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Haematologica 2015 [Epub ahead of print]

doi:10.3324/haematol.2015.128439

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

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5) Hospital Universitario Central de Asturias;
6) Hospital Universitario de Canarias;
7) Hospital Lozano Blesa de Zaragoza;
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10) Hospital Universitario Vall de Hebrón de Barcelona;
11) Hospital Universitario Dr. Peset de Valencia;
12) Hospital Son Llàtzer de Palma de Mallorca;
13) Hospital del Mar de Barcelona;
14) Hospital de la Santa Creu i Sant Pau de Barcelona;
15) Clínica Universidad de Navarra-CIMA

Zoledronic acid in myeloma biochemical relapses
KEY WORDS
Myeloma, bone disease, asymptomatic myeloma, zoledronic acid, skeletal related events

RESEARCH GRANT SUPPORT
This work has been sponsored by the GEM/PETHEMA Spanish group and partially supported by an unrestricted grant from NOVARTIS SA (Spain) and a grant from the Spanish ISCIII (PS09/1450).

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1. ABSTRACT

This study analyzed the anti-myeloma effect of zoledronic acid monotherapy by investigating patients at asymptomatic biochemical relapse. 100 patients were randomized to receive either zoledronic acid (4 mg iv/4 wk, 12 doses) (n=51) or not (n=49). Experimental and control groups were well balanced for disease and prognostic features. Zoledronate did not show antitumor effect according to M-component outcome. However, there were fewer symptomatic progressions in the experimental (n=34) than in control groups (n=41, P=0.05) resulting in a median time to symptoms of 16 vs. 10 months (P=0.161). Median time to next therapy was also slightly longer for treated vs. no treated groups (13.4 vs. 10.1 months), without statistically significant differences (P=0.360). The relapsing pattern was different for treated vs. control patients: progressive bone disease (8 vs. 20), anemia (24 vs. 18), renal dysfunction (1 vs. 2), and plasmacytomas (1 vs. 1, respectively). This concurred with fewer skeletal related events in the experimental (N=2) vs. control (N=14) groups, with a projected 4-year event proportion of 6% vs. 40% (P< 0.001). In summary, zoledronic acid monotherapy does not show antitumor effect in myeloma biochemical relapses but reduces the risk of progression with symptomatic bone disease and skeletal complications. ClinicalTrials.gov: NCT01087008

2. INTRODUCTION

Although current treatment in Multiple Myeloma (MM) induces responses in >90% of patients, it remains incurable for most of them. The pattern of relapse is quite heterogeneous, including frequent biochemical relapses in the absence of clinical symptoms. Although these patients can remain free of therapy for a certain period of time, they are at high at risk of symptomatic progression and therapy requirement. The current recommendation of the International Myeloma Working Group (IMWG) for patients in biological relapse is not to treat until they develop clinical symptoms, except in those cases with the so-called “significant paraprotein relapse” (SPR) in whom the relapse represents a rate of rise or absolute level M protein increase at which the risk is considered very high and myeloma therapy is recommended to be restarted without any delay.

Intravenous Bisphosphonates (BP) are indicated in patients with MM, with or without detectable osteolytic bone lesions on conventional radiography, who are receiving antimyeloma therapy as well as patients with osteoporosis or osteopenia resulting from myeloma. Although the main reason for this indication is because they prevent skeletal related events (SRE), there is also controversial data suggesting an anti-myeloma effect for Zoledronic Acid (ZOL). This hypothetical antitumor effect is based on pre-clinical studies, reproduced in small series of patients, and subanalysis of clinical trials, particularly, the large MRC trial, conducted in newly diagnosed patients treated with either chemotherapy (CVAB) or thalidomide based therapy (CTD), that were assigned to receive either ZOL or clodronate (CLO). The ZOL group showed a significantly longer progression-free survival and overall survival compared with CLO. However, this study included several randomizations, such as thalidomide maintenance, and it is not easy to dissect the real anti-tumor versus other beneficial anti-
myeloma effects of ZOL treatment. Moreover, in patients with smoldering MM, treatment with bisphosphonates did not delay transformation into symptomatic disease but it is associated with a reduction in the SRE onset.\textsuperscript{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 ZOL.

The AZABACHE trial was conducted by the Spanish Myeloma Group (GEM/PETHEMA) in order to evaluate if the use of ZOL delays the time to next therapy (TNT) in patients with MM in biochemical relapse in comparison with observation.

3. METHODS

3.1. Trial design

In 2010, GEM/PETHEMA activated the “Analysis of Zoledronic Acid therapy in MM in BioCHEmical relapses” trial (known from now as AZABACHE, NCT01087008). 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: 1) experimental, in which patients received Zoledronic Acid (ZOL), or 2) control (abstention), where patients did not received any treatment (No ZOL). In the experimental arm patients received ZOL, 4 mg in a 15 minutes’ intravenous infusion every 4 weeks, for a total of 12 doses, plus standard supportive care (experimental group); in the control group only supportive care was permitted. The trial and all procedures were in accordance with the Helsinki Declaration and they were reviewed and approved by the Spanish National Agency and the Ethics Committee of all centers involved.

3.2. Inclusion and exclusion criteria

All patients had to fit the following inclusion criteria: 1) 18 years and older; 2) confirmed biochemical relapse after an initial response, without symptoms derived from the disease and 3) Signed informed consent. Relapse was defined according to the IMWG criteria defined in 2006.\textsuperscript{2} Patients treated with any symptom of myeloma Related Organ or Tissue Impairment or who had received bisphosphonates in the last three months were excluded; this meant that most patients had had a prior response longer than 24 months, which the usual time that bisphosphonates are given in the Spanish trials.\textsuperscript{17}

3.3. Variables for evaluation

The main end-point was TNT, that was calculated as time that elapsed between the inclusion in the protocol, and the moment in which new antmyeloma therapy was initiated based on the appearance of a clinical relapse or death of any cause. The appearance of a SPR was not considered as a clinical relapse but it was qualified as a cause for initiating anti-myeloma when considering the TNT.\textsuperscript{3}
Other end-points for evaluation were: 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;\(^3\) time to clinical symptoms (TCS), as the time between the inclusion in the trial and the development of a clinical (CRAB) relapse;\(^3\) and time to SRE as the time between the inclusion in the trial and the moment of one of the following: bone fracture (vertebral and non-vertebral), bone radiotherapy requirement, bone surgery requirement or hypercalcemia. The presentation of osteonecrosis of the jaw and renal dysfunctions were carefully followed during all therapeutic and follow-up periods. In addition, we also evaluated the characteristics of the symptomatic relapse of the 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 a safe use of BP were specifically followed according to the commercial labeling of ZOL as well as the recommendations of the European Myeloma Network.\(^{17,18}\)

A more detailed description of the methods can be found in the online supplement.

4. RESULTS

4.1. Baseline characteristics and protocol compliance

From June 2010 to July 2012, 100 patients were recruited: 51 in the ZOL group and 49 in the no ZOL group. Baseline characteristics of the patients at the moment of inclusion are shown in Table 1. Median age was 68 years (range: 40-87). The M-component was IgG in 72% of cases, and IgA in 25% of cases; 3% were only light chain MM. The biochemical relapse occurred after 1, 2 or \( \geq 3 \) lines of therapy in 67%, 22% and 11% of cases, respectively. Prior treatment included transplant in 66% of patients, bortezomib in 53% and IMiDs in 32%. Bone lesions at initial diagnostic X-ray skeletal survey were present in 68% of patients. Overall, 32% of patients had developed one to three SRE prior to trial inclusion. Median time between the biochemical relapse and the inclusion in the protocol was 4 months (range 1-21). Bone marrow plasma cell infiltration had a median of 3% (0-96%) by morphology. FISH/cytogenetics was abnormal in 52% of cases: t(11;14) 19%, Rb deletion (alone) 17%, del(p53) 8%, t(4;14) 4% and t(14;x) 4%. Hemoglobin, creatinine, calcium, and B2M were normal (as per protocol). \( \beta_2 \) microglobulin and C-Reactive Protein were also normal in all cases. ZOL and no ZOL groups were well balanced for prognostic features, prior response, and time from diagnosis to the 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 patient refusal (n=2) and development of other diseases (n=2). The remaining 54 patients stopped the trial due to progression before 12 months (n=52), toxicity (n=1, osteonecrosis of the jaw) and initiation of cytotoxic therapy due to SPR (n=1). The distribution among groups 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). Reason for starting therapy was the development of symptomatic disease in all but three cases in which therapy was started due to SPR in the absence of symptoms. Median Time to Clinical Symptoms (TCS) was 11.3 months, superimposable to TNT [figure 2A]. Time to a new SRE was not reached during the trial follow-up, with a projected percentage of SRE of 21.5% at four years and the overall survival from inclusion in the trial was 47 months (Figure 2B).

4.2. Efficacy

Myeloma responses were not observed during the treatment with ZOL, and therefore no antitumor effect of ZOL 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 ZOL group (n=34, 67%) as compared with the no ZOL 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 ZOL group (median of 13.4 months) vs. no ZOL group (median of 10.1 months), with a 3-year projected treatment free interval of 22% vs. 16% \( (P=0.360) \) (Figure 3A). Time to Clinical Symptoms had a similar behavior, yielding a median of 16 vs. 10 months, and a 3-year time free of symptoms of 32% vs. 24% for the ZOL and no ZOL groups, respectively \( (P=0.203) \) (Figure 3B). The pattern of the clinical relapse showed relevant differences according to the group of therapy. In the control group, the progressions were 20 patients developed more advanced bone disease (15 cases with new bone lesions, 3 spinal cord compressions, and 2 cases of hypercalcemia), 18 patients had anemia, two renal dysfunction, and one developed a plasmacytoma while progressions in the ZOL group were anemia (24 patients), new bone lesions (8 patients), renal dysfunction, and extramedullary disease (one each) \( (P<0.01) \) (Table 2). Overall progressive bone disease (osteolytic bone lesions, spinal cord compression & hypercalcemia), was observed in 16% of patients in the experimental group vs. 41% in the control group \( (P = 0.005) \). After the study, patients with progression to symptomatic disease received a subsequent rescue therapy that usually included the continuation with BP. The 25 patients who did not develop clinical symptoms continued with ZOL therapy in 13 cases or received no longer therapy in 12 cases according to their clinician decision.

Concerning SRE, 16 events were reported in the trial: 5 vertebral fractures, 4 non-vertebral fractures, 2 cases of hypercalcemia, 3 skeletal cord compressions, and 2 cases of radiotherapy or bone surgery requirement, and they were related with an important number of total deaths \( (11/37) \). Consequently, the actuarial 3-year OS for patients suffering a new SRE was 31% while it was 66% for patients free of new SREs \( (p=0.047) \). Interestingly, only 2 out of 14 SRE events appeared in the ZOL group. Consequently, the use of ZOL was associated with significantly less SREs than in the ZOL group. The projected 4-year risk of SRE was 6% for patients in the ZOL group vs. 40% in the No ZOL group \( (P<0.001) \) (Figure 3C).
A trend for a longer OS was observed for the ZOL vs. No ZOL groups, with a 3-year projected OS of 73% vs. 46% (Figure 3D). Interestingly, the effects over OS were more evident in those patients who had more advanced bone disease. Thus, there were 68 patients with prior osteolytic lesions (32 treated and 36 not treated with ZOL) and the 3-year OS was longer for patients treated than for not treated with ZOL (61% vs. 32%, p=0.064). In addition, there were 36 patients who had had SREs before inclusion, and the 3-year OS was better for patients treated (n=18) than untreated (n=18) (69% vs. 20%, p=0.016).

4.3. Toxicity

All patients were evaluated for toxicity. Globally, 29 adverse events (AE) were registered in 17 patients (8 for ZOL and 9 for no ZOL. Table 3): 12 grade 1, 9 grade 2 and 8 grade 3. There were no grade 4 AEs and there were no significant differences in the frequency of AE between the experimental and control arms (Table 3). Eight AEs in 6 patients (three in each group) were considered Severe Adverse Events (SAEs). All SAEs were considered related to underlying disease and resolved with appropriate therapy with the exception of the ONJ that was related to ZOL administration and caused trial discontinuation. There were two renal problems that presented in the control group and no patient developed any thromboembolic event during the trial.

5. DISCUSSION

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

The hypothesis of an antitumor effect of BP has long been evaluated in MM and other tumors. Since the initial observation that intravenous pamidronate could prolong the OS in some subsets of MM patients vs. placebo, several groups have highlighted different direct and indirect mechanisms by which BP can exert an antitumor effect, especially in MM. This hypothesis has been partially confirmed in vivo in two different clinical trials, where the use of zoledronic acid resulted in a higher rate of response, and a longer PFS and OS. More specifically, in the MRC IX trial, where almost 2000 patients were treated, the use of ZOL extended the overall survival by 5.5 months and progression-free survival by 2.0 months. However, in all trials in which BPs have demonstrated some survival advantage, the 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 BP monotherapy in patients with asymptomatic/smoldering MM. Although they demonstrated some benefit of BP on bone resorption, no clear tumor responses or benefit in terms of PFS or OS were observed. Probably, smoldering MM is not the ideal target population since due to their low rate of progression it would require a large patient population and long follow up to demonstrate a survival benefit for a drug that, if it has any anti-tumor activity, it would be minor.

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

As above mentioned, in the present study the use of ZOL as single therapy was not directly associated with an antitumor effect, since no reductions in the M-component were seen. However, fewer patients progressed in the ZOL group when compared to those in the abstention arm (67% vs. 87%, P = 0.05). This translated into a trend to longer, but not statistically significant, TCS and TNT (13.4 and 16 in the ZOL group as compared to 10.1 and 10 months in the control group, respectively). Moreover, it is important to highlight that TNT was 10 months in the control group, longer than the expected 5-6 months. 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 the bisphosphonate therapy). This selection could partially explain why the differences between the treatment and abstention groups were not as high as predicted. An important observation was the significantly different pattern of symptomatic progression observed for patients in the experimental vs. control group, since in the latter group myeloma mainly progressed with bone disease, while ZOL patients mainly progressed with other symptoms, such as anemia. Such differential pattern could be related with the marginal benefits observed in OS for ZOL treated patients in the absence of clear improvements in TCS. A similar discrepancy was also observed in the MRC IX trial, where the OS was more pronouncedly increased with ZOL therapy than the PFS. It is conceivable that the low incidence of SREs and other potential MM complications could be the basis this more pronounced benefit for ZOL therapy over the OS.

Development of SRE is an important complication of MM that results in high morbidity, mortality, and costs present report and in the literature. The use of ZOL resulted here in a very important reduction of SRE with respect to controls (4% vs. 33%), with a 4-year accumulated SRE of 6% vs.
40% \((P< 0.001)\). This support several other reports in which the use of BP always translated into a reduction of SRE. \(^8,9,11-16,22\) This reduction in the SREs could also help to explain why the OS was marginally favored by the use of ZOL, with a more pronounced effect in patients with bone disease or SRE, as the MRC trial already demonstrated. \(^9\) However, the number of patients and differences in this study are limited, which should be considered for a correct interpretation. New image techniques could identify patients with no relevant bone disease and low benefit expectations from bisphosphonate therapy, but a global interpretation of our findings point out that use of ZOL has an evident clinical benefit for MM patients in the setting of asymptomatic biochemical relapses. Since ZOL therapy is not an expensive strategy an it is associated with very few AE, it can be considered as a change in the clinical standard of care of these patients in favor of a more active approach versus the current commonly used watch-and-wait strategy. Accordingly, we recommend the use of ZOL therapy in patients under biochemical relapses for at least 12 months; in case of symptomatic disease development, BP use should follow the rules of the rescue protocol, while in those patients who remain asymptomatic after 1 year of ZOL, therapy should be maintained following the current recommendations of the IMWG, that favor the use of BP therapy until progression for patients who are not in complete or very good partial response. \(^4\)

In summary, this randomized trial demonstrates that early single therapy with ZOL reduces the risk of progression with symptomatic bone disease and minimizes the incidence of SREs without significant toxicity in MM patients with asymptomatic relapse, and accordingly it should be considered as a new standard of care for this group of patients.

6. ACKNOWLEDGEMENTS

This work was supported with an unrestricted grant from NOVARTIS FARMACEUTICA S.A., Barcelona, Spain. Part of the work was also done thanks to the 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)”.

7. AUTHORSHIP CONTRIBUTIONS

RG-S and JFSM were the initial designers of the study. MVM was involved in the initial launch of the study, provided strong documental and scientific support and helped in the statistical and clinical interpretation of the data. AO, MJM, JdlR, AR, MTH, LP, AIT, MJB, MG, PR, JB, EA, MG, EMO, and JMR, were clinicians responsible for the patients and those who took care of the protocol accomplishment, sampling and collection of clinical data. RG-S and MVM prepared the initial version of the paper. JFSM and RG-S were the main responsible of the global group. JFSM was the main
representative of the GEM/PETHEMA group. RG-S, JFSM and MVM were the persons responsible of the final revision of the draft, as well as the persons who gave the final approval of the version to be published.

8. DISCLOSURE OF CONFLICTS OF INTEREST

The trial was registered in the clinicaltrials.gov database with the code NCT01087008 and it was sponsored by GEM/PETHEMA with an unrestricted grant from NOVARTIS FARMACEUTICA S.A.

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- Ramón García-Sanz has to disclose, honoraria and research funding from Novartis SA., advisory relationship and honoraria from AMGEN and honoraria from Takeda/Millenium.
- Albert Oriol, has to disclose, honoraria and research funding from Celgene and Janssen.
- María J. Moreno, declares no conflicts of interest.
- Javier de la Rubia, declares no conflicts of interest.
- Ángel R. Payer, declares no conflicts of interest.
- Miguel T. Hernández, declares no conflicts of interest.
- Luis Palomera, declares no conflicts of interest.
- Ana I. Teruel, declares no conflicts of interest.
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- Paz Ribas, declares no conflicts of interest.
- Joan Bargay, declares no conflicts of interest.
- Eugenia Abellá, declares no conflicts of interest.
- Miquel Granell, declares no conflicts of interest.
- Enrique M. Ocio honoraria, research funding and/or advisory relationship with Millennium, Celgene, Novartis, Onyx, Janssen, Bristol-Myers Squibb, Pharmamar, and Merck Sharpe & Dohme.
- Josep M. Ribera declares no conflicts of interest.
- Jesús F. San Miguel has to disclose honoraria, research funding and/or advisory relationship with Millennium, Celgene, Novartis, Onyx, Janssen, Bristol-Myers Squibb, and Merck Sharpe & Dohme.
- María V. Mateos has to disclose honoraria and/or advisory relationship with Janssen Millennium, Celgene, Novartis, Onyx, Janssen, Bristol-Myers Squibb, and Merck Sharpe & Dohme.

REFERENCE LIST


### Table 1: Characteristics of the patients

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<tr>
<th>Feature</th>
<th>No ZOL N=49</th>
<th>ZOL, N=51</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Female</td>
<td>53%</td>
<td>41%</td>
<td>0.316</td>
</tr>
<tr>
<td>More than 1 prior line of therapy</td>
<td>41%</td>
<td>26%</td>
<td>0.103</td>
</tr>
<tr>
<td>High Risk Cytogenetics</td>
<td>17%</td>
<td>15%</td>
<td>0.876</td>
</tr>
<tr>
<td>Prior osteolytic bone lesions</td>
<td>73%</td>
<td>63%</td>
<td>0.288</td>
</tr>
<tr>
<td>Prior skeletal related event</td>
<td>31%</td>
<td>33%</td>
<td>0.947</td>
</tr>
<tr>
<td>Prior Transplant</td>
<td>57%</td>
<td>75%</td>
<td>0.091</td>
</tr>
<tr>
<td>Prior Bortezomib</td>
<td>57%</td>
<td>49%</td>
<td>0.431</td>
</tr>
<tr>
<td>Prior immunomodulatory drug</td>
<td>43%</td>
<td>22%</td>
<td>0.032</td>
</tr>
<tr>
<td>Age&gt;65 yr</td>
<td>63%</td>
<td>62%</td>
<td>0.929</td>
</tr>
<tr>
<td>M-component &gt;10 g/L</td>
<td>89%</td>
<td>92%</td>
<td>0.711</td>
</tr>
<tr>
<td>C-Reactive Protein &gt;1 mg/dL</td>
<td>22%</td>
<td>24%</td>
<td>1.000</td>
</tr>
<tr>
<td>Beta2microglobulin &gt;3 mg/L</td>
<td>33%</td>
<td>36%</td>
<td>1.000</td>
</tr>
<tr>
<td>Hemoglobin&gt;12 g/dL</td>
<td>81%</td>
<td>76%</td>
<td>0.638</td>
</tr>
<tr>
<td>High Lactate DeHydrogenase UI/L</td>
<td>8%</td>
<td>9%</td>
<td>1.000</td>
</tr>
<tr>
<td>Time from diagnosis to recruitment &gt;5 yr</td>
<td>29%</td>
<td>35%</td>
<td>0.469</td>
</tr>
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</table>
Table 2: Characteristics of Progressive disease by therapeutic arm

<table>
<thead>
<tr>
<th>Type of progression</th>
<th>NO ZOL</th>
<th>ZOL</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptomatic progression</td>
<td>8</td>
<td>16%</td>
<td>17</td>
</tr>
<tr>
<td>Anemia (Hb decrease in ≥ 2 g/dL)</td>
<td>18</td>
<td>38%</td>
<td>24</td>
</tr>
<tr>
<td>New lytic lesions or increase of prior lytic lesions*</td>
<td>15</td>
<td>31%</td>
<td>23</td>
</tr>
<tr>
<td>Spinal cord compression*</td>
<td>3</td>
<td>6%</td>
<td>23</td>
</tr>
<tr>
<td>Hypercalcemia (&gt;11.5 mg/dl)*</td>
<td>2</td>
<td>4%</td>
<td>2</td>
</tr>
<tr>
<td>Development of plasmacytomas</td>
<td>1</td>
<td>2%</td>
<td>2</td>
</tr>
<tr>
<td>Serum creatinine &gt;= 2 mg/dL</td>
<td>2</td>
<td>4%</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>51</td>
<td>100</td>
</tr>
</tbody>
</table>

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


Table 3: Adverse events registered by therapeutic arm

<table>
<thead>
<tr>
<th></th>
<th>Experimental (n=51)</th>
<th>Control (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Bone pain</td>
<td>0.00</td>
<td>2.00</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>5.10</td>
<td>3.00</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2.00</td>
<td>1.00</td>
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<tr>
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<td>Retinal detachment</td>
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<tr>
<td>Choledocholithiasis</td>
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<td>0.00</td>
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<tr>
<td>Osteonecrosis of the Jaw</td>
<td>2.00</td>
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</table>
LEGENDS TO FIGURES

Figure 1: Flow-chart of the patient 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 SRE of all patients.

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.
Total included N=100

ZOL N=51
- Development of symptoms N=24
  - IC retrieval N=2
  - Osteonecrosis of the Jaw N=1
  - Cytostatic therapy N=1

- 12 doses completed N=23
  - Progressive disease beyond 12 months N=9
  - Cytostatic therapy N=2
  - No clinical symptoms on follow-up N=14

No ZOL N=49
- Development of symptoms N=28

- 12 months of follow-up N=21
  - Progressive disease beyond 12 months N=13
  - No clinical symptoms on follow-up N=8
A
Proportion Free of Therapy/progression

Time to Clinical Symptoms

Time to Next Therapy

Years since inclusion in the trial

B
Proportion Alive or suffering an SRE

Overall Survival

Skeletal Related Events
SUPPLEMENTAL MATERIAL

Zoledronic acid as compared with observation in Multiple Myeloma patients at biochemical relapse: results of the randomized AZABACHE Spanish trial. By Garcia-Sanz et al (HAEMATOL/2015/128439)

1. METHODS

1.1. Trial design

In 2010, GEM/PETHEMA activated the “Analysis of Zoledronic Acid therapy in MM in BioCHEmical relapses” trial (known from now as AZABACHE, NCT01087008). 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: 1) experimental, in which patients received Zoledronic Acid (ZOL), or 2) control (abstention), where patients did not receive any treatment (No ZOL). In the experimental arm patients received ZOL, 4 mg in a 15 minutes’ intravenous infusion every 4 weeks, for a total of 12 doses, plus standard supportive care (experimental group); in the control group only supportive care was permitted. The trial and all procedures were in accordance with the Helsinki Declaration and they were reviewed and approved by the Spanish National Agency and the Ethics Committee of all centers involved.

1.2. Inclusion and exclusion criteria

All patients had to fit the following inclusion criteria: 1) 18 years and older; 2) confirmed biochemical relapse after an initial response, without symptoms derived from the disease and 3) Signed informed consent. Relapse was defined according to the IMWG criteria defined in 2006,¹ as a re-positivization of a previously negative immunofixation (two samples) or increase of ≥25% in the serum M-component (the absolute increase had to be 0.5 g/dl), or in the urine M-component (the absolute increase had to be ≥200 mg/24 h), or increase of ≥10 mg/dl in the difference between involved and uninvolved FLC levels (this criteria only applies to patients without measurable serum and urine M-protein levels), or increase in the bone marrow plasma cell percentage (the absolute percentage had to be ≥10%). Patients treated with any symptom of myeloma Related Organ or Tissue Impairment or who had received bisphosphonates in the last three months were excluded; this meant that most patients had had a prior response longer than 24 months, which the usual time that bisphosphonates are given in the Spanish trials. ²

1.3. Variables for evaluation

The main end-point was TNT, that was calculated as time that elapsed between the inclusion in the protocol, and the moment in which new antmyeloma therapy was initiated based on the appearance of a clinical relapse (end organ damage) (point 2 of the exclusion criteria), or death of any
cause. The appearance of a SPR was not considered as a clinical relapse but it was qualified as a cause for initiating anti-myeloma when considering the TNT. The only exception to consider therapy and an event for TNT required a doubling of the M-component in 2 consecutive measurements separated by less than or equal to 2 months; or an increase in the absolute levels of serum M protein by more than or equal to 1 g/dL, or urine M protein by more than or equal to 500 mg/24 hours, or involved FLC level by more than or equal to 20 mg/dL (plus an abnormal FLC ratio) in 2 consecutive measurements separated by less than or equal to 2 months.\textsuperscript{3}

Other end-points for evaluation were: 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;\textsuperscript{3} time to clinical symptoms (TCS), as the time between the inclusion in the trial and the development of a clinical (CRAB) relapse;\textsuperscript{3} and time to SRE as the time between the inclusion in the trial and the moment of one of the following: bone fracture (vertebral and non-vertebral), bone radiotherapy requirement, bone surgery requirement or hypercalcemia. The presentation of osteonecrosis of the jaw and renal dysfunctions were carefully followed during all therapeutic and follow-up periods. In addition, we also evaluated the characteristics of the symptomatic relapse of the 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 a safe use of BP were specifically followed according to the commercial labeling of ZOL as well as the recommendations of the European Myeloma Network.\textsuperscript{2,4}

1.4. Statistical analysis and recruitment

The sample size was calculated based on the time to next therapy with one experimental and one control arms with 12 moths of inclusion and 12 months of follow-up. Following data from the VISTA trial,\textsuperscript{5,6} where the Time to Tumor Progression were 24 vs. 16 months (experimental vs. control arms) and Time to Next Therapy were 28 vs. 19 months, we estimated the time between biochemical relapse and new anti-myeloma therapy (equivalent to TNT) as 5 months for the control group. This data was concordant with results from other groups.\textsuperscript{7,8} Thus, with a potential calculation of 5 months of TNT for the control group (No ZOL), we predicted for the experimental arm (ZOL) double TNT (10 months). Based on these estimations we calculated a requirement of 96 patients per group (Log rank test, two tail, $\alpha=0.05$, 1-$\beta=90$%; $\lambda_1=0.138$; $\lambda_2=0.069$), including a 10% of loss of follow-up or protocol violations. The initial plan was to include these 192 patients in 18 months in all Spain in hospitals belonging to the GEM/PETHEMA group.

An interim analysis that was done in the first 75 patients, suggesting a beneficial effect for the use of ZOL for the patients included in the trial. These results were communicated in the EHA-2012 and ASH-2012 annual meetings, and a second analysis was approved by the ethics committee and planned to be done in August 2013. At this point, the recruitment had reached 103 patients in 14 centers, and the subsequent analysis demonstrated again the same benefit, with statistically
significant differences. Due to this benefit and a low possibility to reach the initial planed number of patients, the scientific committee of the trial considered reasonable to close the recruitment and a final analysis and report were done. These results and decision were communicated at the EHA-2014 annual meeting. The final analysis that is here reported corresponds to these 103 patients and a complete follow-up period with attendant monitoring up to AUG-2013, as well as a partial follow-up with mailing and phone monitoring up to DEC-2014.

Collected data were exported to SPSS v15 (SPSS Inc, Armonk, New York) for further statistical analysis. T-test and Chisquare-test were used to identify statistically significant differences between groups. TNT, TNS, and overall survival (OS) distribution curves were plotted using the Kaplan–Meier method, using the log-rank test for comparisons. The effects of multiple parameters on survival were evaluated in all patients using a two-sided log-rank test.

2. REFERENCES