

Multiple Myeloma Bone Disease: 2009 Consensus

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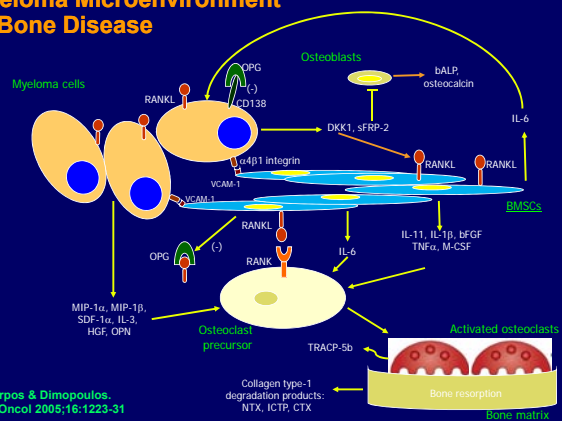
Bone Disease in Multiple Myeloma

- A burdensome and frequent complication in MM
 - Present in up to 80% of patients at diagnosis
- Characterized by osteolytic bone lesions secondary to increased bone resorption and impaired bone formation
- Sequelae
 - Pathological fractures
 - Osteoporosis
 - Hypercalcemia
 - Bone pain
 - Spinal cord compression

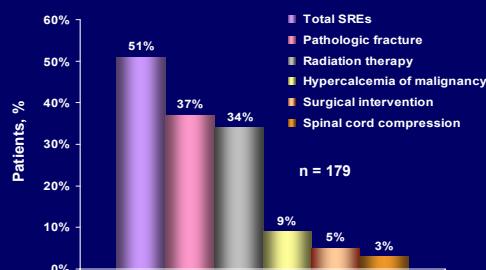


Kyle. Mayo Clin Proc 1975;50:29-40

Myeloma Microenvironment & Bone Disease



Skeletal-Related Events (SREs) in Myeloma Patients

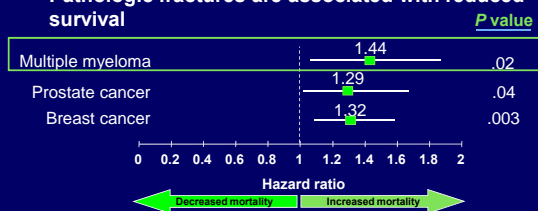


*21-month data (including osteolytic lesions) except for surgical intervention and spinal compression, for which only 9-month data are available from placebo arm of randomized study.

Benenson et al. J Clin Oncol 1998;16:593-602

Early Treatment to Prevent SREs Is Important Because...

- Patients who experience a first SRE are 2-fold more likely to experience subsequent SREs
- Pathologic fractures are associated with reduced survival

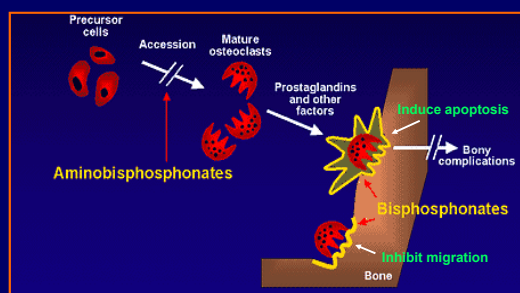


Saad et al. Presented at: ECCO, Oct. 30-Nov. 3, 2005, Paris, France. Abstract 1285.

The Goal of Therapy for Myeloma Bone Disease

- Preserve patient's functional independence and QOL by
 - Preventing skeletal-related events (SREs)
 - Prevent the first SRE
 - Delay the onset of the first SRE
 - Prevent the recurrence of SRE
 - Palliating and controlling bone pain
 - Reduce the need for analgesics and palliative radiotherapy

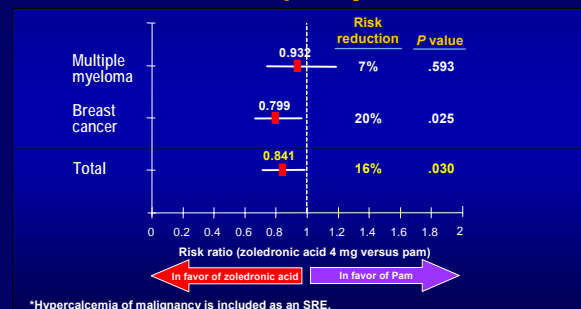
Bisphosphonates



Major Double-Blind, Placebo-Controlled, Trials On Bisphosphonates In MM

Authors/year	Type of BP	No pts	↓ of pain	↓ of SREs	Survival benefit
Belch et al, 1991	Etidronate	173	No	No	No
Daragon et al, '93	Etidronate	94	No	No	No
Lahtinen et al, '92	Clodronate	350	Yes	Yes	NE
McCloskey et al 1998 & 2001	Clodronate	530	Yes	Yes	+/-
Brincker et al, '98	Pamidronate	300	Yes	No	No
Berenson et al, '96	Pamidronate	392	Yes	Yes	+/-
Menssen et al, '02	Ibandronate	198	No	No	No
Berenson et al, '01	Zoledronic acid	108	Yes	Yes	NE
Rosen et al, '01 & '03	Zoledronic acid	513	Yes	Yes	+?

Zoledronic Acid Was at Least as Efficacious as PAM in the Multiple Myeloma Stratum



Bisphosphonates: Adverse Events

- Oral
 - GI intolerance (in up to 33% of pts)
 - Especially esophagitis & esophageal ulcers
- Intravenous (PAM or ZOL)
 - Common adverse events
 - Flu-like symptoms
 - Fever/Myalgias/Arthralgias
 - Uncommon adverse events
 - Renal-function effects
 - Osteonecrosis of the jaw

Bisphosphonates and Renal Insufficiency

- IV bisphosphonates are cleared almost entirely by the kidneys
- 2007 ASCO Multiple Myeloma Guidelines
 - In patients with pre-existing renal impairment (serum creatinine clearance 30-60 mL/min) should receive reduced dosage of zoledronic acid
 - No change in infusion time or interval of zoledronic acid is required
- Use of these bisphosphonates in patients with more severe renal dysfunction has been minimally assessed

ONJ: Novel Complication of Bisphosphonates

- Avascular osteonecrosis of the jaw (ONJ) is a recent complication that has been described in multiple myeloma and other cancer patients who receive potent bisphosphonates.
- ONJ presents as an exposure of the mandible or maxilla that can be either painless or painful.



Kyle et al. J Clin Oncol 2007;25:2464-72

Conte & Guarneri, Oncologist 2004;9(Suppl 4):28-37


ONJ: characteristics

Symptoms

- "heavy jaw", a dull aching sensation
- numbness/tingling of the jaw
- tooth pain
- undiagnosed oral pain

Signs

- rough area on the jawbone
- soft tissue swelling, drainage or infection
- exposed bone in the oral cavity
- sudden change in the health of periodontal tissue
- failure of oral mucosa to heal
- loosening of teeth




Clinical Presentation and Working Diagnosis of ONJ

Clinical features of suspected ONJ

- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing

Working diagnosis of ONJ

- No evidence of healing after 6 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis



Weitzman et al. Crit Rev Oncol Hematol 2007;62:148-152

Incidence of ONJ in Malignant Bone Disease: Prior to Implementation of Prevention Strategies

Study	Study type	Pts treated w BP, n	Pts w suspect or proven ONJ, n	Frequency %
Hoff et al. MDACC (JBMR 2008)	Chart review	3,994	29	0.7%
Durie et al (NEJM 2005)	Web-based survey	1,203	152	12.6%
Badros et al (JCO 2005)	Chart review/observational	340	11	3.2%
Zervas et al (BJH 2006)	Chart review/prospective after 2001	254	28	11.0%
Dimopoulos et al (Haematologica 2006)	Chart review/prospective after 2003	202	15	7.4%

Relative Risk for ONJ Development

15/202 developed ONJ (7.4%)	Relative risk							
	12 months		24 m		36 m		48 m	
	%	95%CI	%	95%CI	%	95%CI	%	95%CI
All (n=202)	1	0-2	3	1-4	6	2-10	13	5-21
Zoledronic acid (n=93)	1	0-3	5	0-11	15	3-27	15	3-27
PA (n=33)	0	0	1	0-3	1	0-3	5	0-11

	ONJ	Yes	No	p-value
Thalidomide				
Yes		8 (7.5%)	99 (92.5%)	0.977
No		7 (7.4%)	88 (92.6%)	

Dimopoulos et al. Haematologica 2006;91:968-71

ASCO Guidelines

- The Update Committee suggests that bisphosphonate treatment continues for a period of 2 years.
- At 2 years, physicians should seriously consider discontinuing bisphosphonates in patients with responsive or stable disease, but further use is at the discretion of the treating physician.
- Re-initiation at relapse.

Kyle et al. J Clin Oncol 2007;25:2464-72

Update for ONJ and Bisphosphonates in Myeloma (1)

- Appropriate preventative measures, such as a detailed assessment of dental status by experienced specialists, and avoidance of dental procedures during treatment with ZOL have the potential to reduce the number of ONJ cases.
- Group A, with no special precautions (n=38) and Group B, with a detailed dental assessment and preemptive dental care (n=90).
- ONJ occurrence was 0.671/100 person-month for Group A vs. 0.230/100 person-month for Group B: **3-fold reduction of ONJ occurrence (p=0.029)**

Dimopoulos et al. Ann Oncol 2009;20:117-120.

Update for ONJ and Bisphosphonates in Myeloma (2)

- ONJ resolved and did not recur in 60/97 cases (62%)
- resolved and then recurred in 12 patients (12%)
- did not resolve over a follow-up period of at least 9 months in 25 patients (26%)
- ONJ recurrence followed re-initiation of bisphosphonate in 6 of 12 patients

Badros et al. J Clin Oncol 2008;26:5904-9

Update for ONJ and Bisphosphonates in Myeloma (3)

- ONJ recurrence was linked to BP re-challenge, mostly in the setting of relapsed MM
- Patients in whom ONJ was precipitated by dental procedures, were less likely to have recurrence or non-healing lesions, after BP re-initiation following ONJ healing, as compared to those who develop spontaneous ONJ lesions ($p=0.007$)

Badros et al. J Clin Oncol 2008;26:5904-9

Recommendations by An Expert Panel on behalf of the EMN (1)

- BPs should be given for 2 years; then at the physician's discretion.
- In patients in CR after 12 months the benefit of an additional 12 months of treatment is debatable.
- BP therapy should be resumed upon relapse.
- Comprehensive dental examination & education on dental hygiene. Existing dental conditions should be treated before initiating BPs.
- After therapy initiation, unnecessary invasive dental procedures should be avoided and dental status should be monitored annually.

Terpos et al. Ann Oncol 2009; in press.

Recommendations by An Expert Panel on behalf of the EMN (2)

- Temporary BPs suspension if invasive dental procedures needed.
- Initial ONJ therapy should include discontinuation of BP until healing.
- The decision to restart BP should be individualized, until prospective long-term studies are available.
- The physician has to take into consideration the advantages and disadvantages of BPs mainly in the relapsed/refractory setting.

Terpos et al. Ann Oncol 2009; in press.

Recommendations by An Expert Panel on behalf of the EMN (3)

Creatinine Clearance rate (mL/min)	Recommended dosage of CLO (1600 mg)
>80	100%
50-80	75%
12-50	50-75%
<12	50% or discontinue

Creatinine Clearance rate (mL/min)	Recommended dosage of ZOL (mg)
> 60	4.0
50-60	3.5
40-49	3.3
30-39	3.0
<30	Not recommended

Creatinine Clearance rate (mL/min)	Recommended infusion time for PAM (90mg)
>30	2-4 hours
<30	Not recommended

CONCLUSIONS

- Bisphosphonates are useful and remain the cornerstone of the management of bone destruction in MM.
- However many questions have not been answered yet. What is the maximum duration for their use? What is the long-term safety profile? **Be careful in renal dysfunction and be aware of ONJ.**
- Novel agents (bortezomib, denosumab) in combination with or without bisphosphonates may help in the better management of myeloma bone disease.