

CLINICAL TRIALS AND OBSERVATIONS

The impact of response on bone-directed therapy in patients with multiple myeloma

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Key Points

- The use of ZOL is better than CLO in the improvement of SREs and survival in symptomatic myeloma patients at diagnosis.
- Response category posttransplant may influence the impact of bisphosphonate therapy.

Significant benefits for zoledronic acid (ZOL) over clodronate acid (CLO) were seen in the Medical Research Council Myeloma IX randomized trial. ZOL significantly reduced skeletal-related events (SREs), and improved progression-free survival and overall survival (OS), making it the bisphosphonate of choice for newly diagnosed myeloma patients. In this analysis of Myeloma IX data, we have investigated the impact of response on bone disease in 1111 transplant-eligible patients. At posttransplant day 100, complete response (CR) was seen in 48% of patients, very good partial response (VGPR) in 20%, and partial response (PR) in 23%. For patients in VGPR or less, ZOL was superior to CLO in reducing SREs ($P = .048$), whereas for patients in CR, both agents were equivalent ($P = .83$). For OS, ZOL was associated with a significant benefit in patients in PR ($P = .0091$). No difference in OS was seen with patients in CR ($P = .91$) or VGPR ($P = .74$). These findings indicate that response category posttransplant may influence the impact of bisphosphonate therapy. This trial was registered as #ISRCTN68454111 at www.isrctn.org. (*Blood*. 2013;122(17):2974-2977)

Introduction

Multiple myeloma (MM) is characterized by an uncontrolled proliferation of clonal plasma cells in the bone marrow.¹ A typical feature at presentation is the presence of osteolytic bone lesions in approximately 70% of patients, resulting in an increased risk of skeletal-related events (SREs).² Mechanistically, it is thought that MM plasma cells and bone marrow stromal cells secrete factors that stimulate osteoclast-mediated osteolysis, and inhibit osteoblast-mediated bone repair, resulting in unbalanced bone remodeling, leading to bone destruction.³ Furthermore, this cytokine dysregulation seems to be acting in a prosurvival fashion for the MM clone. Breaking this loop by therapy could affect survival.⁴

Bisphosphonates are currently the standard approach for the management of bone disease in MM.^{5,6} These pyrophosphate analogs have high bone affinity that inhibits osteoclastic activity, and additionally blocks growth factor release from the bone matrix, impairing MM growth.⁷ Preclinical and clinical evidence has suggested that zoledronic acid (ZOL) is superior to prior generations of such drugs.^{8,9} The Medical Research Council (MRC) Myeloma IX trial compared an intravenous amino-bisphosphonate (ZOL) with the oral first generation bisphosphonate clodronate acid (CLO) in newly diagnosed MM (NDMM), showing a significant benefit on SREs, progression-free survival and overall survival (OS) for ZOL.¹⁰⁻¹²

Based on these results, ZOL is recommended as the bisphosphonate of choice in symptomatic NDMM.¹³ There remains considerable interest in how the achievement of deep responses impact on bone disease and the necessity for ongoing bisphosphonate treatment. Current guidelines lack evidence to support firm decisions regarding the optimal duration of bisphosphonates and the frequency of its dosing for patients achieving a complete response (CR) after effective induction treatments.^{5,13} To be able to fully understand the impact of response on bone disease and how this influences bisphosphonate treatment, we have performed a retrospective analysis of the Myeloma IX trial data, focusing on patients on the intensive pathway who were eligible for autologous stem cell transplantation (ASCT). This pathway is informative because of the high number of CRs achieved, providing insights into bone disease in patients in deep response.

Study design

In the MRC Myeloma IX trial, NDMM patients aged ≥ 18 years were enrolled. Full details of the trial have been previously reported.^{10-12,14} The protocol was approved by the relevant institutional review boards and ethics

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committees and this study was conducted in accordance with the Declaration of Helsinki. Patients were randomized to receive induction chemotherapy with either cyclophosphamide-vincristine-doxorubicin-dexamethasone or oral cyclophosphamide-thalidomide-dexamethasone (CTD) and selected for ASCT (melphalan 200 mg/m²) based on their ability to tolerate it. In addition, at initial randomization, patients were allocated to receive ZOL (4 mg/every 3-4 weeks) or CLO (1600 mg/d), until progression. The presence of bone lesions on axial skeletal survey at baseline were defined as myeloma bone disease. SREs were defined as vertebral fractures, other fractures, spinal cord compression, need for radiation or surgery for bone lesions and new osteolysis, and were recorded every 3 months, until progression. CR was defined as negative immunofixation of serum and urine (100% monoclonal-protein reduction), and very good partial response (VGPR) as at least 95% reduction in paraprotein levels assessed by central laboratory analysis in Birmingham. Analyses were based on the intention-to-treat population. Responses post-transplant were analyzed on the population that received ASCT and were treated per-protocol. Time to first SRE was assessed by use of a cumulative incidence function, and compared with Gray's test.^{15,16} Relapse/death was used as a competing risk event. *P* values for the Kaplan-Meier analyses were calculated using the log-rank test.¹⁷

Results and discussion

Between May 2003 and November 2007, 1114 patients were enrolled in the intensive pathway; 1111 patients were evaluable, of whom 555 were randomly assigned to ZOL and 556 to CLO. Overall, 556 patients were randomized to receive cyclophosphamide-vincristine-doxorubicin-dexamethasone and 555 to oral cyclophosphamide-thalidomide-dexamethasone. After induction, 749 patients went on to ASCT. Baseline characteristics of the patients were already reported and were well balanced between the bisphosphonate groups.¹⁰ At baseline, 73% of patients had bone disease. Median follow-up was 5.71 years and 5.54 years for patients in the ZOL and CLO groups, respectively.

ASCT is an important component of therapy increasing response rates, and, in this study, the CR rate improved from 13% to 48% after ASCT. These high-quality responses translated into extended progression-free survival and potentially into OS.^{18,19} After ASCT, immunofixation negative CR was seen in 359 (48%) patients, VGPR in 150 (20%), and partial response in 171 (23%). CR was defined as negative serum/urine immunofixation and less than 5% plasma cells in the bone marrow, and was confirmed in 326 patients.

Overall, 350 (31.5%) patients had an SRE before progression, or as the first event of progression. Fewer patients assigned to ZOL had an SRE compared with CLO (155 vs 202 patients; *P* = .003), and ZOL significantly reduced the risk for first SRE (*P* = .02).

Looking at the differential impact of ZOL vs CLO on SRE risk, dependent on response status, we found that in patients with VGPR or less after ASCT, there was a significantly reduced risk of SREs associated with ZOL (*P* = .048). In contrast, in patients who achieved CR, no difference in the risk of SREs was observed (*P* = .83) (Figure 1).

We have observed that patients with bone disease at baseline had a significantly shorter OS compared with patients without bone disease (median 63.7 vs 70.9 months; *P* = .047). Looking at the impact of bisphosphonate type, ZOL was associated with a significantly increased survival vs CLO in these patients with bone disease at baseline (median 69.8 vs 58.8 months; *P* = .047). Similarly, the survival of patients treated with ZOL was significantly superior to CLO when a PR was achieved (median not reached vs 65.2 months; *P* = .009). However, in patients achieving

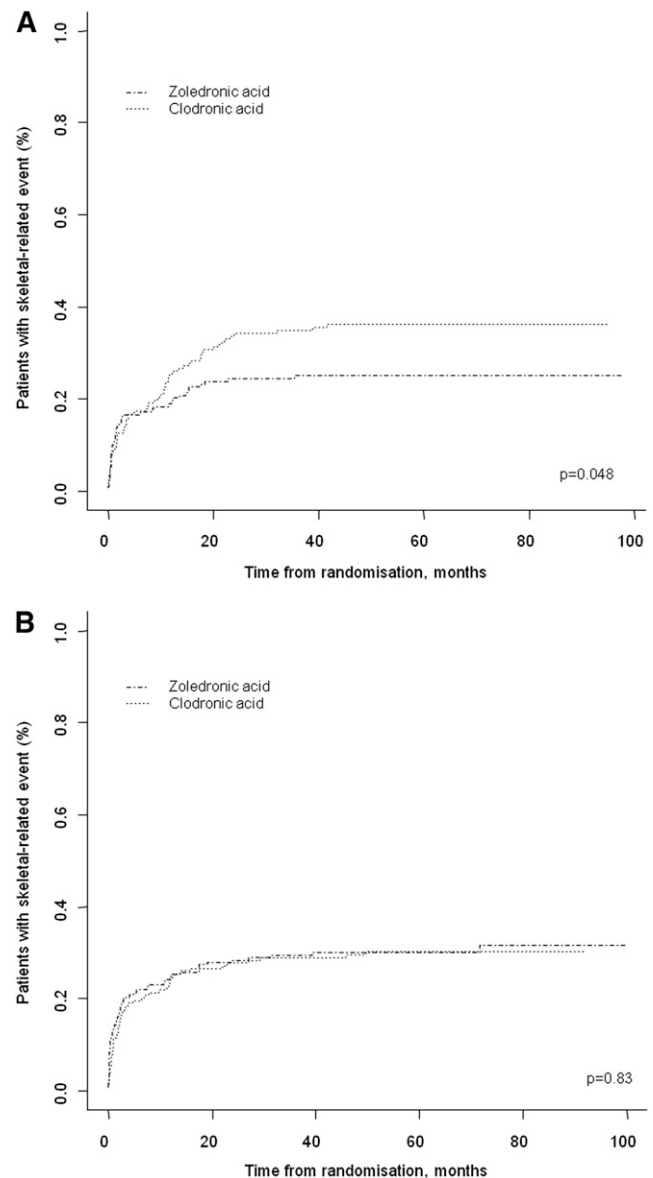


Figure 1. Cumulative incidence for first SRE by bisphosphonate (ZOL vs CLO). (A) Patients who achieved a VGPR or less posttransplant (*P* = .048); PR (hazard ratio 0.74 [HR]; 95% confidence interval [CI], 0.52-1.05); VGPR (HR, 0.87; 95% CI, 0.60-1.27). (B) Patients who achieved a CR posttransplant (HR, 1.05, 95% CI, 0.82-1.35; *P* = .83).

a VGPR or CR, no difference in survival was observed (VGPR median 88 months vs not reached [*P* = .74]; CR 85.3 months vs not reached [*P* = .91]) (Figure 2).

In addition, we found that in patients who achieved a CR, the incidence of SREs was not significantly different dependent on the bisphosphonate type. These results support the notion that when the MM clone is reduced to a minimum, the use of the more potent bisphosphonate has no greater impact on SREs or OS. In contrast, a clear benefit is observed in patients achieving VGPR or less after ASCT with the use of ZOL, suggesting that there is a substantial and ongoing bone resorption that can be significantly impacted by the use of ZOL.

In NDMM treated with ASCT, ZOL remains the mainstay of treatment at presentation, irrespective of the bone disease status. In patients who fail to achieve a CR after ASCT, the use of ZOL

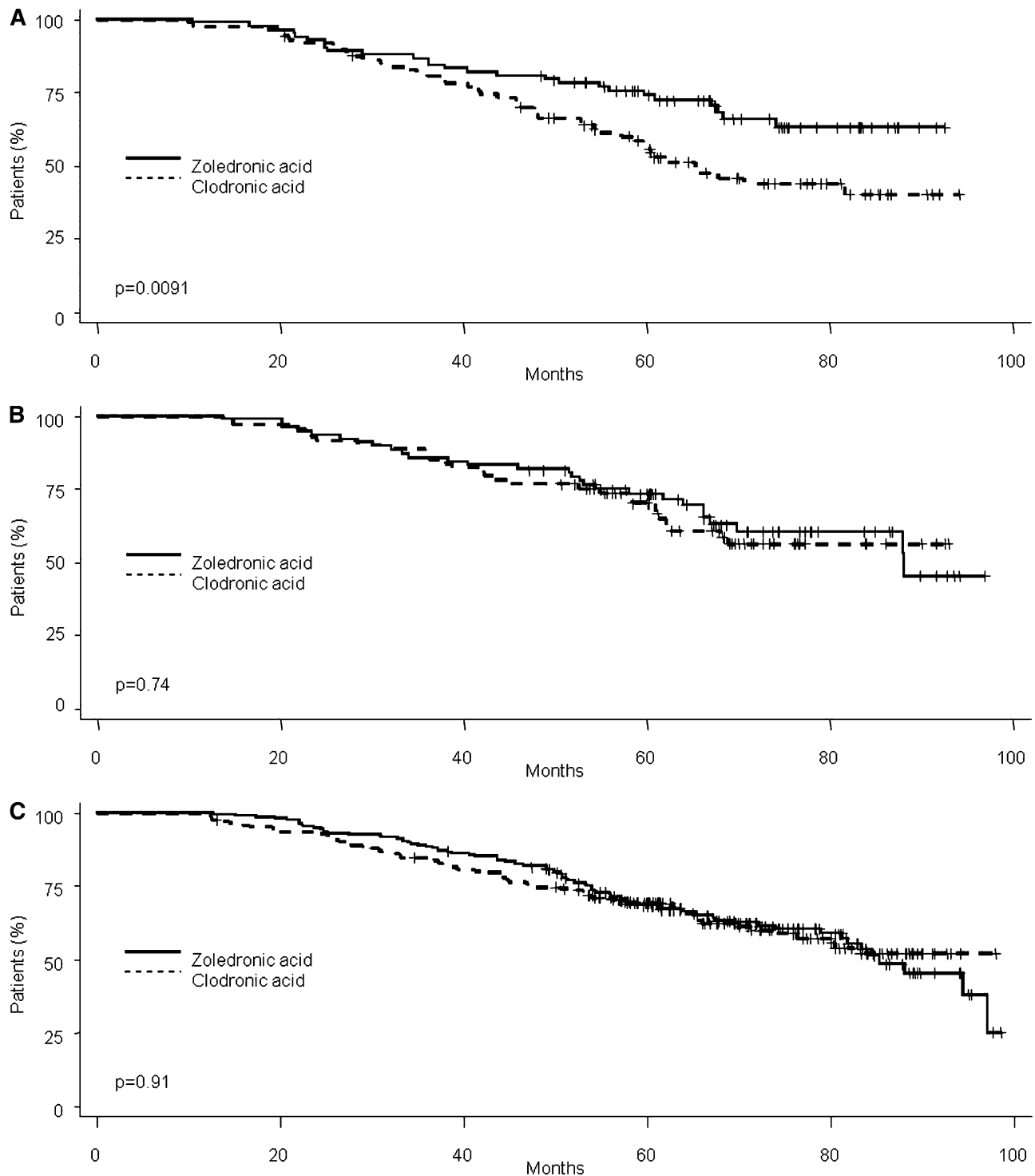


Figure 2. Overall survival for patients randomized to ZOL vs COL. (A) Patients who achieved partial response posttransplant (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.32-0.86; $P = .0091$). (B) Patients who achieved VGPR posttransplant (HR, 0.91; 95% CI, 0.54-1.54; $P = .74$). (C) Patients who achieved CR posttransplant (HR, 0.98; 95% CI, 0.70-1.36; $P = .91$).

significantly reduces the rate of SREs and improves survival, as compared with CLO. In contrast, in patients achieving a CR, this enhanced impact on SRE rate and survival was not seen. However, the available data do not provide definitive evidence that ZOL therapy can be discontinued without detriment in such patients. If decisions are taken to temporarily discontinue bisphosphonate therapy, we would stress that close monitoring and the early reintroduction of ZOL

in the event of clinical suspicion of progression, would be necessary. Although there are some limitations with the current study, such as the retrospective non preplanned nature of the analysis, this is the only study that has evaluated the impact of response on bisphosphonate therapy in myeloma, and supports the continued use of ZOL in MM from its early phases until disease progression, or maybe, in some instances, until the achievement of complete response.

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Authorship

Contribution: G.J.M., J.A.C., and G.H.J. were chief investigators of the MRC Myeloma IX trial; A.L., F.E.D., and G.J.M. designed research; J.A.C., G.H.J., G.C., N.R., R.G.O., M.T.D., and P.W. contributed to writing the report, generation of tables and figures,

or data interpretation; A.L., F.E.D., G.J.M., A.P., M.B., and A.B. wrote the paper; W.M.G. and A.S. collected data; A.L., F.E.D., G.J.M., W.M.G., and A.S. analyzed data; and all of the authors had access to, commented on, and approved the final manuscript.

Conflict-of-interest disclosure: A.L. received honoraria from Celgene and Janssen-Cilag. G.H.J. received honoraria as a speaker and served on the advisory boards for Celgene, Janssen Cilag, Novartis, and Chugai. M.B. received research support, consultancy fees, and served on the scientific advisory board for Celgene and Janssen Cilag. A.P. received honoraria and consultancy fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Millenium, and Onyx. The remaining authors declare no competing financial interests.

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