5 Minute JournalClub

Key ASCO Presentations
Issue 4, 2010

Effects of Zoledronic Acid on Overall Survival in Newly Diagnosed Multiple Myeloma (MM)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Demonstrate knowledge of both the survival benefit and reduction in skeletal-related events exhibited with zoledronic acid in the treatment of newly diagnosed MM.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Medtronic Inc, Otsuka Pharmaceutical Co Ltd; Paid Research: Celgene Corporation, Onyx Pharmaceuticals Inc.

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Key ASCO Presentations
Issue 4, 2010

To go directly to the slides and commentary, **click here**.

Chatting with myeloma investigators nowadays often yields extensive recounting of seemingly limitless clinical trials featuring weird acronyms and incredibly complicated results. What is also eminently apparent from these conversations is just how remarkably the face of this disease has changed with the recent introduction of two major classes of novel agents, the IMiDs® — thalidomide and lenalidomide — and the proteasome inhibitors, specifically bortezomib.

The dozens of cool papers presented at the recent ASCO meeting further affirmed the profound effects of these agents when used individually, in combination or in sequence, and here are our top picks for findings relevant to oncology practice:

1. **Triple therapy continues to impress**
   In a follow-up to a recently published paper in *Blood*, Dana-Farber's Paul Richardson once again wowed the masses as he presented unprecedented efficacy findings (100 percent response rate, 74 percent with VGPR or more) and acceptable toxicity with induction RVD (lenalidomide, bortezomib, dexamethasone). A new, huge trial will address post-transplant consolidation with this combination and also whether transplant can be delayed or avoided. In any event, our surveys of practicing oncologists and investigators show a rapid shift toward three-drug combos like RVD for patients eligible for transplant. In another impressive data set on a triple regimen, French investigators reported similar high response rates to vTD (bortezomib, thalidomide, dexamethasone), which utilized attenuated doses of both bortezomib and thalidomide that dramatically lowered the rate of peripheral neuropathy.

2. **Lenalidomide maintenance after autologous stem cell transplant is effective**
   No question this was one of the most important findings presented in any tumor type at ASCO as both the **CALGB and the French IFM** group demonstrated an impressive 50 percent reduction in disease progression among patients receiving this well-tolerated agent as maintenance therapy following transplant. Many clinical trials in both the transplant and nontransplant settings are now scrambling to add "L maintenance" to their control arms.

3. **Zoledronic acid (ZDA) may slow disease progression and extend survival**
   This MRC trial from the UK is in a sense the myeloma version of the Austrian breast cancer study presented during the ASCO plenary session two years ago. Monthly ZDA resulted in an impressive five months-plus improvement in survival compared to clodronate. Investigators are not yet jumping on the idea of treating patients without bone disease, but this might be coming in the future.

Next up on 5-Minute Journal Club: A smorgasbord of ASCO papers on breast cancer, including some interesting new data on sentinel node biopsy.

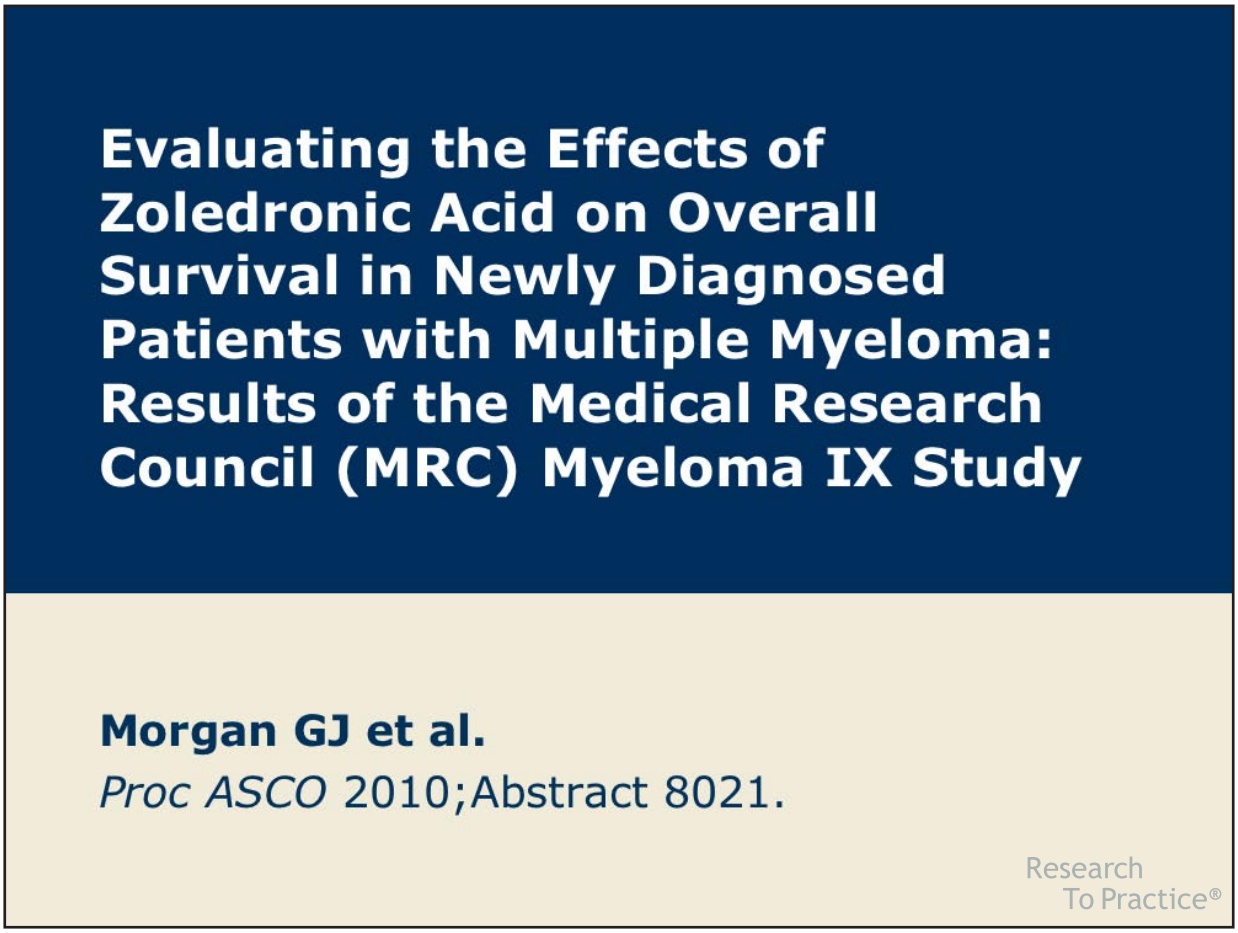
Neil Love, MD
Research To Practice
Miami, Florida

Effects of Zoledronic Acid on Overall Survival in Newly Diagnosed Multiple Myeloma (MM)

Presentation discussed in this issue

Morgan G et al. **Evaluating the effects of zoledronic acid on overall survival in patients with multiple myeloma: Results of the Medical Research Council Myeloma IX study.** *Proc ASCO* 2010;**Abstract 8021**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Michele Cavo, MD (7/1/10), Rafael Fonseca, MD (7/7/10), Sagar Lonial, MD (6/21/10), Robert Z Orlowski, MD, PhD (6/18/10) and Ravi Vij, MD (7/1/10)



Introduction

- Indirect and direct preclinical evidence supports the potential anticancer effects of bisphosphonates in multiple myeloma (MM).
- Clinical evidence supports the anticancer effects of zoledronic acid (ZOL) and clodronate (CLO) in MM:
  - ZOL significantly increased 5-year event-free survival (EFS) and overall survival (OS) rates vs control (*Med Oncol* 2007;24:227).
  - In patients with high bone-specific alkaline phosphatase, ZOL significantly decreased the risk of death by 55% vs pamidronate (*Proc ASH* 2006;Abstract 3589).
  - CLO significantly improved survival in patients with no fractures at baseline vs placebo (*Br J Haematol* 2001;113:1035).
- **Current study objective:**
  - In patients with newly diagnosed MM, determine whether bone-targeted therapy with ZOL versus CLO can improve survival.

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

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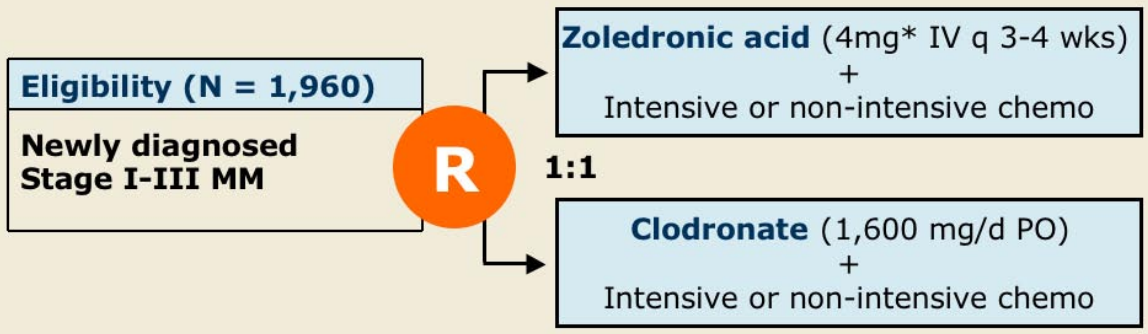
MRC IX Study Design



Primary Endpoints:
PFS, OS, and ORR

Secondary Endpoints:
Time to first SRE, SRE incidence, safety

Treatment continued at least until disease progression

* Dose-adjusted for patients with impaired renal function per prescribing information
PFS = progression-free survival; OS = overall survival;
ORR = overall response rate; SRE = skeletal-related event

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

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Summary of Efficacy (Median Follow-Up: 3.7 Years)

Endpoint	Risk reduction (in favor of ZOL)	*p*-value
Overall survival (OS)*	16%	0.0118
Progression-free survival (PFS)*	12%	0.0179
Skeletal-related events (SREs)†	24%	0.0004
Improvement in median OS (ZOL vs CLO) = 5.5 mo, *p* = 0.04		
Is the observed OS improvement with ZOL due to SRE prevention, or does it represent an anti-myeloma effect?		
OS adjusted for SREs	15%	0.0178

* Adjusted for chemotherapy and minimization factors
† SREs defined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions or the appearance of new osteolytic bone lesions

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

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Adverse Events (AEs): Safety Population

Adverse Event	Intensive treatment			Non-intensive treatment		
	ZOL (n = 555)	CLO (n = 556)	*p*-value	ZOL (n = 428)	CLO (n = 423)	*p*-value
Acute renal failure	5.2%	5.9%	0.70	6.5%	6.4%	1.0
ONJ*	3.8%	0.4%	<0.0001	3.3%	0.2%	0.0009
Thrombo-embolic events	18.7%	14.7%	0.08	12.4%	8.3%	0.06
Infection, serious AE	9.4%	11.2%	0.37	3.7%	6.6%	0.06

* Confirmed by an independent adjudication committee
ONJ = osteonecrosis of the jaw

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

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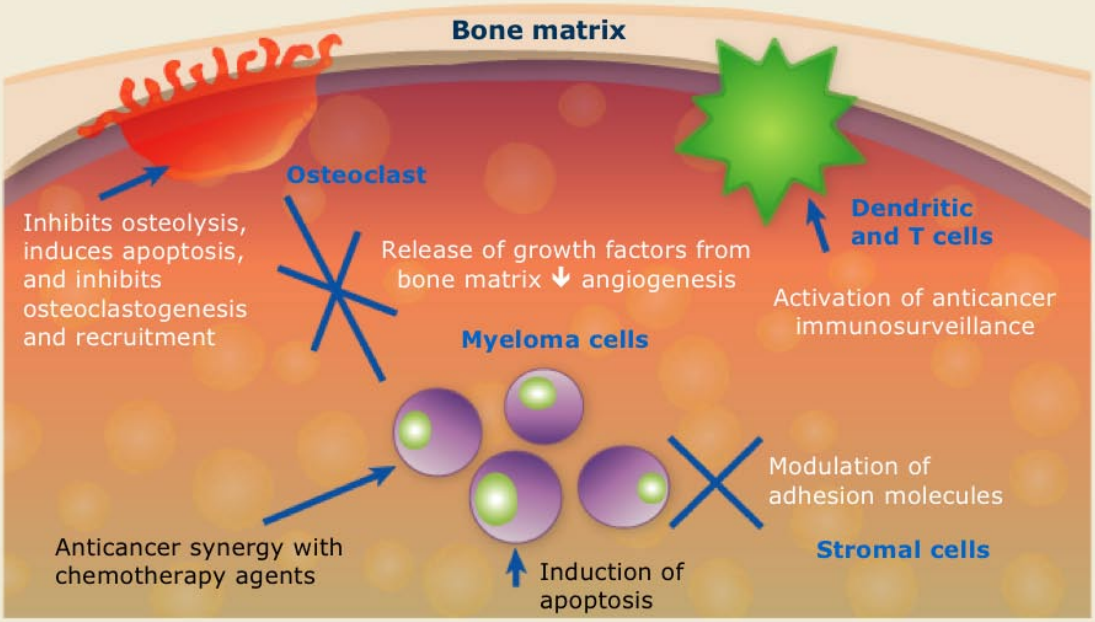
ZOL Exerts Both Direct and Indirect Antimyeloma Effects



Modified from Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

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Conclusions

- After a median follow-up of 3.7 years, ZOL significantly prolonged OS and PFS and reduced SREs compared to CLO.
  - Survival benefit was independent of SRE reduction.
- ZOL and CLO were generally well tolerated, with expected safety profiles.
  - ONJ incidence was low overall, but higher for ZOL vs CLO (3.6% vs 0.3%).
- These data further support the anticancer activity of ZOL and provide evidence that ZOL should be considered for early integration into treatment regimens for patients with newly diagnosed MM.

Morgan GJ et al. *Proc ASCO* 2010;Abstract 8021.

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Investigator comment on the results of the MRC Myeloma IX study

One concern about the study is that the regimens used for induction were not what we would consider the current standard. The possibility exists that had modern induction regimens been used, the difference in overall survival would not have been quite as dramatic.

Regarding adverse events, this is one of the largest studies in which data were collected about ONJ (osteonecrosis of the jaw), and in the zoledronate arm from 3.3 to 3.8 percent of patients developed signs of ONJ. Overall, the data support the use of zoledronate for patients with myeloma-related bone disease. And the data suggest that it may have some benefit beyond bone health — some direct effects against multiple myeloma itself.

This study included patients with and without osteolytic bone disease, and the study population as a whole benefited from zoledronic acid. It would be interesting to see whether the subgroup without bone disease benefited by subset analysis because current ASCO guidelines do not recommend bisphosphonates for those patients.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

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Investigator comment on the results of the MRC Myeloma IX study

It is not easy to evaluate this study because it was designed for younger, transplant-eligible patients and for older, non-transplant-eligible patients, and the results reflect a mix of both younger and elderly patients with myeloma. We will need to perform post hoc subanalyses because the value of zoledronic acid in terms of antitumor activity might be quite different for the younger patient in comparison to the elderly patient.

However, I believe that another important result of this study is the significantly decreased rate of skeletal-related events in a patient population that included a group of patients who had no skeletal disease at the time of diagnosis. Based on this study, I believe that bisphosphonates should be started at the time that treatment is started for all patients with myeloma, independent of the presence or absence of osteolytic lesions.

Interview with Michele Cavo, MD, July 1, 2010

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Investigator comment on the results of the MRC Myeloma IX study

This intriguing abstract adds to data in solid tumors, where zoledronate (ZDA) has been shown to have possible antineoplastic activity. We know that ZDA is active as a therapeutic agent for myeloma in the laboratory, both in vitro and in vivo murine models, where the antineoplastic effects may be somewhat distinct from its effects on bone. This clinical trial tried to control for skeletal-related events and was able to show that the survival advantage with ZDA appeared to exist irrespective of the effects on skeletal-related events, suggesting that it's due to a direct antitumor effect rather than an indirect effect from the reduction of skeletal-related events.

I don't believe that this study has many practical implications at the moment because we already use ZDA as the agent of choice in most settings. I would continue to follow the ASCO guidelines, which at the moment recommend that bisphosphonates be used for two years, after which time, if the disease is inactive, they be stopped and resumed when the disease becomes active again.

Interview with Ravi Vij, MD, July 1, 2010

Investigator comment on the results of the MRC Myeloma IX study

This zoledronate study raised a red flag. I believe that hematologists, myself included, have become a little less careful about the management of bisphosphonates, only to have a study like this show that in a recent time frame, it does matter. Although many caveats apply to this study — the newest regimens were not used and there's potential for improvement in how zoledronate was applied — it still provided patient benefit. So it's something that we need to consider in our practice. I wouldn't say it's practice changing as much as practice reaffirming and a call to more quality, principle-based practice.

Interview with Rafael Fonseca, MD, July 7, 2010

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