Zoledronic acid as compared with observation in multiple myeloma patients at biochemical relapse: results of the randomized AZABACHE Spanish trial

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ABSTRACT

This study analyzed the anti-myeloma effect of zoledronic acid monotherapy by investigating patients at the time of asymptomatic biochemical relapse. One hundred patients were randomized to receive either zoledronic acid (4 mg iv/4 weeks, 12 doses) (n=51) or not (n=49). Experimental and control groups were well balanced for disease and prognostic features. Zoledronic acid did not show an antitumor effect according to changes in M-component. However, there were fewer symptomatic progressions in the experimental group than in the control group (34 *versus* 41, respectively; *P*=0.05) resulting in a median time to symptoms of 16 *versus* 10 months (*P*=0.161). The median time to next therapy was also slightly longer for the treated group than the untreated, control group (13.4 *versus* 10.1 months), although the difference was not statistically significant (*P*=0.360). The pattern of relapses was different for treated *versus* control patients: progressive bone disease (8 *versus* 20), anemia (24 *versus* 18), renal dysfunction (1 *versus* 2), and plasmacytomas (1 *versus* 1, respectively). This concurred with fewer skeletal-related events in the treated group than in the control group (2 *versus* 14), with a projected 4-year event proportion of 6% *versus* 40% (*P*<0.001). In summary, zoledronic acid monotherapy does not show an antitumor effect on biochemical relapses in multiple myeloma, but does reduce the risk of progression with symptomatic bone disease and skeletal complications. *This trial was registered in the ClinicalTrials.gov database with code NCT01087008*

Introduction

Although current treatments for multiple myeloma (MM) induce responses in more than 90% of patients,[1] the disease remains incurable in most of them. The pattern of relapse is quite heterogeneous, including frequent biochemical relapses in the absence of clinical symptoms. Although patients with such relapses may not need therapy for a certain period of time, they are at high risk of symptomatic progression and therapy requirement. The current recommendation of the International Myeloma Working Group (IMWG) is that patients in biological relapse should not be treated until they develop clinical symptoms,[2] except in those cases with the so-called "significant paraprotein relapse" in whom the relapse is represented by a rate of rise or absolute level of M-protein at which the risk is considered very high; in these cases it is recommended that myeloma therapy is restarted without delay.[3]

Intravenous bisphosphonates are indicated in patients with MM, with or without detectable osteolytic bone lesions on conventional radiography, who are receiving antimyeloma therapy as well as in patients with osteoporosis or osteopenia resulting from myeloma.[4] Although the main reason for their indication is that bisphosphonates prevent skeletal-related events, there are also controversial data suggesting that zoledronic acid (ZA) has an anti-myeloma effect. This hypothesized antitumor effect is based on findings in pre-clinical studies,[5-7] reproduced in small series of patients,[8] and subanalyses of clinical trials,[9,10] particularly, the large MRC-IX trial[9] conducted in newly diagnosed patients treated with either chemotherapy (CVAB) or thalidomide-based therapy (CTD), who were assigned to receive either ZA or clodronate. The ZA-treated group had significantly longer progression-free survival and overall survival compared with the clodronate-treated group. However, this study included several randomizations, such as thalidomide maintenance, and it is not easy to dissect the real anti-tumor effect from other beneficial anti-myeloma effects of ZA treatment. Moreover, in patients with smoldering MM, treatment with bisphosphonates did not delay transformation into symptomatic disease although it was associated with a reduction in the onset of skeletal-related events.[11-16] Accordingly, the real anti-tumor effect of bisphosphonates remains to be elucidated. Patients at biochemical relapse, in whom the standard of care is to delay treatment until symptoms emerge, represent an ideal group to investigate the anti-myeloma effect of ZA.

The AZABACHE trial was conducted by the Spanish

 doi:10.3324/haematol.2015.128439
The online version of this article has a Supplementary Appendix.
Manuscript received on March 30, 2015. Manuscript accepted on May 29, 2015
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Myeloma Group (GEM/PETHEMA) in order to evaluate whether treatment with ZA delays the time to next therapy (TNT) in patients with MM in biochemical relapse, compared to the standard management with observation only.

Methods

Trial design

In 2010, GEM/PETHEMA activated the "Analysis of Zoledronic Acid therapy in MM in BioCHEmical relapses" (AZABACHE) trial. This randomized, prospective, open label, phase IV trial included MM patients in asymptomatic biochemical relapse after a prior response to standard therapy. Patients were randomly distributed into two groups: (i) the experimental group, in which patients received ZA, and (ii) the control group in which patients did not receive any treatment. Patients in the experimental group received zolendronic acid, 4 mg in a 15-minute intravenous infusion every 4 weeks, for a total of 12 doses, plus standard supportive care; the control group received only supportive care. The trial and all procedures were performed in accordance with the Helsinki Declaration and were reviewed and approved by the Spanish National Agency and the Ethics Committees of all the centers involved.

Inclusion and exclusion criteria

All patients had to meet the following inclusion criteria: (i) 18 years of age or older; (ii) confirmed biochemical relapse of MM after an initial response, without symptoms derived from the disease and (iii) signed informed consent to participation in the trial. Relapse was defined according to the IMWG criteria of 2006.[2] Patients treated for any symptom of myeloma-related organ or tissue impairment or who had received bisphosphonates in the preceding 3 months were excluded; this meant that most patients had had a prior response longer than 24 months, which is the usual time that bisphosphonates are given in Spanish trials.[17]

Variables for evaluation

The main end-point was TNT, which was calculated as the time that elapsed between inclusion in the protocol, and the moment at which new antimyeloma therapy was initiated based on the appearance of a clinical relapse or death from any cause. The appearance of a significant paraprotein relapse was not considered as a clinical relapse but it was qualified as a cause for initiating anti-myeloma when considering the TNT.[3]

Other end-points for evaluation were: (i) response rate during the follow-up period (12 months of therapy or follow-up, or until drop-out of the trial) according to the IMWG criteria;[3] (ii) time to clinical symptoms, defined as the time between inclusion in the trial and the development of a clinical (CRAB) relapse;[3] and (iii) time to a skeletal-related event, defined as the time between inclusion in the trial and the occurrence of any the following: bone fracture (vertebral and non-vertebral), requirement for bone radiotherapy, requirement for bone surgery, or hypercalcemia. The presence of osteonecrosis of the jaw and/or renal dysfunction was carefully assessed throughout the treatment and follow-up periods. In addition, we evaluated the characteristics of symptomatic relapses occurring in patients included in the trial (i.e. type of CRAB) and associated clinical and biological variables. All patients were monitored every 4 weeks for disease response, CRAB symptoms and adverse events. Recommendations for the safe use of bisphosphonates, as stated in the commercial labeling of ZA, were specifically followed, as were the recommendations of the European Myeloma Network.[17,18]

A more detailed description of the methods can be found in the *Online Supplement.*

Results

Patients' baseline characteristics and protocol compliance

From June 2010 to July 2012, 100 patients were recruited: 51 in the ZA group and 49 in the control group. The baseline characteristics of the patients at the moment of inclusion in the trial are shown in Table 1. Their median age was 68 years (range, 40-87). The M-component was IgG in 72% of cases, and IgA in 25% of cases; 3% had only light-chain MM. The biochemical relapse occurred after one, two or three or more lines of therapy in 67%, 22% and 11% of cases, respectively. Prior treatment included transplant in 66% of patients, bortezomib in 53% and immunomodulatory drugs in 32%. Bone lesions were present at the initial diagnostic X-ray skeletal survey in 68% of patients. Overall, 32% of patients had developed one to three skeletal-related events prior to trial inclusion. The median time between the biochemical relapse and inclusion in the protocol was 4 months (range, 1-21). The median bone marrow plasma cell infiltration was 3% (range, 0-96%) by morphology. Fluorescence *in situ* hybridization/cytogenetic findings were abnormal in 52% of cases: t(11;14) in 19%, Rb deletion (alone) in 17%, del(p53) in 8%, t(4;14) in 4% and t(14;x) in 4%. Hemoglobin, creatinine, and calcium levels were normal (as per protocol). β_2-microglobulin and C-reactive protein levels were also normal in all cases. Patients in the ZA-treated and control groups were well balanced for prognostic features, prior response, and time from diagnosis to inclusion in the trial (Table 1).

Regarding protocol compliance, 44 patients completed the 12 visits for the interventional phase of the trial and four terminated before completion due to patients' refusal to continue participation (n=2) and development of other diseases (n=2). The remaining 54 patients stopped the trial because of progression before 12 months (n=52), tox-

Table 1. Characteristics of the patients.

	Control group (n=49)	ZA Group (n=51)	P
Female gender	53%	41%	0.316
More than one prior line of therapy	41%	26%	0.103
High-risk cytogenetics	17%	15%	0.876
Prior osteolytic bone lesions	73%	63%	0.288
Prior skeletal-related event	31%	33%	0.947
Prior transplant	57%	75%	0,091
Prior bortezomib	57%	49%	0,431
Prior immunomodulatory drug	43%	22%	0.032
Age >65 years	63%	62%	0,929
M-component >10 g/L	89%	92%	0.711
C-reactive protein >1 mg/dL	22%	24%	1.000
β_2-microglobulin >3 mg/L	33%	36%	1.000
Hemoglobin >12 g/dL	81%	76%	0,638
High lactate dehydrogenase	8%	9%	1.000
Time from diagnosis to recruitment >5 years	29%	35%	0.469

icity (n=1, osteonecrosis of the jaw) and initiation of cytotoxic therapy due to a significant paraprotein relapse (n=1). The distribution of patients in the trial is summarized in Figure 1.

With a median follow-up for surviving patients of 38 months, TNT since inclusion in the study was 10.9 months for the overall series of patients (Figure 2A). The reason for starting therapy was the development of symptomatic disease in all but three patients in whom therapy was started because of a significant paraprotein relapse in the absence of symptoms. The median time to clinical symptoms was 11.3 months, which was essentially the same as the TNT (Figure 2A). Time to a new skeletal-related event was not reached during the follow-up of the trial, with a projected percentage of skeletal-related events of 21.5% at 4 years. The median overall survival from inclusion in the trial was 47 months (Figure 2B).

Efficacy

Myeloma responses were not observed during the treatment with ZA and, therefore, no antitumor effect of ZA therapy was demonstrated. Of note, two patients in the control group experienced small M-component reductions that were not sustained over time. However, the proportion of patients progressing to symptomatic disease was lower in the ZA-treated group (n=34, 67%) than in the control group (n=41, 83%, *P*=0.05), although this only partially translated into differences in the survival curves. Accordingly, TNT was slightly longer for the ZA-treated group than the control group (median: 13.4 months *versus*

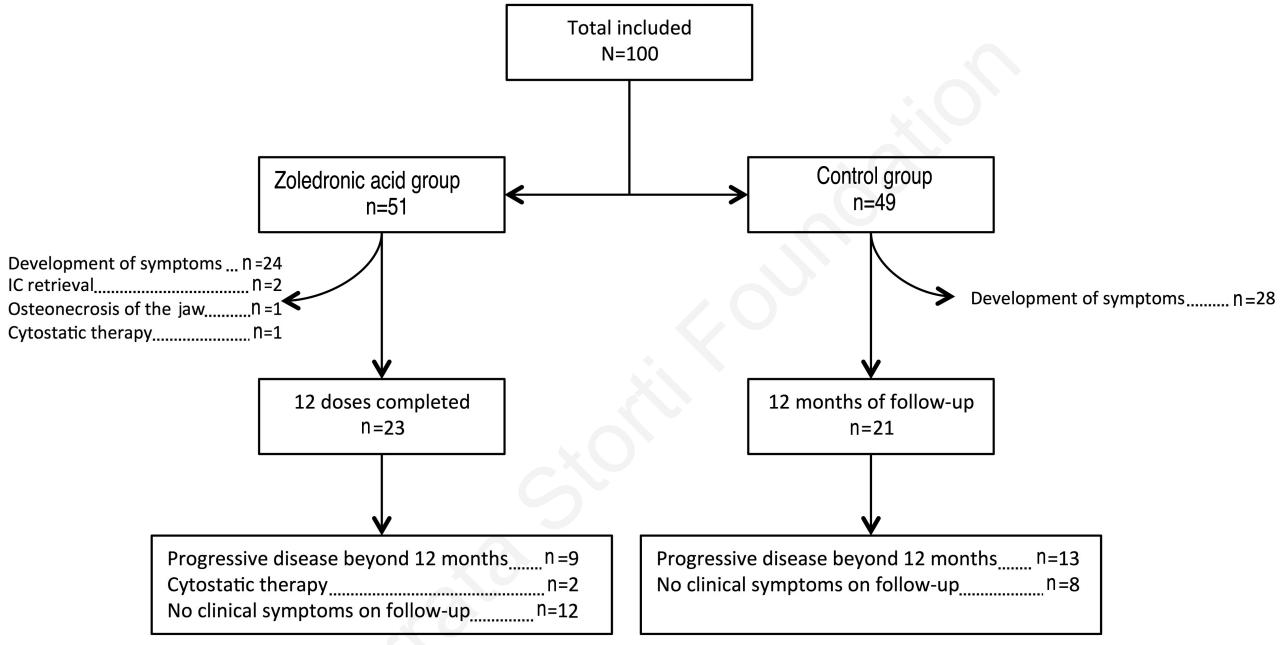

Figure 1. Flow-chart of the patients' distribution through the trial.

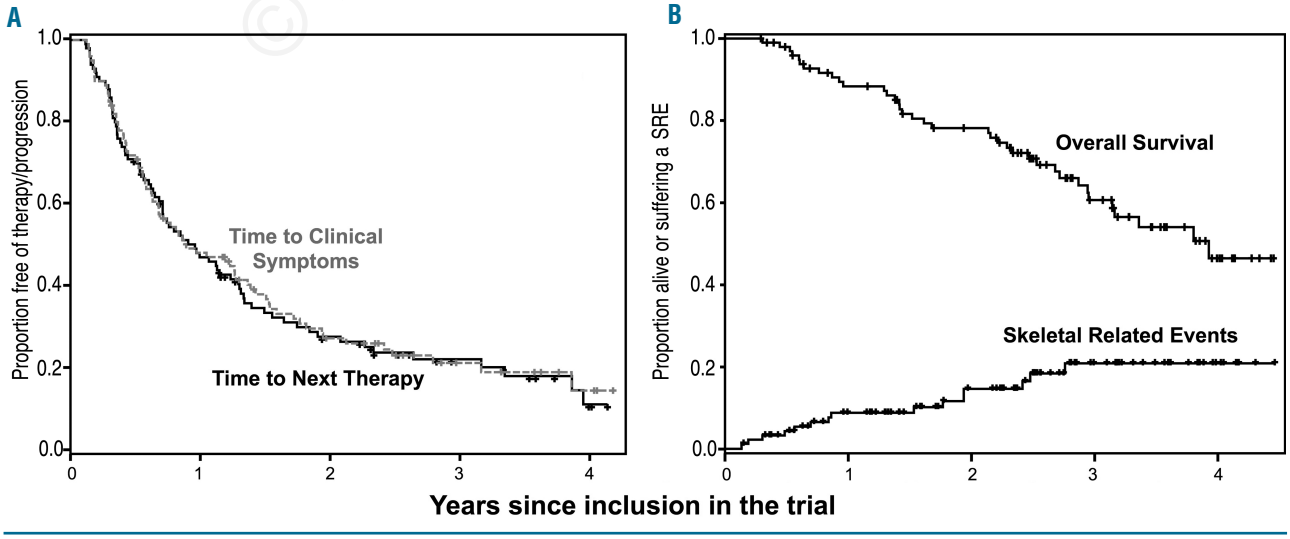

Figure 2. (A) Time to next therapy and time to clinical symptoms of the global series of patients. (B) Overall survival overlapped with the time to the next skeletal-related event (SRE) for all patients.

10.1 months), with 3-year projected treatment-free rates of 22% *versus* 16%, respectively (P=0.360) (Figure 3A). The behavior of time to clinical symptoms was similar, with the median being 16 *versus* 10 months in the ZA and control groups, respectively, and the 3-year time free of symptom rates being 32% *versus* 24%, respectively (P=0.203) (Figure 3B). The pattern of the clinical relapses showed relevant differences according to trial group. In the control group 20 patients developed more advanced bone disease (15 cases with new bone lesions, 3 cases with spinal cord compression, and 2 cases of hypercalcemia), 18 patients had anemia, two developed renal dysfunction, and one developed a plasmacytoma. In the ZA-treated group, progressive disease was manifested by anemia (24 patients), new bone lesions (8 patients), renal dysfunction (1 patient) and extramedullary disease (1 patient) (P<0.01) (Table 2). Overall, progressive bone disease (osteolytic bone lesions, spinal cord compression and hypercalcemia) was observed in 16% of patients in the experimental group *versus* 41% in the control group (P=0.005). After the study, patients with progression to symptomatic disease received subsequent rescue therapy which usually included continuation with bisphosphonates. The 25 patients who did not develop clinical symptoms continued with ZA therapy in 13 cases or no longer received therapy in 12 cases, according to their clinicians' decisions.

As far as concerns skeletal-related events, 16 events were reported in the trial (five vertebral fractures, four non-vertebral fractures, two cases of hypercalcemia, three cases of skeletal cord compressions, and two cases of radiotherapy or bone surgery requirement) and they were related with an important number of overall deaths (11/37). Consequently, the actuarial 3-year overall survival rate for patients suffering a new skeletal-related event was 31% while it was 66% for patients free of new skeletal-related events (P=0.047). Interestingly, only two out of 14 skeletal-related events appeared in the ZA group. Consequently, the use of ZA was associated with significantly fewer skeletal-related events than simple observation. The projected 4-year risk of skeletal-related events was 6% for patients in the ZA group *versus* 40% in the control group (P<0.001) (Figure 3C).

A trend to a longer overall survival was observed for the ZA group *versus* the control group, with 3-year projected overall survival rates of 73% *versus* 46%, respectively (Figure 3D). Interestingly, the effects on overall survival were more evident in those patients who had more advanced bone disease. There were 68 patients with prior osteolytic lesions (32 treated and 36 not treated with ZA)

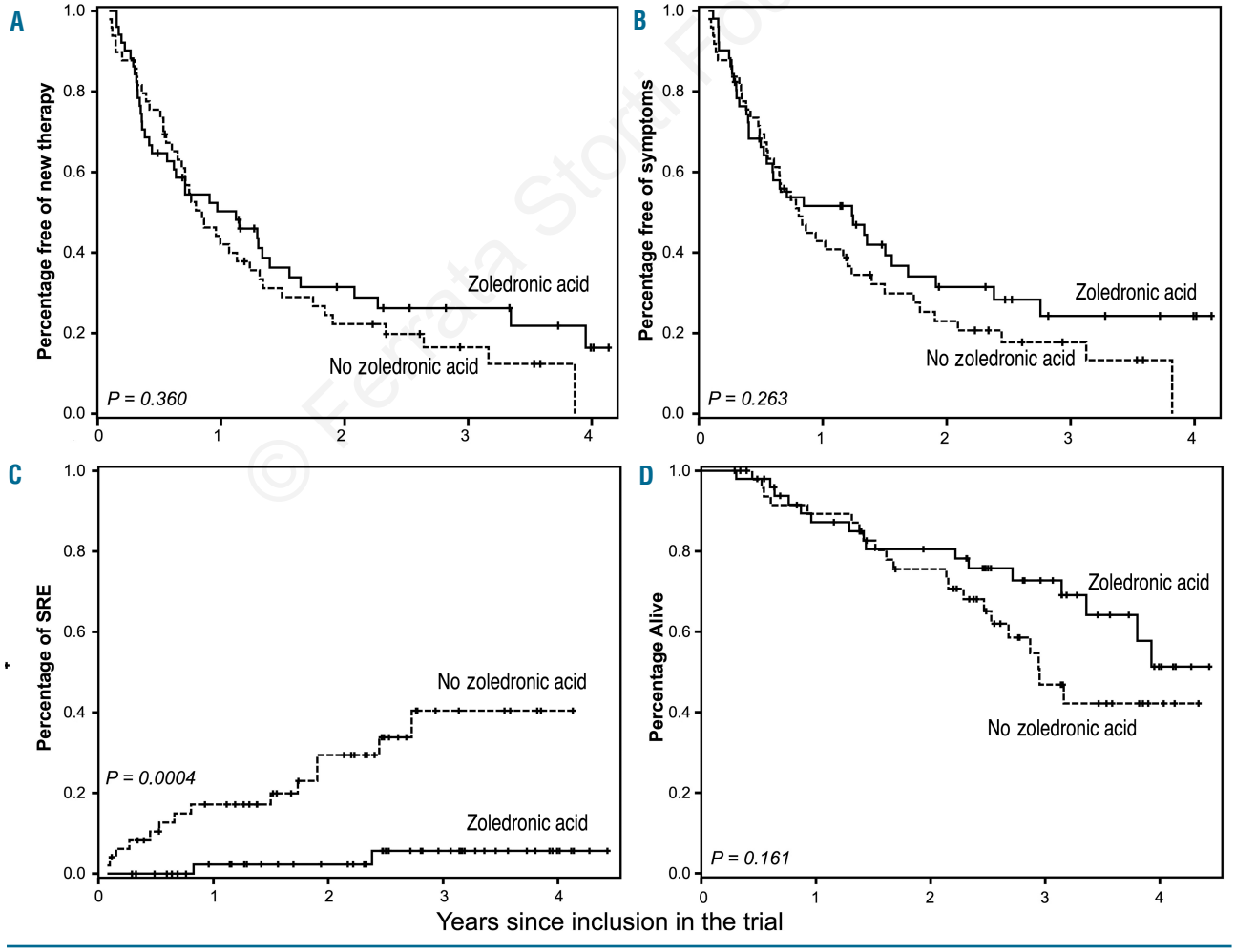

Figure 3. Differences in survival according to the treatment group. (A) Time to the next therapy. (B) Time to clinical symptoms. (C) Time to the next skeletal related event (SRE). (D) Overall survival. Solid line, experimental group; dashed line, control group.

and among these patients the 3-year overall survival rate was higher for patients treated with ZA than for those not treated with the bisphosphonate (61% *versus* 32%, *P*=0.064). In addition, there were 36 patients who had had skeletal-related events before inclusion in the trial, and the 3-year overall survival rate was higher among treated patients (n=18) than untreated ones (n=18) (69% *versus* 20%, respectively; *P*=0.016).

Toxicity

All patients were evaluated for toxicity. Globally, 29 adverse events were recorded in 17 patients (8 in the ZA group and 9 in the control group) (Table 3): 12 grade 1, nine grade 2 and eigth grade 3 events. There were no grade 4 adverse events and there were no significant differences in the frequency of adverse events between the experimental and control groups (Table 3). Eight adverse events in six patients (3 in each group) were considered severe. All serious adverse events were considered related to the underlying disease and resolved with appropriate therapy with the exception of osteonecrosis of the jaw that was related to ZA administration and caused trial discontinuation. Two patients in the control group developed renal problems. No patient developed any thromboembolic event during the trial.

Discussion

Intravenous bisphosphonates are the standard of care for the prevention of skeletal-related events and treatment of hypercalcemia in patients with MM.[4] In addition, some randomized trials have shown clinical benefits for bisphosphonates in these patients when they are administered during cytotoxic therapy.[8-10] These results and some preclinical studies argue in favor of an antimyeloma effect for the most potent bisphosphonates. The present randomized trial does not support a direct antitumor effect of intravenous ZA when administered as single therapy in myeloma patients at biochemical relapse since no reduction in M-component or prolongation in TNT was observed. However, considering that clinical progressions in the control group were mainly due to bone disease, we may counter-argue in favor of the use of ZA in patients at biochemical relapse.

The possible antitumor effect of bisphosphonates has long been evaluated in MM[19,20] and other tumors.[21] Since the initial observation that intravenous pamidronate could prolong the overall survival of some subsets of MM patients,[22] several groups have highlighted different direct and indirect mechanisms by which bisphosphonates can exert an antitumor effect, especially in MM.[5-7,23] The hypothesized antitumor effect was partially confirmed *in vivo* in two different clinical trials, in which the use of ZA acid resulted in a higher rate of response,[8] and longer progression-free survival and overall survival.[8,9] More specifically, in the MRC IX trial, in which almost 2,000 patients were treated, the use of ZA extended the overall survival by 5.5 months and progression-free survival by 2.0 months. However, in all trials in which bisphosphonates have demonstrated some survival advantage,[8,9,22] the

Table 2. Characteristics of progressive disease by trial arm.

Type of progression	Control group		ZA group		Total
No symptomatic progression	8	16%	17	33%	25
Anemia (hemoglobin decrease ≥2 g/dL)	18	38%	24	47%	42
New lytic lesions or increase of prior lytic lesions*	15	31%	8	16%	23
Spinal cord compression*	3	6%	0	0%	3
Hypercalcemia (>11.5 mg/dL)*	2	4%	0	0%	2
Development of plasmacytoma	1	2%	1	2%	2
Serum creatinine ≥2 mg/dL	2	4%	1	2%	3
Total	49		51		100

(*) Clinical progression with worsening bone disease: new or increasing bone lesions, spinal cord compression or hypercalcemia: 41% vs. 16%, P=0.005.

Table 3. Adverse events recorded by trial arm.

	ZA group (n=51)								Control group (n=49)							
	Grade 1		Grade 2		Grade 3		Total		Grade 1		Grade 2		Grade 3		Total	
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
Bone pain	2	4	1	2	0	0	0	0.0	3	6	1	2	0	0	4	8.2
Respiratory infection	0	0	1	2	1	2	2	5.1	3	6	3	6	1	2	7	14.2
Neuropathy	1	2	0	0	0	0	1	2.0	2	4	0	0	0	0	2	4.0
Renal dysfunction	1	2	0	0	0	0	1	2.0	0	0	1	2	1	2	2	4.0
Transient ischemic attack	1	2	0	0	0	0	1	2.0	0	0	0	0	0	0	0	0.0
Aortic lesion	0	0	0	0	0	0	0	0.0	0	0	0	0	1	2	1	2.0
Angina pectoris	0	0	0	0	0	0	0	0.0	0	0	0	0	1	2	1	2.0
Retinal detachment	0	0	0	0	1	2	1	2.0	0	0	0	0	0	0	0	0.0
Genital surgery	0	0	0	0	1	2	0	0.0	0	0	0	0	0	0	0	0.0
Choledocholithiasis	0	0	1	2	0	0	0	0.0	0	0	0	0	0	0	0	0.0
Osteonecrosis of the jaw	0	0	0	0	1	2	1	2.0	0	0	0	0	0	0	0	0.0

assessment of the antitumor effect of these drugs was complicated by the antitumor effect of the chemotherapy or novel antimyeloma drugs that were given at the same time. Several studies have also evaluated the antitumor effect of bisphosphonate monotherapy in patients with asymptomatic/smoldering MM.[11-16] Although these studies demonstrated some benefit of bisphosphonates on bone resorption, no clear tumor responses or benefits in terms of progression-free or overall survival were observed. Patients with smoldering MM probably do not constitute the ideal target population for such studies because, given their low rate of progression,[24] a large number of patients and long follow up would be needed to demonstrate a survival benefit for a drug that would have only a minor antitumor activity, if any.

In our study, we decided to evaluate the potential antitumor efficacy of ZA as a single agent with a similar approach, but targeting a different patient population (those with biochemical relapses) for three reasons. First, biochemical relapses are very frequent.[25,26] Second, most patients who have biochemical relapses very soon require therapy; Fernandez-Larrea *et al.* recently reported that most such patients need therapy at a median time of 5.6 months after transplantation,[27] which is concordant with the estimations from the VISTA trial in non-transplant candidates upon comparing time to progression and TNT.[28] Third, there is no universal consensus on how to treat these patients and many physicians prefer not to treat until symptoms emerge.[29]

As mentioned above, in this study the use of ZA as single therapy was not directly associated with an antitumor effect, since no reductions in the M-component were seen. However, the rate of progression was lower in the ZA group than in the untreated group (67% *versus* 87%, P=0.05). This translated into trends, albeit not statistically significant, to longer time to clinical symptoms and TNT (13.4 and 16 months in the ZA group *versus* 10.1 and 10 months in the control group, respectively). It is important to highlight that TNT was 10 months in the control group, which is longer than the expected 5-6 months.[27,28] This can be explained because patients included in this trial were a selected low-risk population, since they were patients in biochemical relapse who had had a previous long response (longer than 24 months, the time that Spanish protocols maintain bisphosphonate therapy). This selection could partially explain why the differences between the treatment and control groups were not as high as predicted. An important observation was the significantly different pattern of symptomatic progression observed in patients in the experimental group compared to those in the control group, since in the latter group myeloma mainly progressed with bone disease, while ZA-treated patients mainly progressed with other symptoms, such as anemia. This different pattern could be related to the marginal benefits observed in overall survival for ZA-treated patients in the absence of clear improvements in time to clinical symptoms. A similar discrepancy was also observed in the MRC IX trial, in which the increase in overall survival with ZA therapy was more pronounced than the increase in progression-free survival.[9] It is conceivable that the low incidence of skeletal-related events and other potential MM complications could be the basis for this more pronounced benefit of ZA therapy on the overall survival.

Development of skeletal-related events is an important complication of MM and results in high morbidity, mortality, and costs.[30-33] In this study, the use of ZA resulted in a very important reduction of skeletal-related events with respect to the rate in the control group (4% *versus* 33%), with 4-year accumulated skeletal-related event rates of 6% *versus* 40%, respectively (P<0.001). This supports the findings of several other studies in which the use of bisphosphonates always translated into a reduction of skeletal-related events.[8,9,11-16,22] This reduction in skeletal-related events could also help to explain why the overall survival was marginally favored by the use of ZA, with a more pronounced effect in patients with bone disease or skeletal-related events, as the MRC trial had already demonstrated.[9] However, the number of patients and differences in this study are limited, which should be taken into consideration when interpreting the results. New imaging techniques could identify patients with no relevant bone disease and low expectations of benefit from bisphosphonate therapy, but a global interpretation of our findings suggests that ZA treatment has an evident clinical benefit for MM patients in the setting of asymptomatic biochemical relapses. Since ZA therapy is not an expensive strategy and it is associated with very few adverse events, it could be considered as a change in the clinical standard of care of patients with asymptomatic biochemical relapses, in favor of a more active approach than the current, commonly used, watch-and-wait strategy. Accordingly, we recommend the use of ZA therapy in patients under biochemical relapses for at least 12 months; in the case of development of symptomatic disease, bisphosphonate use should follow the rules of the rescue protocol, while in those patients who remain asymptomatic after 1 year of ZA treatment, therapy should be maintained following the current recommendations of the IMWG, which favor the use of bisphosphonate therapy until progression for patients who are not in complete or very good partial response.[4]

In summary, this randomized trial demonstrates that early monotherapy with ZA reduces the risk of progression with symptomatic bone disease and minimizes the incidence of skeletal-related events without significant toxicity in MM patients with asymptomatic biochemical relapse, and accordingly it should be considered as a new standard of care for this group of patients.

Acknowledgments

This work was supported by an unrestricted grant from Novartis Farmaceutica S.A., Barcelona, Spain and sponsored by GEM/PETHEMA. Part of the work was also done thanks to grants PS09/01450 and PI12/02311 from the Spanish "Instituto de Salud Carlos III (ISCIII)" and Fondo Europeo de Desarrollo Regional (FEDER), the Spanish Ministry of Economy and Competitiveness and the European Regional Development Fund (ERDF) "Una manera de hacer Europa" (Innocampus; CEI-2010-1-0010), the grant RD12/0036/0069 from "Red Temática de Investigación Cooperativa en Cáncer (RTICC), and grant GCB-120981SAN from the "Asociación Española Contra el Cáncer (AECC)".

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Mateos M-V, San Miguel JF. How should we treat newly diagnosed multiple myeloma patients? Hematology Am Soc Hematol Educ Program. 2013;2013:488-495.
2. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-1473.
3. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.
4. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma–related bone disease. J Clin Oncol. 2013;31(18):2347-2357.
5. Croucher PI, De Hendrik R, Perry MJ, et al. Zoledronic acid treatment of 5T2MM-bearing mice inhibits the development of myeloma bone disease: evidence for decreased osteolysis, tumor burden and angiogenesis, and increased survival. J Bone Miner Res. 2003;18(3):482-492.
6. Corso A, Ferretti E, Lunghi M, et al. Zoledronic acid down-regulates adhesion molecules of bone marrow stromal cells in multiple myeloma: a possible mechanism for its antitumor effect. Cancer. 2005;104(1):118-125.
7. Shipman CM, Rogers MJ, Apperley JF, Russell RG, Croucher PI. Bisphosphonates induce apoptosis in human myeloma cell lines: a novel anti-tumour activity. Br J Haematol. 1997;98(3):665-672.
8. Aviles A, Nambo MJ, Neri N, Castaneda C, Cleto S, Huerta-Guzman J. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. Med Oncol. 2007;24(2):227-230.
9. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet. 2010;376(9757):1989-1999.
10. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol. 1998;16(2):593-602.
11. Caparrotti G, Catalano L, Feo C, Vallone R, Pagnini D, Rotoli B. Perspective study on pamidronate in stage I multiple myeloma. Hematol J. 2003;4(6):459-460.
12. Martin A, Garcia-Sanz R, Hernandez J, et al. Pamidronate induces bone formation in patients with smouldering or indolent myeloma, with no significant anti-tumour effect. Br J Haematol. 2002;118(1):239-242.
13. Martini G, Gozzetti A, Gennari L, Avanzati A, Nuti R, Lauria F. The effect of zoledronic acid on serum osteoprotegerin in early stage multiple myeloma. Haematologica. 2006;91(12):1720-1721.
14. Musto P, Falcone A, Sanpaolo G, et al. Pamidronate reduces skeletal events but does not improve progression-free survival in early-stage untreated myeloma: results of a randomized trial. Leuk Lymphoma. 2003;44(9):1545-1548.
15. Musto P, Petrucci MT, Bringhen S, et al. A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. Cancer. 2008;113(7):1588-1595.
16. D'Arena G, Gobbi PG, Broglia C, et al. Pamidronate versus observation in asymptomatic myeloma: final results with long-term follow-up of a randomized study. Leuk Lymphoma. 2011;52(5):771-775.
17. Garcia-Sanz R, Alegre A, Capote FJ, et al. [Guidelines for the use of bisphosphonates in multiple myeloma: Recommendations of the expert committee of the Spanish Myeloma Group from the PETHEMA group]. Med Clin (Barc). 2010;134(6):268-278.
18. Terpos E, Sezer O, Croucher PI, et al. The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. Ann Oncol. 2009;20(8):1303-1317
19. Raje N, Anderson KC. Introduction: the evolving role of bisphosphonate therapy in multiple myeloma. Blood. 2000;96(2):381-383.
20. Locke FL, Morgan GJ. What is the evidence for the use of bisphosphonate therapy in newly diagnosed multiple myeloma patients lacking bone disease? Hematology Am Soc Hematol Educ Program. 2012;2012:350-353.
21. Gnant M, Clezardin P. Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature. Cancer Treat Rev. 2012;38(5):407-415.
22. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. New Engl J Med. 1996;334(8):488-493.
23. Kunzmann V, Bauer E, Feurle J, Weissinger F, Tony HP, Wilhelm M. Stimulation of gammadelta T cells by aminobisphosphonates and induction of antiplasma cell activity in multiple myeloma. Blood. 2000;96(2):384-392.
24. Kyle RA, Durie BG, Rajkumar SV, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia. 2010;24(6):1121-1127.
25. Dimopoulos M, Kyle R, Fermand JP, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood. 2011;117(18):4701-4705.
26. Zamarin D, Giralt S, Landau H, et al. Patterns of relapse and progression in multiple myeloma patients after auto-SCT: implications for patients' monitoring after transplantation. Bone Marrow Transplant. 2013;48(3):419-424.
27. Fernandez de Larrea C, Jimenez R, Rosinol L, et al. Pattern of relapse and progression after autologous SCT as upfront treatment for multiple myeloma. Bone Marrow Transplant. 2014;49(2):223-227.
28. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28(13):2259-2266.
29. Garcia-Sanz R, Mateos MV, San Miguel JF. [Multiple myeloma]. Med Clin (Barc). 2007;129(3):104-115.
30. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer. 2007;110(8):1860-1867.
31. Sonmez M, Akagun T, Topbas M, et al. Effect of pathologic fractures on survival in multiple myeloma patients: a case control study. J Exp Clin Cancer Res. 2008;27:11.
32. Delea T, McKiernan J, Brandman J, et al. Retrospective study of the effect of skeletal complications on total medical care costs in patients with bone metastases of breast cancer seen in typical clinical practice. J Support Oncol. 2006;4(7):341-347.
33. Groot MT, Huijgens PC, Wijermans PJ, Uyl-de Groot CA. Costs of multiple myeloma and associated skeletal-related events in the Netherlands. Expert Rev Pharmacoecon Outcomes Res. 2004;4(5):565-572.