

**I BIFOSFONATI NEL PAZIENTE ONCOLOGICO ED
EMATOLOGICO**

**OTTIMIZZAZIONE DELLA TERAPIA NEL
MIELOMA MULTIPLO**

Patrizia Falco

ALESSANDRIA

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Multiple Myeloma Patients Are at Serious Risk of Developing Bone Complications

Disease	5-year world prevalence, thousands¹	Incidence of bone metastases in cancers, %²	Median survival, months²⁻⁵
Myeloma	183	70 - 95	6 - 54
Breast	4,406	65 - 75	19 - 25
Prostate	2,369	65 - 75	12 - 53
Lung	1,362	30 - 40	6 - 7
Bladder	1,110	40	15
Melanoma	643	14 - 45	6
Renal	586	20 - 25	12

1. Ferlay J, et al. IARC GLOBOCAN 2002. Cancer Incidence, Mortality, and Prevalence Worldwide.

2. Coleman RE. *Cancer Treat Rev.* 2001;27:165-176.

3. Coleman RE. *Cancer.* 1997;80(suppl):1588-1594.

4. Zekri J, et al. *Int J Oncol.* 2001;19:379-382.

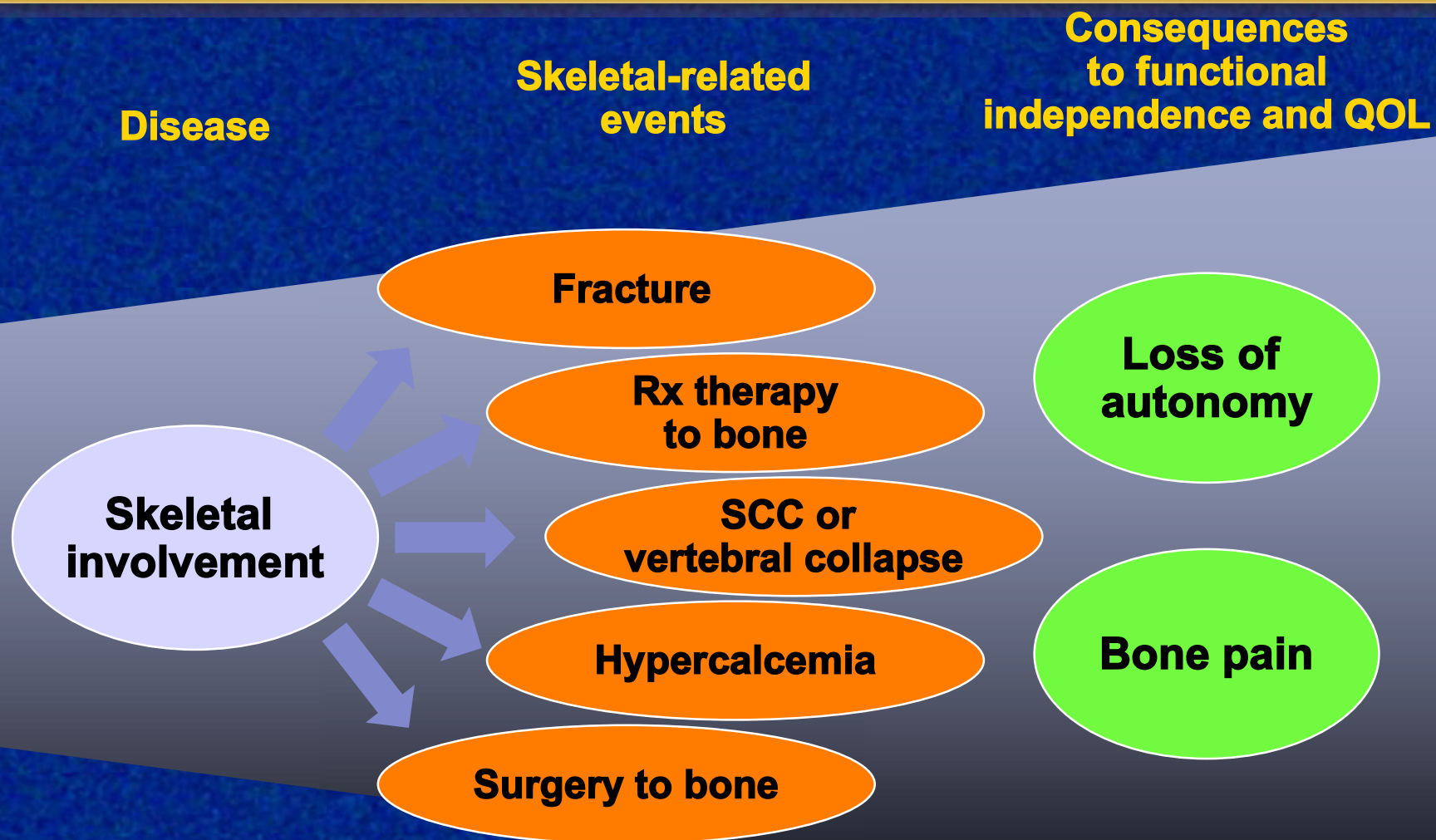
5. Hussain M, et al. *J Clin Oncol.* 2001;19:2527-2533.

Pathological fractures : A Significant Complication of Multiple Myeloma

“Bone metastasis is a catastrophic complication for most patients with cancer. Not only does it cause intractable pain... [but also] fracture after trivial injury, spinal cord compression, and hypercalcemia, it also signifies that the malignant process is incurable.”

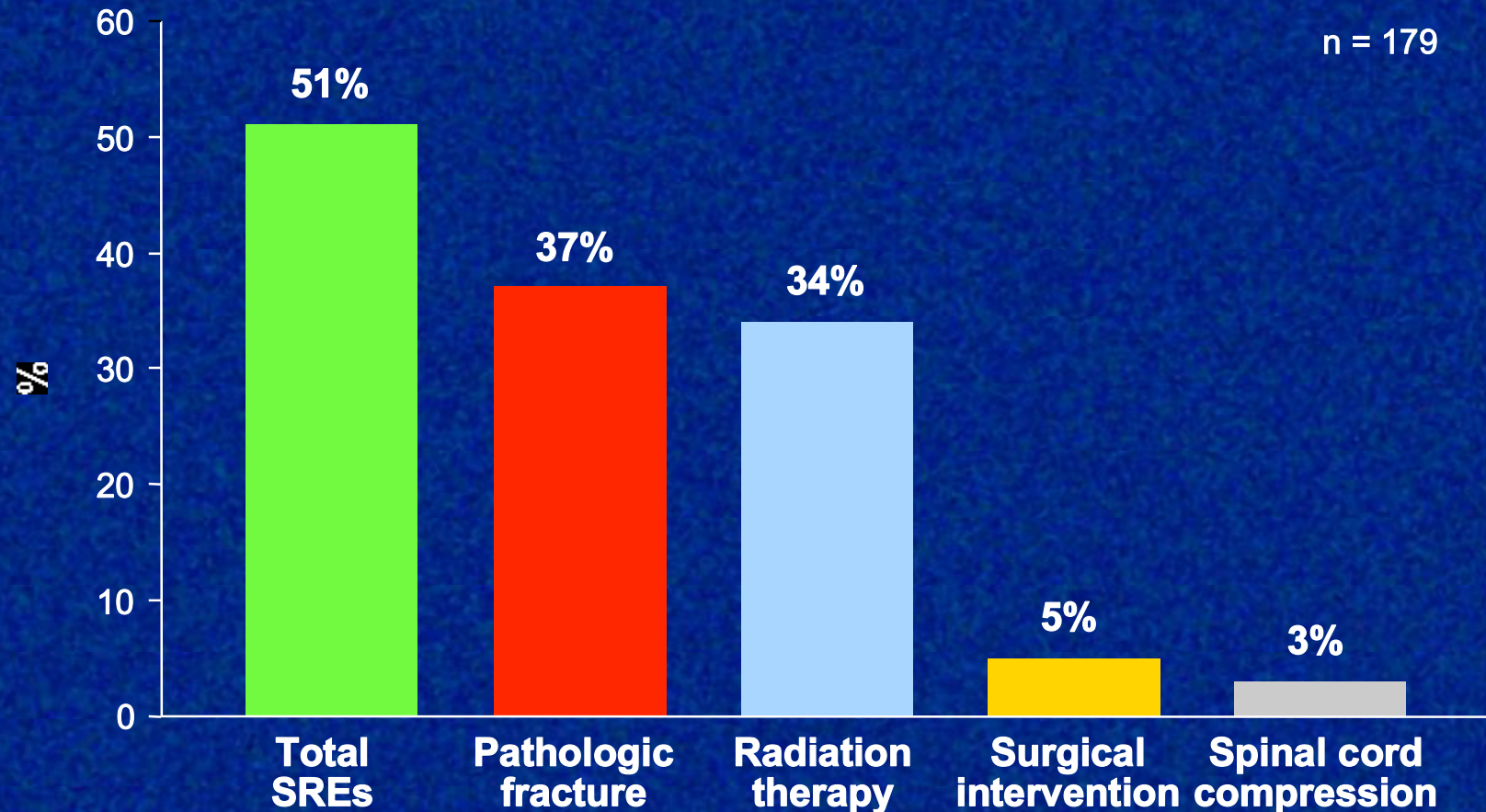


Skeletal involvement Has Debilitating Consequences



QOL = Quality of life;
SCC = Spinal cord compression.

Clinical Trials Indicate That Skeletal-Related Events Are a Serious Threat To Multiple Myeloma Patients*



SRE = Skeletal-related event.

*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.

Adapted from: Berenson JR, et al. *J Clin Oncol*. 1998;16:593-602.

Avoiding the First Skeletal-Related Event Is Critical

- Multiple myeloma patients are at long-term risk for skeletal-related events
- Risk increases 2-fold after prior SRE¹



1. Conte PF, et al. Presented at: 29th ESMO Congress; 29 Oct-2 Nov, 2004; Vienna, Austria. Abstract 463PD.
2. Berenson JR, et al. *N Engl J Med*. 1996;334:488-493.
3. Kyle RA, et al. *Mayo Clin Proc*. 2003;78:21-33.

Symptomatic Treatment: Management of Skeletal-Related Events

● Bisphosphonates

- ↓ Incidence of additional SREs
- ↓ Bone pain and need for analgesics and RT

● Surgery

- Repair pathologic fracture
- ↓ Neurologic complications from spinal cord compression ↑

Stability

● Radiotherapy

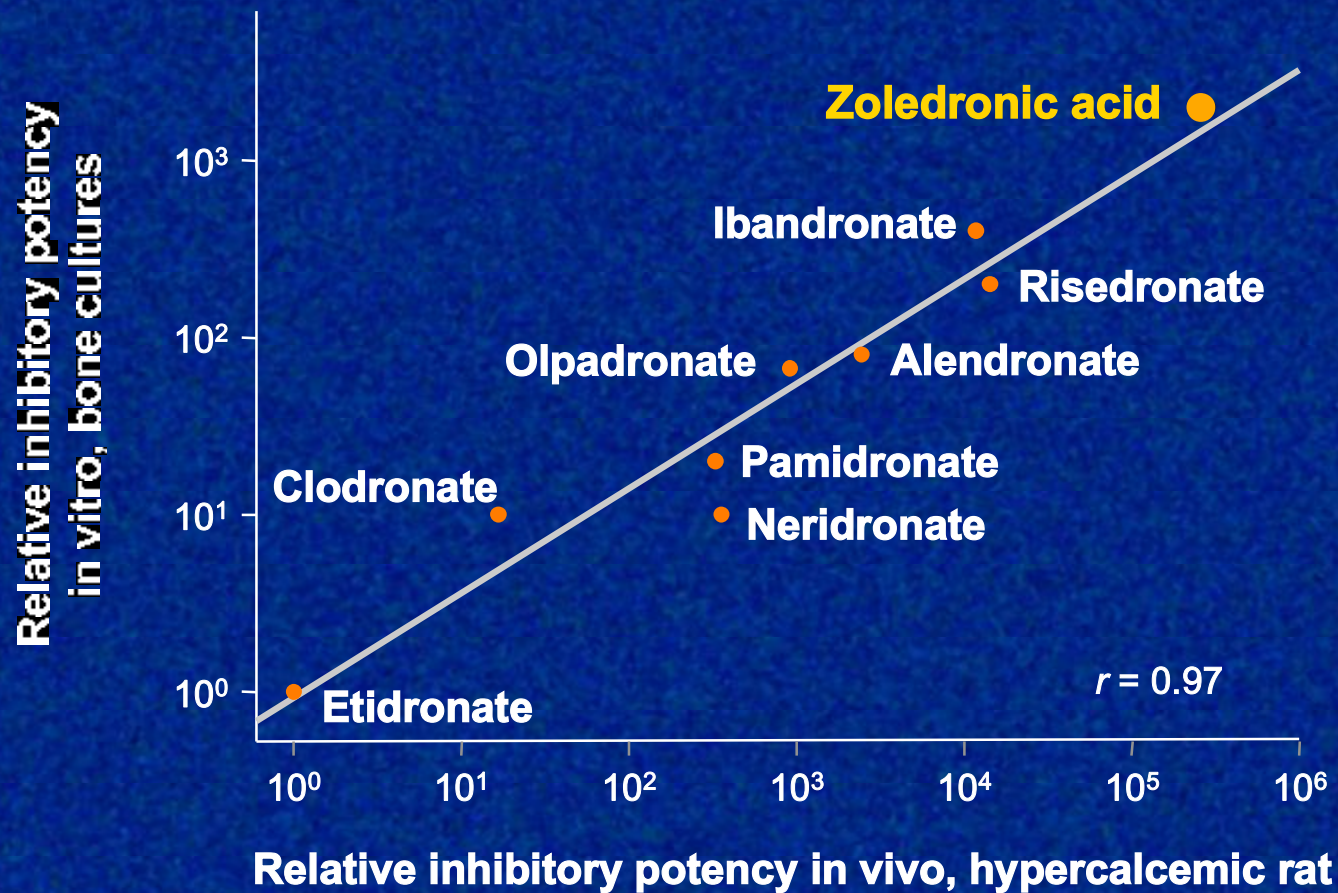
- ↓ Bone pain
- ↓ Neurologic complications from spinal cord compression

● Analgesics

- ↓ Bone pain

Correlation Between In Vitro and In Vivo Models of Osteoclast-Mediated Bone Resorption

Zoledronic acid is the most potent inhibitor of bone resorption



ASCO Guidelines For The Use of Bisphosphonates in Patients With Multiple Myeloma

MM patients who have:

**on plain radiograph or imaging lytic destruction of bone or
compression fracture of the spine from osteopenia**

Pain control secondary to bone involvement

IV Zoledronic Acid 4 mg

or

IV Pamidronate 90 mg

RECOMMENDED

ASCO Guidelines For The Use of Bisphosphonates in Patients With Multiple Myeloma

**MM patients who have osteopenia but not
radiographic evidence of lytic bone disease**

treatment with intravenous bisphosphonates

IS REASONABLE

ASCO Guidelines For The Use of Bisphosphonates in Patients With Multiple Myeloma

solitary plasmocytoma

smoldering (asymptomatic) myeloma

MGUS

treatment with intravenous bisphosphonates

IS NOT RECOMMENDED

ASCO Guidelines For The Use of Bisphosphonates in Patients With Multiple Myeloma

Frequency and duration of therapy

**Bisphosphonates infusion on per monthly basis
for 24 months , and then...**

- Consider discontinuing in pts with responsive or stable disease**
- Re-initiate BPs if patient has an SRE**

Mayo Clinic Consensus Statement for the Use of Bisphosphonates in Multiple Myeloma

Frequency and duration of therapy

Bisphosphonates infusion for 2 yrs in patients in plateau phase then...

- Changing frequency to q 3 months in patients who require active treatment is suggested**

Safety Profile of Bisphosphonates

- **Intravenous bisphosphonates**
 - **Mild to moderate flu-like symptoms**
 - **Effects on renal function**
 - **Osteonecrosis of the jaw**

- **Oral bisphosphonates**
 - **Upper gastric toxicity (eg, esophagitis and mucositis)**
 - **Diarrhea**

Safety Profile of Bisphosphonates:

**Transient myalgia, arthralgias, flu-like symptoms
with fever**

**Usually occur only after the first and/or second
infusion**

Responsive to paracetamole

Are not an indication to discontinue drug treatment

Safety Profile of Bisphosphonates

Effects on renal function

RENAL IMPAIRMENT IS A COMMON FEATURE IN MM:

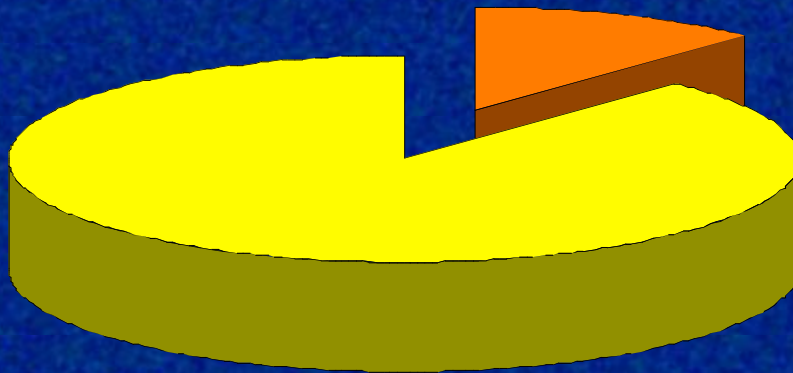
- 20-30% of patients at diagnosis show renal insufficiency;
- 2-10% require dialysis;
- 50% of patients experience renal impairment during the course of the disease

Alexanian R, *Arch Intern Med.* 150:1693 (1990).
Knudsen LM, *Eur J Hematol.* 53:207 (1994).
Winearls CG. *Kidney Intern.* 48:1347(1995).

Safety Profile of Bisphosphonates

Effects on renal function

12% of patients with MM, breast cancer, solid tumor developed evidence of renal deterioration during treatment with Bisphosphonates*



* ↑ Crs $\geq 0,5$ mg/dl

↑ Crs ≥ 2 times the baseline value in pts with normal Crs at baseline

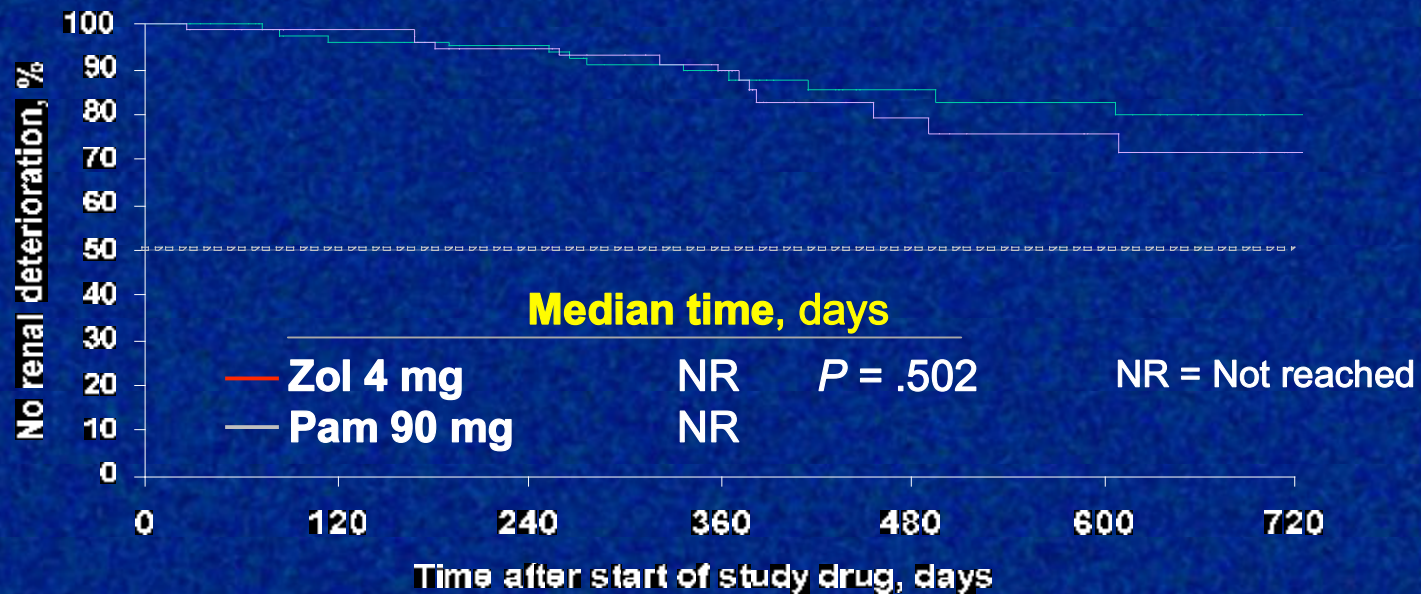
Rates of Grade 3-4 Serum Creatinine Increases Are Low for Zoledronic Acid, Pamidronate, and Placebo

Incidence of grade 3 and 4 serum creatinine abnormalities, n (%)

	ZOL (n = 529)	PAM (n = 268)	Placebo (n = 241)
Grade 3	7 (1.3)	4 (1.5)	4 (1.7)
Grade 4	2 (0.4)	1 (0.4)	0

Rosen LS, et al. *Cancer*. 2003;98:1735-1744.
Saad F, et al. *J Natl Cancer Inst*. 2004;96:879-882.
Rosen LS, et al. *Cancer* 2004;100:2613-2621.

No Difference Between Zoledronic Acid and Pamidronate in Time to First Serum Creatinine Increase



ZOL 4 mg	91	76	71	57	32	30	18
PAM 90 mg	84	71	62	50	23	17	8

Guidelines for Dose Adjustment in Patients With Poor Renal Function


Baseline CrCl, mL/min	Recommended dose, mg
50 - 60	3.5
40 - 49	3.3
30 - 39	3.0

Baseline CrCl < 30 ml/min → PAMIDRONATE 90 mg 4-6 hr

Administration Schedules

Bisphosphonate	Protocol, minutes	Treatment frequency per month	Route
Zoledronic acid	66 ¹	1*	IV
Pamidronate	172 ¹	1*	IV

Bisphosphonate	Protocol, minutes	Treatment frequency per month	Route
Zoledronic acid	< 15	1*	IV
Pamidronate	< 120	1*	IV



1. DesHarnais Castel L, et al. *Support Care Cancer*. 2001;9:545-551.

Monitoring

SERUM CREATININE before each dose of iv bisphosphonate

SERUM CALCIUM, ELECTROLYTES, PHOSPHATE, MAGNESIUM, HEMATOCRITE/HEMOGLOBIN regularly during therapy

ALBUMINURIA every 3 months

**IF PATIENTS DEVELOPES RENAL DETERIORATION OR ALBUMINURIA
BISPHOSPHONATE SHOULD BE DISCONTINUED**

Osteonecrosis of the Jaw: Background

- **Osteonecrosis of the jaw (ONJ) is an uncommon event that has been reported in cancer patients receiving complex treatment regimens, including intravenous (IV) bisphosphonates**
- **ONJ has been reported in a very small number of patients who are receiving oral bisphosphonates for noncancer indications**
- **Reports of ONJ have primarily been in patients with advanced malignancies and skeletal metastases**

Zoledronic Acid Prescribing Information

- **Before initiation of bisphosphonate therapy**
 - **A dental examination with appropriate preventive dentistry should be considered in patients with concomitant risk factors (eg, cancer, chemotherapy, corticosteroids, poor oral hygiene)**
- **During bisphosphonate therapy**
 - **Patients should avoid invasive dental procedures if possible**
 - **Patients should maintain excellent oral hygiene**

Zoledronic Acid Prescribing Information

- **Patients who develop ONJ while on bisphosphonate therapy**
 - **Dental surgery may exacerbate the condition**
 - **For patients requiring dental procedures, there are no data to suggest whether discontinuation of bisphosphonate therapy reduces the risk of ONJ**
 - **Clinical judgment of the treating physician should guide the management plan of each patient based on individual **benefit/risk assessment****

Conclusions: Multiple Myeloma

- **Patients with multiple myeloma are at serious risk of developing SREs**
- **SREs threaten functional independence, impair QOL, and are potentially life threatening**
- **SREs increase cost of managing patients with bone lesions**
- **Goal of therapy is to preserve patient independence by preventing first and subsequent SREs**

Conclusions: Bisphosphonate in Multiple Myeloma

- **Zoledronic acid and Pamidronate has proven efficacy in the prevention of SREs in patients with multiple myeloma**
- **Zoledronic acid and Pamidronate demonstrated an acceptable safety profile in patients with multiple myeloma**