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Melphalan, Dexametasone and Thalidomide, Autoloogous Stem Cell and Maintenance with Low Doses of Thalidomide

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Melphalan; Dexamethasone; Extramedular

1. Abstract

1.1. Background: Treatment of patients with multiple myeloma (MM) have a great advances, however, it is appear that relapse and refractory stage continued to be the rule in this setting of patients, thus recently MM will be considered as an chronic disease, and the strategies will be adequate, employ regimens with minor and toxicities.

1.2. Patients and Methods: We performed an open label clinical trial, employed drugs wit limited toxicities: melphalan, dexamethasone and low doses of thalidomide, following for autologous stem cell transplant, and after were allocated to received Thalidomide at low doses for 18 months or no (control group)

1.3. Results: From July 2013 to December 2018,164 patients with diagnostic of untreated MM, initially the received an induction phase with melphalan, dexamethasone and low doses of thalidomide, following by autologous stem cell transplant and after allocate to received maintenance therapy by 18 months or no (control group)

1.4. Results: Complete response and very good partial response were achieved in 131 (79.8%), at final analysis, actuarial curves at 5-years, show that the use of maintenance therapy improved out. Acute toxicities grade III or IV were not observed, delay in treatment was observed in only 1.2 % of the cycles. No second neoplasms has been observed.

1.5. Conclusion: The use of an les toxic regimen in induction phase ,is feasible and results were at least no inferior a more toxic and expensive regimens. The use Thalidomide at low doses by 18 months improve outcome, without the risk of late toxicities.

2. Introduction

Multiple myeloma (MM) is a B-cell malignancy characterized by a monoclonal expansion and accumulation of abnormal plasma cells in the bone marrow. The clinical symptoms of MM are heterogenous, and include bone complications, impairment of hematopoiesis, renal dysfunction, and extramedular disease. A greater advance has been achieved in pathology, biology of neoplastic cells and identification of prognostic factors.

However, MM remains as an incurable neoplasia, even the introduction of new drugs, than has been employed in combination, most of those combinations, with improvement in overall survival (OS) [1]. However, relapse is the rule, at this time, treatments for relapsing/refractory MM, can achieved complete response in about 30 to 45 %, [2,3] but, progression-free survival (PFS) and OS are minor to 2 years and another regimen will the probed. Thus, recently MM, has been considered as a chronic disease, and taking in consideration that age are ,generally > 70 years, presence of comorbidities and organ toxic effects as previous treatment, has been suggested that initial treatment will be employment with less toxicities [4-8].

Thalidomide (Th), an immunomodulator, has been employed in the treatment of MM, combined with steroids , and response and outcome,where better that combined chemotherapy [9-16]. Thus, the search of another effective drug, shows that lenalidomide (L), another immunomodulator, achieved an excellent drug, but associated with severe acute and late toxicities with the same response

rate and outcome. Although Th, show no-severe toxicities, surprisingly, L has been adopted as the drug, more employed in the treatment of MM, even L show a high rate of severe hematological toxicities, and an increase (3-12%) of second neoplasms , an also is expensive that Th (). L, is not available in our institution, and some years ago, we show that an combination of biological modifiers: acid all transretinoic, interferon an dexamethasone as cytoreduction regimen previous of autologous stem cell transplant (ASCT), with excellent results and tolerable toxicities [10], acid transretinoic was eliminated in our institution ; thus, we performed an combined regimen that include: melphalan, dexamethasone and low doses of Th, followed by ASCT and doses of Th, as maintenance treatment. The end points were, If the use of Th as maintenance therapy at low-doses can be effective and improved outcome, at if the use of this combined regimen is effective, with low toxicities, as previous cytoreductive after ASCT, the second end-points were to analyze acute and late toxicities.

3. Patients and Methods

From July 2013 to December 2018, patients were eligible, if the fulfilled the following criteria entry: symptomatic myeloma bone disease, bone marrow with > 20 % abnormal plasma cells, serum monoclonal protein more of 1.0 g/dL, and/or urine monoclonal protein > 2.0 g/dL, normal levels of hemoglobin, platelets and granulocytes, performance status (PS) < 2, age > 30 to 70 years, patients between 70 to 75 years, were eligible if they have an performance status of 0, and did not have comorbidities, previously untreated, normal hepatic, cardiac and renal function, if the patient at diagnosis show high levels of creatinine, were treated with steroids and saline solutions, until normal creatinine were normal. Negative for human immunodeficiency, hepatic B and virus tests.

3.1. All Patients Received the Following Treatment

Cytoreductive treatment, melphalan 6 mg/m2, , oral , daily for 1-4 days, dexamethasone 40 m standard dose , oral, days 1 to 4, 8 to 12 and 19 to 21 days, Th oral 100 mf standard dose, oral, days 1 to 21 of each cycle of the six planned cycles. If patient achieved complete response (CR), or, very good partial response (VGPR); ASCT transplant was performed, as previously were reported [10]. Four weeks after ASCT, oral Th, 100 mg, oral daily, from 1 to 21 days of each 28-days cycles, for 18 months.

Radiotherapy was administered if the bone myeloma disease were evident: fracture, eminence of fracture or severe pain, doses and fields were according to the anatomical site. Zoledronic acid, 4mg, standard dose, intravenously every 28 days of 24 months [14,15].

Stage was defined according with the International Revised Criteria [13].

4. Statistically Analysis

All patients were included and analyzed on an intention-to treat basis. The method of Kaplan and Mier were used to calculate progression-free survival (PFS) and overall survival (OS), and the groups were compared using the log-rank test stratified by baseline characteristics. Sensitivity analyses included using an unadjusted log-rank test, a generalized Wilcoxon test.

5. Results

An total of 164 patients were included in the study; baseline characteristics are show in the Table 1, no statistically differences were observed; 131 patients achieved CR or VGPR, an ASCT were performed according the protocol. With a median follow-up of 5.1 and range of 2.3 to 8.9 (years); actuarial curves at 5 years, show that PFS were statistically significant in patients, whose received maintenance: 71.3 % (95 %Confidence interval CI: 63.4 % - 78.%) and 53.6 (95% CI: 45.3%-61.8%) , $p < 0.001$. Also OS were better in patients with maintenance: 65.6 % (95%CI: 59 % -71%), that control group: 58% (95% CI: 51-63%) $p < 0.001$.Neither prognostic factors showed any statistically differences.

Toxicity: no hematological toxicities grade III or Iv were observed. No delay or diminished doses of all drugs were reduced or delayed were observed.

Radiotherapy was well tolerated, only local grade II toxicity was observed. No differences in PFS and PS were observed between patients that received or not radiotherapy.

Zoledronic acid was well tolerable, previously we show that the use of zoledronic acid reduce the risks of fracture.

Table 1: Baseline characteristics:

Number (%)	All patients	CR/VGPR	Maintenance		P
			Yes	No	
Number	164 (100)	131 (79.)	67 (51.0)	64 (48.8)	0.868
Age (years) median	64.8	66.2	66.0	64.1	0.675
Range	34-76	45-77	42-71	44-76	0.810
Sex					
Male	76 (46.3)	70 (53.6)	36 (53.7)	34 (53.1)	0.666
Female	88 (53.6)	61 (46.5)	31 (46.2)	30 (46.8)	0.910
Stage					
II	15 (9.6)	10 (7.6)	8 (11.9)	2 (3.1)	0.126

III	149 (90.8)	121 (92.3)	59 (88)	62 (96.8)	0.301
M-compoment					
G	97 (59.1)	89 (67.9)	44 (65.6)	45 (70.3)	0.187
A	41 (25.1)	29 (22,3)	16 (23.8)	13 (20.3)	0.665
Light-chain	26 (15.8)	13 (9.9)	7(10.4)	13 (20.3)	0.124
PS *					
0,1	64 (31.5)	54 (41.2)	23 (34.3)	31 (48.4)	0.127
2	83 (50.6)	66 (50.3)	36 (53.0)	30 (46.8)	0.788
2	21 (12.8)	11 (8.3)	8 (11.9)	3 (4.6)	455
Bone lesions	130 (79.2)	97 (74.6)	65 (97.1)	50 (74.6)	0.03

• Performance status

6. Discussion

We show in this prospective clinical trial, that the use of a treatment with moderate toxicity, would be to achieve the same results, when a more aggressive treatments has been employed; also, we show that Th remain to be an excellent drug in the treatment of patients with MM, as maintenance therapy at low doses improve outcome.

During the las 20 years, multiple approaches has been developed in the treatment, as induction therapy, although improvement in PFS and OS, acute (infections) and late (second neoplasm) reduce the ossibility of that the patients could be cured [16].

Some recent papers , has been to analyze what will be the best strategies in the sequent of treatment , and it is appear that the possibility of cure is not currently available in MM patients. Thus, they suggested that the initial treatment will be diminished the excessive toxicities of some of these regimens, because they regimens could produce organ damage and limited the use of more aggressive treatment, when relapse occur [2,3]. Thus, our results could be promissory, because CR and VGPR were similar or best to another approaches, with an reduce acute and late effects. It is evident, that some bias are evident, it an study performed in a single center, central pathology revision was no performed, but, it is a uniform group of patients , and longer follow-up.

Maintenance therapy in MM, is accepted always in all treatments, but, the principal problem is, what drug and duration of treatment. Th was the first immunomodulator that show clinical efficacy against MM, with good tolerance and increased in response type, when as employed in induction phase, and maintenance. Lenalidomide, a immunomodulator agent, with the same efficacy, but, acute toxicities, specially hematological, has been limited the use, in most cases, reduced or delay treatment will ne to employed, thus, it is appear that the best dose has not been defined, moreover is more expensive, and sites with limited founds, cannot be employed, moreover, the risk of the apparition of a second neoplasms, generally aggressiveness and lethal, appear to be as considered as dangerous agent.

Thus, taking in consideration, we performed the present study, with a “low” doses of Th, that compared with the control group, show that is feasible, because no delay and reduced doses, but a prolonged time. Recently, an observational study in some countries of Latin America, and Th is more employed, probably by expensive cost of lenalidomide [17].

Present of lytic lesions, is frequent patients with MM that need treatment, to avoid the risk of fractures, surgery, and use of drugs to the pain, not has been analyzed, recently Nehlsen, show that radiation could be employed local radiation, without limitations in the treatment [12]. We employed radiotherapy, to sites that could be dangerous, the fields and the doses were according the radiotherapists; although no improvement in outcome, neither produce delays or reduce the use the chemotherapy.

Finally, zoledronic acid will be indicated in all patients, because reduce the risks to developer bone myeloma disease, as previously reported [14,15].

7. Footnotes

Study design and concept, adquisition of dates, analysis and interpretation of data, drafting of the manuscript , critical revision of the manuscript for important intellectual concepts , write the manuscript were performed by both authors.

7.1. Ethical Approval: The studies were performed according the guidelines of the Helsinki Proyect, and was approved by the Ethical and Scientific Committees of our institution.

7.2. Funding Support: The study did not receive any grants or funding and was performed with the owner resources of The Mexican Social Security Institute.

References

1. Kumar S, Balzer L, Calander NS, Giralt SA, Hillengass J, Freidlin B, et al. Gaps and opportunity in the treatment of relapse/refractory multiple myeloma. Blood Cancer J. 2022; 12: 98.
2. Costello G, Mikhail OR. Therapy sequential strategies in multiple myeloma. Who, What and why. Fut Oncol. 2018; 2018:95-99
3. Derudas D, Caprano F, Cerchione C. Old and new generations of immunomodulators drugs in multiple myeloma. Pan Min Med. 2020; 62: 207-19.
4. Palumbo A, Facont T, Sonnelved P, Bladè J, Offidani M, Gay F, et al. Thalidomide for treatment of multiple myeloma. 10 years later. Blood. 2008; 111: 3965-77.
5. Hoisten SA, McCarthy PI. Immunodulators a drugs in multiple myeloma. Drugs. 2017; 77: 505-20.
6. Moreau O, Hulin G, Macron M, Caillot D, Chaleteix C, Roussel M, et al. VTP is superior to prior intensive therapy in multiple myeloma. Blood. 2016; 2016: 2569-74.
7. Hulig C, Facont T, Rodon P. Pegourie B, Benboubker L, Doyen C, et al. Efficacy of melphalan and prednisone post-thalidomide patients older,75 with newly diagnosed multiple myeloma. J Clin Oncol. 2009; 27: 364-70.
8. Stewart AH, Trudel S, Bahlis NJ, et al. Optimal maintenance and consolidation therapy for multiple myeloma in actual clinical practice. Blood. 2013; 1219.
9. Wang X, Li Y, Yan X. Efficacy and safety novel agents based therapy in multiple myeloma. Biomed Res Int. 2016; 2016: 6848902
10. Lagman G, Tremplay P, Barley K, Barlogie B, Cho HJ, Jagannath S, et al. The effect of novel therapies in High molecular risk multiple myeloma. Clin Adv Hematol Oncology. 2017; 15: 870-874.
11. Aviles A, Nambo MJ, Neri N. Biological modifiers as cytoreductive therapy before stem cell transplant. Ann Oncol. 2005; 16: 219-21.
12. Nehlsen AP, Sidhu KK, Moshier E, Richter J, Richard S, Chari A, et al. The safety and efficacy of radiation therapy with concurrent cyclophosphamide, etoposide and cis-plates systemic therapy for multiple myeloma. Clin Lymp Leuk Myel. 2022; 22: 192-7.
13. Palumbo A, Avet L, Sehn H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised international strategies system for multiple myeloma. J Clin Oncol. 2015; 2015: 2863-9.
14. Aviles A, Cleto S. Long-term analysis of efficacy and toxicity of zoledronic acid in patients with multiple myeloma,. Clin Res Clin Trials. 2023; 7(2).
15. Aviles A, Nambo MJ, Huerta-Guzman J, Cleto S, Neri N. Prolonged use of zoledronic acid (4 years) dot not improve outcome in multiple myeloma patients. Clin Lymph Leuk Myeloma. 2017; 207-10.
16. Yine L, Yin N, Huit T, Yuang Z, Sun H. Lenalidomide and the risks of severe infections in patients with multiple myeloma. Oncotarget. 2017; 8: 4659-600.
17. Tietsche -Morais V, Martinez-Banos D, Penafield DM, Miguel CE, Vela-Ojeda J, Remaggi G, et al. Multiple myeloma patterns and clinical outcome in the Latin America haemato-Oncology (HOLA) observational study, Br J Haematol. 2020; 188: 383-9.