Novel therapies for Myeloma bone disease

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Introduction

- Multiple myeloma (MM) is a plasma cell dyscrasia characterized by malignant proliferation of monoclonal plasma cells in the bone marrow.
- MM-induced bone disease is a hallmark of MM; up to 80% of patients present with osteolytic bone lesions at diagnosis and have an increased risk of skeletal-related events (SREs) associated with increased morbidity and mortality.
- Approximately 60% of myeloma patients will develop a fracture during the disease course.
- Histomorphometric studies have demonstrated that in MM patients with bone lesions there is uncoupled or severely imbalanced bone remodeling with increased bone resorption and decreased or absent bone formation.
Bone Disease

Terpos: Pathogenesis of bone disease in multiple myeloma: from bench to bedside
Pathophysiology & Novel targets

Terpos: Pathogenesis of bone disease in multiple myeloma: from bench to bedside
Current Treatment of MBD

• A multidisciplinary approach is needed to ensure that a patient’s quality of life is maintained through the use of analgesia for pain, surgery or radiotherapy for MBD.

• MBD will progress without adequate anti-MM treatment, and thus a patient management plan needs to treat the underlying MM through the use of anti-MM treatment and combine this with MBD treatment.

• Preventative therapies are needed to delay disease progression in MBD, with the mainstay of treatment being antiresorptive agents.
Anti-resorptive Therapies
Bisphosphonate (Pamidronate & Zoledronic acids)

• Bisphosphonates are the only treatment licensed for the prevention of MBD worldwide. However, they do not completely prevent osteolytic lesions and fail to promote new bone formation or repair of existing lesions.

• Renal toxicity requiring dose reduction in patients with renal impairment, flu-like symptoms and gastrointestinal upset during administration, atrial fibrillation, atypical femoral fracture and osteonecrosis of the jaw (ONJ), which can occur in 3.5% of patients are known side effects.
Bisphosphonate

• Because of that longevity of their use is limited due to their side effects.

• BPs are recommended for up to 2 years only before a break in treatment and the continuation to be administered at much longer intervals.
Pamidronate (90 mg) as a four-hour intravenous infusion given every four weeks for 9 cycles in addition to ant myeloma therapy.

**Purpose**
To determine the efficacy and safety of 21 monthly cycles of pamidronate therapy in patients with advanced multiple myeloma.

**Patients and Methods**
Patients with stage III myeloma and at least one lytic lesion received either placebo or pamidronate 90 mg intravenously administered as a 4-hour infusion monthly for 21 cycles. At study entry, the patients were stratified according to whether they were to receive first-line (stratum 1) or second-line (stratum 2) antmyeloma chemotherapy. Skeletal events (pathologic fracture, radiation or surgery to bone, and spinal cord compression) and hypercalcemia were assessed monthly.

**Results**
The results of the first nine previously reported cycles are extended to 21 cycles. Of the 392 randomized patients, efficacy could be evaluated in 198 who received pamidronate and 179 who received placebo. After 21 cycles, the proportion of patients who

Pamidronate (90 mg) as a four-hour intravenous infusion given every four weeks for 21 cycles in addition to ant myeloma therapy

**Conclusion**
Long-term monthly infusions of pamidronate as an adjunct to chemotherapy are superior to chemotherapy alone in reducing skeletal events in stage III multiple myeloma.
**Zoledronic Acid Versus Placebo in the Treatment of Skeletal Metastases in Patients With Lung Cancer and Other Solid Tumors: A Phase III, Double-Blind, Randomized Trial—The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group**

Lee S. Rosen, David Gordon, Simon Tishkoff-Malyi, Ronald Magnaghi, Ying Hing M. Kowalski, Paul P. de Sousa, Ming Zheng, Bradly Urbanowicz, Rick Rehmans, John J. Seaman

From the Cancer Institute Medical Group, Santa Monica, Pacific Shores Medical Group, Long Beach; and Gilroy, CA. US Oncology, San Antonio, TX. McGill Department of Oncology, Montreal, Quebec, Canada. The M. Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, and Klinika Chemoterapeutika Centrum Onkologii, Krakow, Poland; St George Hospital Cancer Care Center, Kogarah, Australia; Novartis Pharmaceuticals Corp, East Hanover, NJ.

**Zoledronic Acid Is Superior to Pamidronate in the Treatment of Hypercalcemia of Malignancy: A Pooled Analysis of Two Randomized, Controlled Clinical Trials**


From the Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada; Centre Paul Lapin, Angers, France; Comprehensive Cancer Institute, Huntsville, AL; Bengodi Hospital, Benigdo, and Andrew Love Cancer Centre, Geelong, Australia; Fecht-Weiler Cancer Center, Shreveport, LA; Medizinische Klinik III, Universitätsskilinikum, Berlin, Germany; Boston Cancer Group, Memphis, TN; Institut Jules Bordet, Brussels, Belgium; and Novartis Pharma, Basel, Switzerland.

**Purpose:** To assess the efficacy and safety of zoledronic acid in patients with bone metastases secondary to solid tumors other than breast or prostate cancer.

**Patients and Methods:** Patients were randomly assigned to receive zoledronic acid (4 or 8 mg) or placebo every 3 weeks for 3 months, with concurrent antineoplastic therapy. The primary efficacy analysis was proportion of patients with at least one skeletal-related event (SRE), defined as pathologic fracture, spinal cord compression, radiation therapy to bone, and surgery to bone. Secondary analyses (time to first SRE, skeletal morbidity rate, and multiple event analysis) counted hypercalcemia as an SRE.

**Results:** Among 773 patients with bone metastases from lung cancer or other solid tumors, the proportion with an SRE was reduced in both zoledronic acid arms compared with the placebo arm (38% for 4 mg and 35% for 8 mg)

4 mg zoledronic acid as an infusion every 3–4 weeks & therapy continued until 9 months

common adverse events in all treatment groups included bone pain, nausea, anemia, and vomiting.
Bisphosphonates in multiple myeloma: a network meta-analysis.


Abstract

BACKGROUND: Bisphosphonates are specific inhibitors of osteoclastic activity and used in the treatment of patients with multiple myeloma (MM). While bisphosphonates are shown to be effective in reducing vertebral fractures and pain, their role in improving overall survival (OS) remains unclear. This is an update of a Cochrane review first published in 2002 and previously updated in 2010.

OBJECTIVE(S): To assess the evidence related to benefits and harms associated with use of various types of bisphosphonates (aminobisphosphonates versus nonaminobisphosphonates) in the management of patients with MM. Our primary objective was to determine whether adding bisphosphonates to standard therapy in MM improves OS and progression-free survival (PFS), and decreases skeletal-related morbidity. Our secondary objectives were to determine the effects of bisphosphonates on pain, quality of life, incidence of hypercalcemia, incidence of bisphosphonate-related gastrointestinal toxics, osteonecrosis of jaw and hypocalcemia.

SEARCH METHODS: We searched MEDLINE, EMBASE, EMBASE (November 2009 to October 2011) and the Cochran Database of Systematic Reviews Register (all issues, September 2011) to identify all randomized trials in MM up to October 2011 using a combination of text and MeSH terms. We also handsearched relevant meeting proceedings (December 2009 to October 2011).

SELECTION CRITERIA: Any randomized controlled trial (RCT) assessing the role of bisphosphonates and observational studies or case reports examining bisphosphonate-related osteonecrosis of the jaw in patients with MM were eligible for inclusion.

DATA COLLECTION AND ANALYSIS: Two review authors extracted the data. Data were pooled and reported as hazard ratio (HR) or risk ratio (RR) under a random-effects model. Statistical heterogeneity was explored using meta-regression.

AUTHORS’ CONCLUSIONS: Use of bisphosphonates in patients with MM reduces pathological vertebral fractures, SREs and pain. Assuming a baseline risk of 20% to 50% for vertebral fracture without treatment, between 8 and 20 MM patients should be treated to prevent vertebral fracture(s) in one patient. Assuming a baseline risk of 31% to 78% for pain amelioration without treatment, between 5 and 13 MM patients should be treated to reduce pain in one patient. With a baseline risk of 35% to 86% for SREs without treatment, between 6 and 15 MM patients should be treated to prevent SRE(s) in one patient. Overall, there were no significant adverse effects associated with the administration of bisphosphonates identified in the included RCTs. We found no evidence of superiority of any specific aminobisphosphonate (zoledronate, pamidronate or ibandronate) or nonaminobisphosphonate (etidronate or clodronate) for any outcome. However, zoledronate appears to be superior to placebo and etidronate in improving OS.
Bone Disease

- All patients receiving primary myeloma therapy should be given bisphosphonates (category 1) or denosumab²
- A baseline dental exam is recommended.
- Monitor for relapse.
- Monitor for colonization.
- Use of bisphosphonates preferably in patients with skeletal disease.

The NCCN Guidelines for Multiple Myeloma recommend bisphosphonates for all patients receiving myeloma therapy for symptomatic disease regardless of documented bone disease (category 1). In patients with smoldering or stage I MM, according to the NCCN panel, bisphosphonates may be considered but preferably in a clinical trial. Skeletal survey annually or as clinically indicated is recommended for these patients. Bone densitometry or other metabolic studies should be reserved for clinical trials.

²Denosumab is preferred in patients with renal insufficiency.
Denosumab – Novel approved agent

- Denosumab is an anti-RANKL monoclonal antibody, designed to prevent osteoclast function and osteoclast genesis by preventing the RANK–RANKL interaction.
- It significantly has lower renal toxicities compared to zoledronic acid and can be used in ESRD/HD.
Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study

Prof Noopur Raje, MD, Evangelos Terpos, MD, Wolfgang Willenbacher, MD, Prof Kazuyuki Shimizu, MD, Ramón García-Sanz, MD, Prof Brian Durie, MD, Wojciech Legieć, MD, Prof Marta Krejčí, MD, Kamel Laribi, MD, Li Zhu, PhD, Paul Cheng, MD, Douglas Warner, MD, Prof G David Roodman, MD

The Lancet Oncology

DOI: 10.1016/S1470-2045(18)30072-X
Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study

• Phase III 482 study, denosumab demonstrated no inferiority to zoledronic acid (Zometa) at delaying the time to the first SRE in patients with multiple myeloma (HR, 0.98; 95% CI, 0.85-1.14; \( P = .01 \)).

• The median time to first on-study SRE was similar between the treatments, at 22.83 months with denosumab versus 23.98 months with the bisphosphonate zoledronic acid. The median progression-free survival was 10.7 month higher in the denosumab arm (HR, 0.82; 95% CI, 0.68-0.99; \( P = .036 \)). There was also a nonstatistically significant trend in overall survival (OS) favoring denosumab (HR, 0.90; 95% CI, 0.70-1.16; \( P = .41 \)).
Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study

• The most common grade 3 or worse treatment-emergent AE for denosumab and zoledronic acid were neutropenia (15% vs 15%), thrombocytopenia (14% vs 12%), anemia (12% vs 10%), febrile neutropenia (11% vs 10%), and pneumonia (8% vs 8%).

• Renal toxicity was reported in (10%) patients in the denosumab group versus (17%) in the zoledronic acid group; hypocalcaemia adverse events were reported in (17%) versus (12%).

• Incidence of osteonecrosis of the jaw was not significantly different between the denosumab and zoledronic acid groups (4% vs 3%; p=0.147)
Figure 2

A

Number at risk (censored)

Dacarbazine

-450

(0)

Zoledronic acid

-450

(0)

Time since randomisation (months)

Patients without a skeletal-related event (%)

0 5 10 15 20 25 30 35 40 45

HR 0.65 (95% CI 0.44-0.97; p=0.033)

B

Number at risk (censored)

Dacarbazine

-450

(0)

Zoledronic acid

-450

(0)

Time since randomisation (months)

Patients without a skeletal-related event (%)

0 5 10 15 20 25 30 35 40 45

HR 0.78 (95% CI 0.55-1.11; p=0.16)
Figure 3

A

HR 0.90 (95% CI 0.70-1.16; p=0.41)

Number at risk (censored)

- Denosumab: 859, 809, 737, 640, 565, 477, 395, 344, 288, 229, 175, 130, 85, 48, 19
  (0) 32, 58, 81, 60, 81, 76, 44, 45, 57, 41, 43, 39, 34, 29

- Zoledronic acid: 859, 810, 737, 652, 568, 488, 444, 348, 289, 233, 179, 127, 87, 49, 33
  (0) 17, 74, 85, 57, 69, 64, 52, 59, 55, 47, 40, 37, 27, 27, 27

B

HR 0.82 (95% CI 0.68-0.99; p=0.36)

Number at risk (censored)

- Denosumab: 859, 789, 703, 583, 501, 411, 329, 269, 214, 157, 125, 82, 57, 35, 14
  (0) 38, 55, 85, 73, 63, 49, 42, 47, 25, 28, 21, 21, 20

- Zoledronic acid: 859, 806, 690, 584, 495, 404, 344, 252, 206, 159, 117, 78, 53, 30, 9
  (0) 22, 150, 129, 66, 65, 61, 43, 49, 46, 33, 34, 27, 12, 11, 11, 11, 11
FDA Approves Denosumab for Multiple Myeloma

The FDA has approved denosumab (Xgeva) for the prevention of skeletal-related events (SREs) in patients with multiple myeloma, according to Amgen, the developer of the RANK ligand inhibitor.

The approval is based on data from the phase III A82 study, which were presented at the 16th International Myeloma Workshop in New Delhi. In the trial, denosumab demonstrated noninferiority to zoledronic acid (Zometa) at delaying the time to the first SRE in patients with multiple myeloma (HR, 0.98; 95% CI, 0.85-1.14; P = .01).

The median time to first on-study SRE was similar between the treatments, at 22.83 months with denosumab versus 23.98 months with the bisphosphonate zoledronic acid. The median progression-free survival was 10.7 month higher in the denosumab arm (HR, 0.82; 95% CI, 0.68-0.99; P = .036). There was also a nonstatistically significant trend in overall survival (OS) favoring denosumab (HR, 0.90; 95% CI, 0.70-1.16; P = .41).
When to use Denosumab over BPs?

• Denosumab is recommended when BPs cannot be prescribed, for example due to renal toxicities.

• There is also a recommendation to use Denosumab if hypercalcemia of malignancy occurs and is refractory to BPs.

• Denosumab is not nephrotoxic and can be given as a subcutaneous injection, which allows easier access for patients to this treatment and provides a potential alternative to those that cannot have BPs.
Anabolic Agents
Parathyroid Hormone

• has been shown to have anabolic affects in bone remodeling in osteoporosis. Intermittent doses have been shown to be anabolic in nature rather than resorptive.

• Teriparatide, a recombinant form of PTH, has been approved for use in women with osteoporosis.

• The mechanism for teriparatide’s anabolic effect is unclear, but it is thought to be due to PTH having a direct effect on osteoblasts.

• The safety and efficacy of PTH in MM are therefore still to be established, but warrant further enquiry given promising results obtained in patients with osteoporosis.
Anti-Dkk-1

- Dkk-1 is a potent regulator of the Wnt signaling pathway and inhibits the Frizzled co-receptor LRP6.
- Dkk-1 is produced by BMSCs and MPCs and it has been found to be elevated in MM patients. However, it is not expressed by all myeloma cells.
- BHQ880 (humanized IgG) anti-Dkk-1 novel monoclonal antibody was tested in Phase I trials.
- Novartis sponsored Phase II clinical trial has been completed (NCT01337752) and results are awaited since 2014.
Anti-sclerostin

• Sclerostin is an osteocyte-specific Wnt antagonist that inhibits bone formation.

• Sclerostin has been shown to be an important mechanism in osteoporosis; however, its importance has not been established in MBD apart from in vivo mice studies.

• In mice: Treatment with anti-sclerostin antibody increased osteoblast numbers, bone formation rate and reduced tumor burden.

• Currently there are no clinical trials for MM but the potential for a dual target with Dkk-1 may also be a promising therapeutic in the future.
Activin A and Sotatercept

- Sotatercept is a soluble recombinant activin receptor type IIA (ActRIIA) ligand fused to the human FC-IG fragment and binds activin A/B plus members of the TGFβ superfamily to disrupt downstream cascades.

- Sotatercept as an addition to melphalan, prednisolone and thalidomide caused an anabolic effect and increased the biomarker bone alkaline phosphatase (bALP), indicating improved bone turnover.

- Ph1 study in human w/ MPT confirmed its safety and increased bone mass.

- Currently, a clinical trial (NCT01562405) recruiting patients for the use of sotatercept in combination with lenalidomide or pomalidomide and dexamethasone is being undertaken.
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<th>Molecular target</th>
<th>Use in MM/therapeutic implication</th>
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<td><strong>Increased osteoclast activity</strong></td>
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| RANK/RANKL pathway | Denosumab (anti-RANKL, mAb), Phase 3 clinical trial completed; denosumab was not inferior to zoledronic acid; possibly superior regarding PFS.²⁴  
RANKL/OPG is reduced by ASC²⁵  
RANKL is reduced by bortezomib-based regimens.⁵⁶ |
| Syndecan-1 | Preclinical setting²⁷ |
| Notch pathway | Preclinical setting |
| Osteopontin | Preclinical setting |
| CCL-3 (MIP-1α) / CCL-20 | Preclinical setting⁵⁵⁴⁶⁴² |
| Activin A | Sotatercept (ACT-516) (ligand trap fusion receptor). Phase 2 clinical trial completed; sotatercept increased BMD in MM patients who received MPT⁴⁶  
Lerakidomide-Activin A inhibitor. Phase 1 clinical trial⁵⁵ |
| Interleukin-6 | Anti-L6 mAbAnti-MM activity in clinical trials⁵¹ |
| Interleukin 3 and 17 | Preclinical setting⁵²⁴³ |
| PI3K/AKT/mTOR pathway | Preclinical setting³⁴ |
| TNF-α | Preclinical setting |
| BAFF | Tabalumab (anti-BAFF mAb); Negative results in a phase 2 clinical trial⁵⁷ |
| BTK and SDF-1α | Ibrutinib (selective BTK inhibitor). Ongoing clinical trials |
| Annexin II | Preclinical setting |
| PU.1 | Downregulated by IMiD.⁵²⁶³ |
| **Suppressed osteoblast activity** | |
| WNT pathway | Preclinical setting⁵⁵⁶⁶ |
| Sclerostin | Preclinical setting in MM⁵⁰ |
| DKK1 (DKK1) | Romosozumab, an anti-sclerostin mAb, for benign bone disorders⁴ |
| Peristin | BIBQ80 (DKK1 neutralizing Ab), increased bone anabolic activity in a phase 2 clinical trial⁴⁴ |
| RUNX2, Cbf1 and Ile-7 | Preclinical setting⁹¹⁹² |
| TGFR and BMPs | Preclinical setting |
| TGF-α and LIGHT | Preclinical setting |
| EphrinB2/EphB4 signaling pathway | Preclinical setting⁹⁶ |
| Adiponectin | Preclinical setting⁴⁰ |

Terpos: Pathogenesis of bone disease in multiple myeloma: from bench to bedside
Conclusion

• MM survival outcomes and quality of life have dramatically improved with the introduction of many new encouraging agents.

• With patients surviving longer with their disease, this therefore highlights the need to introduce more effective agents for the treatment of MBD.

• BPs remain the mainstay of treatment for MBD. However, their limited efficacy, inability to promote new bone formation and concerns over their side effect profile demonstrate the strong potential utility of bone anabolic agents.
Conclusion

• The mounting evidence of the benefits being exhibited by bone anabolic agents, such as anti-RANKL (Denosumab) anti-Dkk-1, antisclerostin and Anti-Activin (Sotatercept), does bring promise to improvements in the treatment of MBD.

• With many agents in clinical trials and a plethora of factors to target, combination treatment presents the most potential for the management of MBD.

• Bone anabolic agents in combination with both antiresorptive agents and anti-myeloma therapies may pave the way for future treatment of MBD
Thanks for your attention.