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Research Article

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Long-Term Analyis of Efficacy and Toxicidad of Zoledroinic Acid in Patients with Multiple Myeloma

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ABSTRACT

Myeloma bone disease MBD) is the most common and dangerous effects in patients with multiple myeloma. Bisphosphonates (BP), are the treatment of choice. But, efficacy and adverse events has not been evaluated at longer follow-up. Thus, we review our experience in a tertiary cancer center, whose received zoledronic acid (ZO): in a large number of cases (1041) and longer follow-up: 4.2 to 21.6 years (median 13.8).Skeletal event (SE) were statistically better in patients who received ZA: 52 events: 8.96%,compared to 207 (42.6) $p < 0.001$ in patients whose did not received ZA, independently if the patients received autologous stem cell transplant or not. But, progression free survival and overall survival did not show any benefit. Adverse events were minimal, and jaw necrosis were not observed.

Thus, we considered that ZA, remain to be the best treatment of MBD, but, we confirm that ZA did not show at longer follow-up any antitumor effect.

Keywords: Multiple Myeloma, Myeloma Bone Disease, Bisphosphonates, Zoledronic Acid

Introduction

Multiple mieloma (MM) is an hematological disease that cause osteolytic lesions,excess immunoglobulin secretion, renal impairment , and myelosuppression. In this patients 80-90% development myeloma bone disease (MBD) that is associated with pathological fractures, spinal cord compression and pain that produce imported condition in quality of life and need specific treatments: surgery, radiotherapy, and strong use of drugs to ameliorate the pain, that can cause interference in the treatment of MM, affected the possibility of a better response and overall survival (OS) [1,2]. MBD is the result of multiple biological changes in the microenviroment that produce an accelerated overall bone loss and the formation of focal osteolytic lesions. Almost 40 years ago bisphosphonates (BP) and recently monoclonal antibody were introduced in the treatment of BMD, that reduced the risks of skeletal event (SE) and any anti-tumor effect was observed in some studies. Mechanisms of action has been extensively analyzed [3-5]. Thus, the use of these drugs has been considered as obligatory treatment in patients with MM [6-9]. However, until now, dosage, interval and duration of treatment, and presence of late toxicities has not been stablished. Thus, we revised our experience in a large number of patients, with longer follow-up, the first -point was to evaluate the benefit of zoledronic acid (ZA) in relationship to delay the appearance of SE, secondly observed the late adverse events; and finally evaluate the antitumor effect.

Material and Methods

From March 1999 to December 2017, 1041 patients with MM and received ZA, were found, the criteria entry was a follow-us: Pathological and biochemical diagnostic of MM, high risk according to the ISS model, without previous treatment, age > 18 years old without upper limits, presence of a last one lytic lesion, if renal damage were observed this were under control, whit no-history of smoldering myeloma or monoclonal gammopathy, performance status < 2. The chemotherapy employed at these time was a combination of biological agents, followed by autologous stem cell transplant if the patient were eligible, if not, they treated with a combination of thalidomide, dexamethasone an melphalan (); at relapse or progression, treatment was based on the clinical conditions or state of MM, the most common was bortezomib, dexamethasone: lenalidomide is not available in our institution [10,11]. Taking in consideration that jaw necrosis has been reported as frequent adverse event, dental care was carefully performed, every 6 moths for an expert in dental care. ZO acid was administered when chemotherapy was beginning at dosage of 4mg every 28 days, and continue during until progressive disease, or death from any cause.

Ethical Statement

All patients signed an inform consent to participate in the study, and Ethical and Scientific Committee approved the study.

Results

Table 1 show the demographic characteristics of the patients; as expected more younger patients was observed in the transplantation

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patients, but, another prognostic factors did no showed any statical differences. Table 2, show that SE were statistically more frequent in patients that did not received ZA, independently of the primary treatment. At longer follow-up, outcome measured for PFS and OS, were not statistically different. Acute adverse events, were minimal and well controlled. Surprisingly, jaw necrosis has not been observed.

Table 1: Demographic Characteristics

	Transplant			No-Transplant		
	No (%)					
	Zoledronic Acid					
	Yes	Not	P	Yes	Not	P
Number	368 (53.1)	324 (46.8)	0.817	188 (53)	161 (46.3)	0.799
Age: Median	59.8	50.1		68.4	70.3	
Age: Range	36-70	30-70		57-79	59-81	
Sex: Male	209 (56.2)	199 (61.4)	0.607	87 (46.0)	88 (54.1)	0.211
Sex: Female	159 (43.2)	125 (37.0)	0.112	101(53.7)	73 (45,4)	0.344
High risk	368 (100)	(324) 100	(NA)	188 (100)	161 (100)	NA
Subtype						
IgG	224 (60.8)	201 (62.8)	0.886	99 (53.9)	93 (57.7)	0.944
IgA	82(22.2)	89 (23.8)	0.776	59 (31.1)	48 (29.1)	0.665
Light -chain	50 (13.9)	32 (9,8)	0.332	28 (14.8)	20 (13.6)	0.212
Non-secretory	12 (3.2)	13 (09)	0.111	2 (10.2)	0	
Anemia	355 (96.4)	320 (98,7)	0.775	164 (87.2)	156 (96.8)	0.125
Bone lesion	359 (97.3)	315 (98;7)	0.901	170 (87.2)	156 (96.8)	0.454

Table 2: Results

	Transplant			No-Transplant		
	Yes	Not	P	Yes	Not	P
Skeletal event	24 (6.5)	106 (32.7)	p < 0.001	26 (13.8)	107 (63.3)	p <0.001
Relapse	162 (44.0)	224 (66,0)	p <0.01	89 (97.1)	122 (64.0)	p < 0.01
PFS *	38 (30.2-45.6)	39 (33.0-46.4)	0.213	34 (28.0-41)	35 (29-43)	p 0.878
OS **	57 (49-63.2)	58 (50.1-64.4)	0.755	49(44-56.3)	54 (47 -58.4)	p .450

*Actuarial curves at 5 years, PFS progression-free survival (Confidence interval; (95%).

**Actuarial at 5-years, overall survival (Confidence interval 95%).

Discusion

We show the results of retrospective in patients with MM and BMD who were treated with ZA, from the beginning of the treatment until refractory disease, or death secondary to any causes. ZA was administered from a large time: 2 to 136 (median 76) months. We confirm that the use of prolonged time, remain to be benefit to BMD, because SE, were statistically better in patients whose received ZA compared with patients whose did not received ZA. Multiple studies have been demonstrated that the use of BP, will be employed in all cases of BMD [12-15]. Also BP has been employed in patients with biochemical relapse, in maintenance therapy, asymptomatic disease [6,7]. Himmeltein et al, as confirm that are benefit in another malignancies and BMD associated, but the intervals of doses will be more longer [12]. In previous study we show that ZA is effective to diminished the risk of SE, with and better quality of life, because adverse events are no severe and were well controlled, in neither of our patients we observed jaw necrosis [13,14]. Recently, denosumab, an monoclonal antibody has been proven that are effective to diminished the risk of SE, when this drug was compared with ZA, show the same efficacy, and toxic profile, thus both could employed, the unique advantage of denosumab is these drug is administered orally [15]. Recently, new drugs has been tested in BMD, with the same effectiveness in BMD, but these drugs no appear to be better , and comparative studies has not has been performed [16,17].

Conclusion

We confirm in this study that ZA remain to be useful in the treatment of BMD, reducing the risks of SE, and the complications associated, late toxicities were not observed, including jaw necrosis, the interval between doses will be every 4 weeks, the dosage remain to be 4 mg, as standard dose. Administration will be continued during all the course of MM, until death.

Conflict of Interes: Both authors disclose any conflict of interest
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