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

Ramón García-Sanz,[1] Albert Oriol,[2] María J. Moreno,[3] Javier de la Rubia,[4] Angel R. Payer,[5] Miguel T. Hernández,[6] Luis Palomera,[7] Ana I. Teruel,[8] María J. Blanchard,[9] Mercedes Gironella,[10] Paz Ribas,[11] Joan Bargay,[12] Eugenia Abellá,[13] Miquel Granell,[14] Enrique M. Ocio,[1] Josep M. Ribera,[2] Jesús F. San Miguel,[15] María V. Mateos,[1] and Spanish Myeloma Group (GEM/PETHEMA).

[1]Hospital Universitario de Salamanca-IBSAL, IBMCC (USAL-CSIC); [2]ICO - Hospital Germans Trias i Pujol, Fundació Josep Carreras; [3]Hospital Morales Meseguer; [4]Hospital Universitario La Fe and Universidad Católica de Valencia; [5]Hospital Universitario Central de Asturias; [6]Hospital Universitario de Canarias; [7]Hospital Lozano Blesa de Zaragoza; [8]Hospital Clínico Universitario de Valencia; [9]Hospital Universitario Ramón y Cajal de Madrid; [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; and [15]Clínica Universidad de Navarra-CIMA, Spain

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Correspondence: rgarcias@usal.es

SUPPLEMENTAL MATERIAL

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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 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.

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 antimyeloma 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.[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. [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,[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.[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, α=0.05, 1-β=90%; λ1=0.138; λ2=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

1. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473.

2. 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.

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, 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. *AnnOncol*. 2009;May 22. [Epub ahead of print].

5. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008;359(9):906-917.

6. 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.

7. 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.

8. 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.