 30 years old. Osteolytic lesions were found in 96% of patients, with involvement in one region (24%), two (24%), three (13%) and four (35%); injuries were more frequent in the MM03 arm, and had 37% of patients (p = 0.0001).

Table 1. General characteristics observed when entering. Its distribution is similar among treatments (p>0.22)

DATA	RESULT
Female. (Number/%)	121/51
Age (median/limits)	59/30-92
Hemoglobine g/dL. (Median/limits)	10.7/4.8-16.0
Albumine g/dL. (Median/limits)	2.8/0.9-4.7
B^2microglobuline mg/L. (Median/limits)	2.1/0.1-14.0
Calcium mg/dL. (Median/limits)	10.1/8.5-16.0
Creatinine mg/dL. (Median/limits)	1.7/0.4-14.5
Renal Insufficiency. (Number/%)	63/27
Hyperviscosity. (Number/%)	10/4.2
Lactic deshydrogenase UI/L. (Number/%)	183/73-1'153
C-reactive protein mg/L. (Number/%)	13.3/0.2-162

Table 2. Multiple Myeloma characteristics in relation to the initial treatment

DATA	MM01	MM02	MM03	MM04	P=
TypeIgA (N=)	10	9	21	7	0.22
TypeIgG (N=)	19	29	52	27	0.22
Non Secretor (N=)	10	24	15	11	0.22
Peak (g/L, media)	3.6	3.9	4.9	4.1	0.44
Kappa (%)	90	94	93	88	0.92
Lambda (%)	9	28	39	23	0.92
Bence-Jones (%)	26	33	48	18	0.007
Plasmoblasts %	32	22	25	24	0.09
Plasmocytoma (%)	21	16	36	19	0.21

Bone fractures were found in 70 cases; only one in 66, two in 3 and three in 1; in the patients included in the arm MM03 these changes were more repeated, 37% with p = 0.0001. In Table 2 are the characteristics of the MM and its distribution among the different initial treatments. The maximum value of the monoclonal immunoglobulin was 31.0 mg / dL. Bence-Jones protein was found in 82 patients more frequently in the arm MM03 (p = 0.007). Plasmacytoma was found in 29 patients, distributed according to the same table. The frequency of first-line treatments was: MM01 39 (17%); MM02 63 (27%); MM03 85 (37%); MM04 44 (19%). Six patients were not evaluable for initial response, they died before the first month; the cause of death was infection. Only the arms MM01 and MM02 were used until 2000. The MM03 was used from 2001, and MM04 from 2007. The use of the MM03 and MM04 was related to the availability of thalidomide and bortezomib. Initial responses for each program are noted in Table 3.

Table 3. Associated response to the initial therapeutic program (p= 0.0001)

PROGRAM	CR	PR	NR	NE	TOTAL
MM01 (N/%)	14/36	20/51	5/13	0	39/100
MM02 (N/%)	13/21	33/52	17/27	0	63/100
MM03 (N/%)	52/59	29/33	4/5	0	85/100
MM04 (N/%)	26/58	12/27	6/13	0	44/100
Sin tratamiento	0	0	0	6/3	6/100

CR: Complete Response. PR: Partial Response
NR: No response. NE: Not evaluable

The highest relative frequency of patients who went to follow up, with complete or partial remission, was with MM03 and MM04. The probability of PFS after receiving initial treatment, is in Figure 1. For MM04, whose employment began 84 months before the end of the study, the mean is 63 months (confidence interval 59-67), for MM03 86 (69-103); MM02 with the mean of 38 months (28-49); with the MM01 the mean was 24 (20-28). The fate, after receiving initial treatment only, is summarized in Table 4. 49 patients died: 22 by infection, 16 by disease activity, 7 various causes (comorbidities) and 4 by renal failure. The program MM02 accumulated the highest relative number of deaths, 35% (p = 0.0001). Fifteen patients were eliminated because of abandonment. One hundred seventy-three patients are still in follow-up. Eighty-one received a second therapeutic program: 70 of them because of progression and progression and 11 because of failure after the first program.

Table 4. Behavior after receiving only the initial therapeutic program (p= 0.0001).

PROGRAM	IN FOLLOW UP	DEATH	ELIMINATED	TOTAL
Non (N/%)	0	6/100	0	6/100
MM01 (N/%)	29/74	6/15	4/10	39/100
MM02 (N/%)	37/59	22/35	4/6	63/100
MM03 (N/%)	70/82	9/11	6/7	85/100
MM04 (N/%)	37/84	6/14	1/2	44/100

Most were treated with the same schemes, without repeating the already used. The combination of vincristine, adriamycin and dexamethasone (VAD) was used in 20 patients; in one lenalidomide was administered. The responses are detailed in Table 5. 11 complete responses and 40 partial were achieved, and in 30 cases there was no improvement.

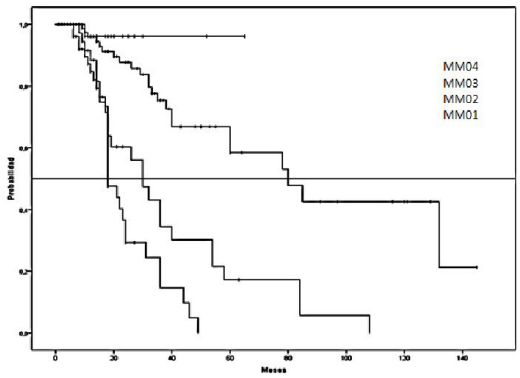

Figure 1. Only with initial treatment, progression free survival possibility with each option (p=0.003)

PROGRAM	CR	PR	NR	TOTAL
MM01 (N/%)	0	10/83	2/17	12/100
MM02 (N/%)	0	4/33	8/67	12/100
MM03 (N/%)	6/29	11/52	4/19	21/100
MM4 (N/%)	4/27	8/53	3/20	15/100
VAD /N/%)	0	7/35	13/65	20/100
LEN (N/%)	1/100	0	0	1/100

CR: Complete Response. PR: Partial Response. NR: No Response. VAD: Vincristine, Adriamicine, Dexametasone. LEN: Lenalidomide

The largest percentage amount of remissions were obtained with MM03 and MM04. With the MM01, MM02 and VAD only partial responses were achieved or the progression did not stop. The progression-free survival ranged from 11 to 46 months (p = 0.335). In Figure 2, are included the final results of progression-free survival or death at the end of the study, after all the treatments used, and in relation to the initial response: complete remission, partial remission or failure. The patients who had complete remission had not yet reached median survival; when they obtained partial remission the median was 37 months (CI 34 to 40); if there were no response to treatment the mean was 8 (CI 2-14).

Table 6. State at the end of the study of all patients, related to the initial response (p= 0.0001)

	FINAL STATE					
INITIAL R	CR	PR	PRO	DEA	ELI	TOTAL
RC (N/%)	47/86	15/39	7/26	15/20	21/52	105/43
RP (N/%)	8/14	23/58	14/52	32/42	17/43	94/40
FALLA (N/%)	0	1/3	6/22	23/30	2/5	32/14
WTx (N/%)	0	0	0	6/8	0	6/3

INITIAL R: initial response. CR: Complete Response. PR: Partial Response. PRO: In Progression. DEA: Dead. ELI: Eliminated. WTx: Without treatment

Table 6 is the clinical state, at the end of the study, of all patients initially included. Fifty-five (23%) in complete remission; 39 (17%) in partial remission; 76 deaths (32%); with progression 27 (11%) and the removed were 40 (17%).
The OS, figure 3, is related to the magnitude of the initial remission, indicating that patients with complete remission had not yet reached the median; with partial remission the median is 69 months (CI 28 to 110); with failure 9 months (CI 0-19). The OS of all patients at the end of the study, compared to initial treatment received is in Figure 4. There is difference between the four treatments (p = 0.003); there is no difference between MM03 and MM04 (p = 0.20). Multivariate analysis was performed with all data. The results are in Table 7.

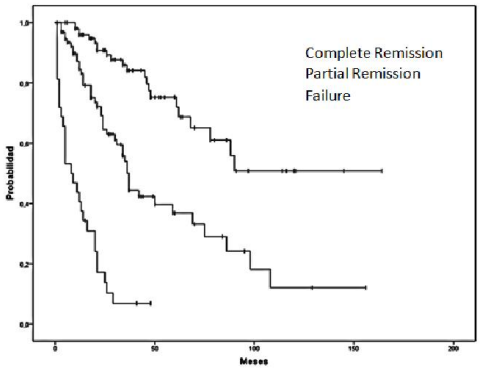

Figure 2. Only with initial treatment, Event free survival probability (Progression or dead), related to the obtained response (p=0.0001)

Table 7.Variables with prognostic influence, on the final evolution of patients

VARIABLE	P=
Salmon-Durie	0.023
ISS	0.03
Plasmocytomas	0.003
Albumine (<3.0 g/dL)	0.001
Plasmoblasts (>20%)	0.001

ISS: International StagingSystem

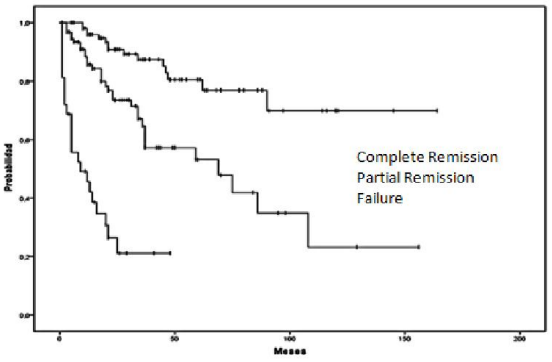

Figure 3. Only with the initial treatment, Overall survival probability, related to the obtained response(p=0.0001)

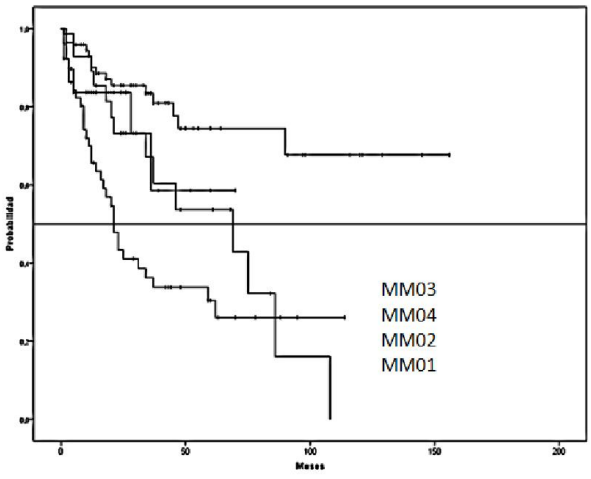

Figure 4.At the end of the study, Overall survival probability, related to the initial treatments (p=0.002)

The findings with negative prognostic influence: stages II and III of the Durie-Salmonstaging system and those indicated in the IPI, including hypoalbuminemia (<3.0 g / dL). The existence of plasmacytomas and the amount of plasmablasts (> 20%) also showed negative predictive value. Intolerance to treatment was apparent in MM03 and MM04. MM03: drowsiness 33 (40%); myalgia and arthralgia 17 (20%); thrombotic events in 6 (7%). MM = 4: neuropathy 29 (65%); diarrhea 20 (45%); 20 nausea (45%) and anorexia (21 (48%). In MM02 pancytopenia 18 (29%).

DISCUSSION

In the 20 years were attended 305 patients with diagnosis of MM, including those who went to ABMT and analyzed in another publication (Alvarado Ibarra *et al*., 2015). During that time, the most common hematologic neoplastic disease was acute leukemia (N = 698); MM is the second. Other authors have reported similar findings (Renshaw *et al*., 2004). Its debut, in relation to the gender, is almost equal with little predominance in males. This observation is in other report (Rosenberg *et al*., 2015). In our patients, the disease appeared in lower than usually reported ages. The measures of central tendency, in our patients, indicate prevalence in less than 60 years of age, including mode. It is a younger population than approximately 65 years in the Mexican[14]and foreign population[11]. The official registry of United States (http://www.seer.cancer.gov/seerstat) marks 70 years as median presentation. We have no explanation for this characteristic of our group. Based on the knowledge of the high prevalence of obesity present in Mexicans and reports that indicate that overweight appears to be a contributory factor in the appearance of MM (Wallin and Larsson, 2011), it is convenient to formally study this possible relation. In addition to epidemiological considerations, the immediate significance of the relative youth of this population indicates the need to use, more often, aggressive and effective treatments. Practically all patients showed osteolytic lesions in one to four regions. They were defined only with conventional radiographs of the skeleton. With the same technique the frequency of osteolytic lesions and osteopenia, have been reported in 70% of patients with MM. In our cases, osteolysis, although very frequent, did not have prognostic implications in the evolution of the disease although it had implications in the quality of life for its association with fractures.

The target organ damages are not different from those reported by other authors (Kyle and Rajkumar, 2009). Disease own characteristics regarding the frequency of types A, G and Nonsecretory is comparable to other reported in Mexico (Ruiz_Arguelles *et al*., 2004). We did not found asignificantly difference between their fate. Recently it is reported that, with the use of new drugs, Nonsecretory MM has better pronóstico (Chawla *et al*., 2014). There is predominance, as in other series, of light chains kappa; before the present century, the determination of light chains was rarely made. Patients positive for Bence Jones had no different prognosis. Both, the staging system of Durie and Salmon, and the ISS showed the expected impact prognosis previouslly described[1]. Additionally, the amount of plasmoblasts in bone marrow, and the existence of plasmacytomas, negatively influenced the destiny of the disease.

Both situations are indicative of the magnitude of neoplastic invasion and represent, in our universe, evidence of MM with bad prognosis. The assessment of prognostic data in our review, is deficient in the study of genetic and molecular factors that are not made and are increasingly more necessary (Fonseca *et al*., 2007; Debes-Marun *et al*., 2003; Mai *et al*., 2015). The four evaluated therapeutic arms, include the available drugs and to the therapeutic strategy used in last years of past century (except bortezomib). The melphalan-prednisone combination was the usual treatment and the first to show real benefits in the survival of patients with MM. In a review in which 13 prospective, comparatives and randomized studies of patients with MM were comparedwith patients with MM whom received Melphalan – Prednisone or Combined chemotherapy, sometimes referred to as polychemotherapy, there is no significant difference in the frequency of reference and overall survival between the two grupos (Bergsagel, 1989). In a demonstrative study, at that time, with these programs, it was informed: 45% response (total or partial) and median overall survival of 30 months[22]. Those results are not different from many others, including those presented here.

The introduction of thalidomide for MM, before 2000, associated with melphalan and prednisone, initially in cases of relapsed or refractory, showed very favorable changes in remission and OS (Kneller *et al*., 2000). Soon, it begun to be used in various combinations in patients de novo. Its effectiveness still justifies it a recommended treatment[24]. Our experience begun in 2001 and its significance in the number of remissions and progression-free survival and overall, is very superior to that obtained with only melphalan-prednisone or polychemotherapy. The results are comparable to other reports (Palumbo *et al*., 2008; Palumbo *et al*., 2005), including a meta-analysis (Hicks *et al*., 2008). However, the efficacy of thalidomide is accompanied by frequent adverse reactions (Wu *et al*., 2005): drowsiness, constipation, myalgias and venous thrombosis. Although low doses have comparable activity, with higher doses, toxicity does not go away and can be a limiting factor in adherence to treatment. We found comparable adverse reactions, including frequency of thrombotic events, as in other reports (Palumbo *et al*., 2008; Palumbo *et al*., 2005).

Since its introduction, bortezomib has been used in association with other drugs. When used as first-line drug, it was initially combined with melphalan and prednisone (San Miguel *et al*., 2008). After that, it has been integrated in programs with anthracycline or cyclophosphamide. In a recent study which analyzes 504 patients with previously untreated MM (Mai EK, Bertsch *et al*., 2015), the combination bortezomib-doxorubicin-cyclophosphamide-dexamethasone versus bortezomib-dexamethasone, reported similar frequencies of remission and survival. These data is similar to that reported here and, as is reported in this and other publications, superior to melphalan-prednisone-thalidomide. Bortezomib, however, is accompanied by the known adverse effects that limit its use. Its SC administration decreases such adverse events and makes it more tolerable, apparently without reducing its effectiveness. In a meta-analysis (Jin *et al*., 2015) the conclusion is that it does not diminish the effectiveness and patients prefer the SC administration. We have started using this scheme of administration. Side reactions, in our case, are abundant in terms of neuropathy. Using bortezomib intravenously is a good explanation for this finding and we hope it decreases when passing to the SC administration (Jin *et al*., 2015).

Currently there are several different drugs in different associations, for treating patients who are not candidates for ABMT. There are contemplated several, which has as main drug: bortezomib, lenalidomide, carfilzomib or other morerecent options. In most options, dexamethasone is a welcome host (Rajkumar, 2016). It is very apparent that the treatments tested in this review are already behind current and forthcoming options. Great strides are evident from the melphalan-prednisone old combination. Second-line treatments are always less effective than first line treatments. In a very recent communication (Andrzej Jakubowiak, 2012), apropos of drugs used by us, complete remissions are reported, second line, from 7% to 18% and partials from 32% to 89%; progression-free survival is from 14 to 57% at 3 years of follow-up. Our results are in these limits. When included new drugs, complete remissions are reported from 15% to 29%, partials from 20% to 94% and progression-free survival at 2 years, is reported from 15% to 64%. The impact is less, with the same drugs than that obtained when used at first-line in patients de novo.

Is an indispensable goal, according to different opinions, to obtain maximum possible response (Palumbo *et al*., 2009) with the treatment used; in effect, the impact of the magnitude of the initial remission translates into increased progression-free survival. This is found in patients seen by us even when the levels of remission are less stringent than those recommended[33], by the necessity to adjust them to include, with the same criteria, treated patients from different times.

Modern therapeutic strategy includes the use of ABMT and new drugs; combinations withmelphalan, dexamethasone, cyclophosphamide, thalidomide, bortezomib, lenalidomide, carfilzomib and pomalidomide (Rajkumar, 2016) are contemplated. Others are beginning to be used. With these resources significantly increases progression-free survival and overall survival. It should be noted that, under present conditions, these clear progress in therapy will not be available to all patients suffering MM because of the high cost. Conclusion.The age of presentation of the MM is several years younger in the population here referred, if contrasted with other identified in Mexico and the United States. The inclusion ofbortezomib and thalidomide in different combinations, doubles the overall survival and the progression-free survival, compared to treatments with melphalan-prednisone, and combinations of alkylating added with interferon.

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