Bisphosphonates in management of pain due to metastatic cancer

Muhammad Mansoor Alam MD
Case

- H S is 68 y.o. Filipino American female
- Admitted with complaints
  - Progressively worsening back
  - Left shoulder pain
  - LE numbness tingling and weakness.
  - 20 lb weight loss within last 3 months.
  - Non smoker.
- Pain
  - Worst 7/10
  - Best 2/10
  - Average 4/10.
- Location
  - Left shoulder,
  - Back
  - Left leg
- Description
  - Numb, cold, achy
Case

- MRI cervical thoracic lumbar spine, CT head
  - Right lung mass
  - Metastatic disease
    - Extensive bony involvement of the thoracic and lumbar spine with replacement of L4
    - Diffuse infiltration of the left scapula and shoulder joint by cancer.
    - Left parietal bone involvement seen on CT head.
    - Compression fractures involving L1, L2 and L3
    - Moderate spinal canal compromise at L1 with mild compression conus.
    - No abnormal signal was identified within the spinal cord.
    - There was also multilevel neural foraminal narrowing, most prominent at L2-L3 and the left and L3-L4 bilaterally.
Pain control

- She had better pain control since being started on a morphine PCA pump.
- She was however still experiencing pain with pain level of 4.
- Calcium is 9.8
Can Bisphosphonates be used to help control patients pain?
Bone metastases are associated with substantial morbidity in patients with cancer.

Skeletal complications of bone metastases, often referred to as skeletal-related events (SREs), include:

- Fracture
- Skeletal instability/loss of skeletal integrity
- Spinal cord compression
- Hypercalcemia
- Need for surgery or radiation therapy for a symptomatic bone metastasis
- Bone pain
Bisphosphonates have become an integral component of cancer treatment in patients who have metastatic bone disease.

Bisphosphonates reduce the morbidity of metastatic bone disease by decreasing the prevalence of SREs.
Bisphosphonates mechanism of action

- Bisphosphonates
  - Decrease bone resorption
  - Increase mineralization by inhibiting osteoclast activity

- Effect on osteoclasts
  - Direct apoptotic effect on osteoclasts
  - Affect their differentiation and maturation and thereby act as potent inhibitors of bone resorption.
  - In preclinical models, the bisphosphonates have also been shown to influence macrophages, gamma delta T cells, osteoblasts, and tumor cells.

- In addition to their effects on osteoclast inhibition, bisphosphonates may also have antitumor and/or antiangiogenic effects, but this is a controversial area.
Bisphosphonates Types

- The nitrogen containing bisphosphonates are more potent osteoclast inhibitors.
- Non-nitrogen containing bisphosphonates,
  - Etidronate
  - Clodronate
  - Tiludronate
- Nitrogen containing bisphosphonates
  - Pamidronate
  - Alendronate
  - Ibandronate
  - Risendronate
  - Zoledronic Acid
Pamidronate in Multiple Myeloma

- **Study Methods**
  - Patients with stage III multiple myeloma and at least one lytic lesion received
    - placebo
    - pamidronate (90 mg) as a four-hour intravenous infusion given every four weeks for nine cycles in addition to antimyeloma therapy.
  - The patients were stratified according to whether they were receiving first-line (stratum 1) or second-line (stratum 2) antimyeloma chemotherapy at entry into the study.

- **Events**
  - Pathologic fracture
  - Irradiation of or surgery on bone, and spinal cord compression
  - Hypercalcemia,
  - Performance status
  - Quality of life
  - **Bone pain** were assessed monthly.
RESULTS

Among 392 treated patients, the efficacy of treatment was evaluated in
- 196 who received pamidronate
- 181 who received placebo.

The proportion of patients who had any skeletal events was significantly lower in the pamidronate group (24 percent) than in the placebo group (41 percent, P<0.001).

The patients who received pamidronate had significant decreases in bone pain in both strata and no deterioration in performance status and quality of life
Zoledronic Acid in Multiple Myleoma and Breast cancer

Goal
- To evaluate the dose–response relation for zoledronic acid, a new generation high potency bisphosphonate, given as a 5-minute infusion in patients with malignant osteolytic disease.

Methods
- 280 patients with osteolytic lesions due to metastatic breast carcinoma or multiple myeloma were randomized to double-blind treatment with
  - either 0.4, 2.0, or 4.0 mg of zoledronic acid or
  - 90 mg pamidronate.

Endpoints.
- The primary efficacy endpoint was the proportion of patients receiving radiation to bone.
- Other skeletal-related events,
- bone mineral density (BMD)
- Eastern Cooperative Oncology Group performance status,
- pain scores
Zoledron Acid

- RESULTS

- Zoledronic acid at doses of 2.0 and 4.0 mg and pamidronate at a dose of 90 mg each significantly reduced the need for radiation therapy to bone ($P < 0.05$) in contrast with 0.4 mg zoledronic acid, which did not.

- Skeletal-related events of any kind, pathologic fractures, and hypercalcemia also occurred less frequently in patients treated with 2.0 or 4.0 mg zoledronic acid or pamidronate than with 0.4 mg zoledronic acid.
Patients in the 0.4-mg zoledronic acid group and the pamidronate group had smaller mean decreases in pain score than patients in the two higher dose zoledronic acid groups.

End-of-study mean pain scores, similar for the 2.0- and 4.0-mg zoledronic acid groups and pamidronate group and higher for the 0.4-mg zoledronic acid group.

Among the 232 patients with pain at study entry, a decrease in pain score was reported by a greater proportion of patients in the 4.0-mg zoledronic acid group (67%) than in the 0.4-mg and 2.0-mg zoledronic acid groups and the pamidronate group (51%, 48%, and 50%, respectively, not statistically significant).

<table>
<thead>
<tr>
<th>Time point</th>
<th>Zoledronic acid</th>
<th>Pamidronate (90 mg; n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.4 mg (n = 68)</td>
<td>2.0 mg (n = 72)</td>
</tr>
<tr>
<td>Mean</td>
<td>3.8</td>
<td>3.4</td>
</tr>
<tr>
<td>SD</td>
<td>2.70</td>
<td>2.51</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Zoledronic Acid in Prostate Cancer

- Use of Zoledronic Acid in men with bone metastases from prostate cancer

- Clinical trial 643 men with bone metastases that were progressing while on Androgen deprivation therapy.

- Men were randomly assigned to
  - One of two doses of zoledronic acid (4 mg or 8 mg) or
  - Placebo, each given every three weeks.
  - The 8 mg dose of zoledronic acid was reduced to 4 mg early in the trial because of excessive renal toxicity.
Zoledronic Acid

- **Results**
  - At an average follow-up of 24 months, there was a significant reduction in the frequency of SREs in men receiving
    - Zoledronic Acid 38%
    - Placebo 57%
  
  - Median time to develop an SRE was significantly longer with
    - Zoledronic acid 488 days
    - Placebo 321 days
  
  - Pain and analgesic scores were significantly higher in men who received placebo than in those who received zoledronic acid,
  
  - There were no differences in disease progression, performance status, or quality-of-life scores among the groups.
Zoledronic Acid in Prostate Cancer

- BACKGROUND: Zoledronic acid
  - Reduces skeletal-related events associated with prostate cancer
  - Long-term efficacy in pain outcomes. Findings of treatment group differences in pain early in treatment are less reliable.

- METHODS
  - Zoledronic acid 4 mg (n = 214) versus placebo (n = 208),
  - Brief Pain Inventory to assess pain at baseline, 3 weeks, 6 weeks and every 6 weeks thereafter for a total of 60 weeks.
  - End Point Clinically meaningful reduction in pain.
Zoledronic Acid

RESULTS

- 67 of 214 patients (35.5%) receiving zoledronic acid and 62 of 208 patients (29.8%) receiving placebo completed the 60-week visit (P = 0.22).

- Patients receiving zoledronic acid reported more favorable, clinically meaningful changes in pain scores. Overall,
  - Patients receiving zoledronic acid had a 33% chance of a favorable response,
  - Patients on Placebo 25% chance of a favourable response (P = 0.04; 95% CI 0.5% to 15.6%).

- CONCLUSIONS: Zoledronic acid was more likely than placebo to be associated with clinically meaningful reductions in pain. Thus, zoledronic acid may help to avert the pain experienced by patients with progressing metastatic disease secondary to prostate cancer.
Zoledronic Acid

- Pr(Z>>P), proportion favoring zoledronic acid 4 mg
- Pr(P>>Z), proportion favoring placebo

$P = .036$
Zoledronic Acid in Prostate Cancer

- METHODS: A multi-centered observational study evaluated the efficacy of zoledronic acid in patients with prostate cancer and bone metastasis for:
  - improving pain and mobility,
  - preventing skeletal-related events (SRE) (fracture, spinal compression, pain-relieving radiotherapy),

- Patients (n = 218) with prostate cancer and bone metastasis undergoing oncologic therapy received zoledronic acid (4 mg iv/month) for 6 months.

- Parameters evaluated
  - 1) pain and movement after 2 consecutive doses
  - 2) quality of life
  - 3) SRE incidence and time-to-appearance.
Zoledronic Acid

RESULTS:
- A total of 170 that matched all the inclusion criteria (78%) out of 218 were evaluable for efficacy.
- There was a measurable statistically significant reduction in pain at rest and on movement as well as an improvement in the quality of life compared with baseline.
- As assessed on the VAS the at-rest scores decreased from 3.7 (SD 2.5) to 2.7 (SD 2.3) and reached 2.3 points (SD 2.3) at the third evaluation.
- The at-rest pain was maintained close to this score over the subsequent months.
- Differences between baseline score and the remaining months of follow-up were statistically significant ($p < 0.0001$).
- Best results were obtained with early treatment. Overall incidence of bone events was 11.2%.
- 212 patients were evaluable for safety, 16% suffered adverse events and 66% expressed satisfaction with the treatment.

DISCUSSION:
- Zoledronic acid is effective for
  - reducing pain,
  - improving mobility,
  - increasing the quality of life in patients with prostate cancer with bone metastasis.
- Its easy administration and is well tolerated.
Pamidronate in Breast Cancer

- Methods
- Patients with breast cancer with bone metastases receiving cytotoxic chemotherapy
  - 180 patients Pamidronate 90 mg every 4 weeks,
  - 197 patients on placebo
- Pain and analgesic consumption, performance status (ECOG), and quality of life (Spitzer index) over 12 months
- The pamidronate group showed striking pain relief, as opposed to increasing pain intensity in the placebo group.
- Significant improvement was observed for analgesic consumption and performance status.
- Quality of life deteriorated in both groups, with no significant difference.
- Measured pain intensity increased in both groups, but significantly more so in the placebo group than in the pamidronate group.
Fig. Long-term effect of pamidronate on pain score in patients with breast cancer
In a second study with a similar design, except that patients were receiving hormonal therapy rather than chemotherapy,
- 182 women were treated with pamidronate 90 mg every 4 weeks and
- 189 received placebo.

Findings were similar. Bone pain decreased significantly in the bisphosphonate group ($P=0.002$) while increasing continuously in the placebo group. At 24 months, pain intensity had increased in both study arms but significantly less so in the pamidronate group ($P=0.007$). ECOG performance status and quality of life deteriorated in both groups, with no significant difference between them.

Both studies reviewed jointly in a follow-up study after treatment for 24 months (pamidronate 90 mg, $n=367$; placebo, $n=387$).

The results of this long-term study again showed no fundamental difference from the original trials.
- Pain intensity and analgesic consumption increased throughout the study period but significantly less so in the pamidronate group ($P<0.001$).
- Bone pain was present in 80% of patients at baseline and increased over the 2-year study duration in 40% of pamidronate-treated patients compared with 52% of placebo patients ($P=0.003$). QOL and ECOG status deteriorated in both groups, with no significant differences between treatments.
Zoledronic Acid in Metastatic Breast Cancer.

**Methods**
- Large Sample Size n=1130
- 1st study to compare different bisphosphonates in this case pamidronate 90 mg rather than vs just placebo alone in improving symptoms in patients with breast cancer.
- The measurement instruments for the secondary study endpoints were the Brief Pain Inventory (BPI) scores from 0 to 10, an analgesic score, and ECOG status.

**Results**
- Sustained and similar decline in pain intensity in both groups.
- Analgesic consumption scores showed no statistically significant changes.
- ECOG status deteriorated to a similar extent in both groups.
- Interestingly, the extended follow-up showed zoledronic acid to be superior to pamidronate in the reduced requirement for radiotherapy and surgery.
Zoledronic Acid

Fig. Long-term effect of zoledronic acid vs pamidronate in patients with breast cancer or multiple myeloma
Zoledronic Acid in Metastatic Breast Cancer.

- Japanese placebo-controlled study.

- 2 arms
  - Placebo
  - Zoledronic Acid 4mg

- Patients were followed for 52 weeks.

- Pain was measured by BPI score and analgesic consumption on a scale from 0 (no analgesics) to 4 (opiates).

- Impressive and sustained pain relief was shown with 4 mg zoledronic acid, whereas pain intensity continued to increase significantly in the placebo group ($P<0.05$).

- As in other previous studies, no significant difference was found in analgesic consumption between the two groups.
Zoledronic Acid

Fig. Long-term effect of zoledronic acid vs placebo in patients with breast cancer

*P<0.05 vs baseline
Zoledronic Acid as second line treatment

- PURPOSE: This study evaluated whether additional palliative benefits could be derived from the second-line use of the more potent bisphosphonate zoledronic acid in metastatic breast cancer patients despite first-line therapy with either pamidronate or clodronate.

- PATIENTS AND METHODS:
  - Prospective study
  - Pamidronate was the most commonly used agent with 25 (80.6%) of 31 patients having received this agent as first-line therapy while six patients were receiving oral clodronate.
  - Median duration of prior bisphosphonate therapy was 22 months

- End points
  - Pain,
  - Quality of life,
  - Markers of bone turnover

- Patients received monthly zoledronic acid (4mg) for 3 months.
- Study evaluations were made weekly during the first month and again at week 8.
- No changes in chemotherapy or endocrine therapy were allowed in the month before or after commencing study treatment.
Zoledronic Acid as second line treatment

- **RESULTS:**
  - 31 women completed this study.

  - By week 8, patients had experienced significant improvements in pain control ($P < .001$).

  - There was a downward trend in urinary NTX levels over the same time period ($P = .008$).

  - Overall, there was a trend towards a positive correlation between improvement in pain control and reduction in week one urinary NTX relative to baseline.

- **CONCLUSION:** Patients with either progressive bone metastases or SREs while on clodronate or pamidronate can have relevant palliative benefits with a switch to the more potent bisphosphonate zoledronic acid.
Zoledronic Acid as second line treatment

**Fig.** The impact of zoledronic acid on the average pain score
Ibadronate

PURPOSE: Investigate the effects of short-term intensive treatment with intravenous (i.v.) ibandronate on opioid-resistant bone pain in patients with skeletal metastases.

PATIENTS AND METHODS:

18 patients with advanced tumors and metastatic bone disease received 4 mg of ibandronate administered i.v. (2-hour infusion) for 4 consecutive days (16-mg total dose).

Baseline opioid analgesic use was equivalent to 400 mg/d of morphine.

Patients were assessed for 6 weeks or until death.

Changes from baseline were determined for

- Bone pain,
- Opioid consumption,
- Patient functioning,
- QOL,
- Performance status,
- Biochemical markers of calcium metabolism and bone turnover.

Assessments of key efficacy variables were made on days 0, 7, 21, and 42 of the study period, or until death (if before day 42).

Bone pain was assessed using a visual analog scale from 0 (no pain) to 10 (maximum pain).
RESULTS:

Short-term, intensive ibandronate treatment significantly reduced bone pain scores within 7 days (P<.001).

Pain reductions were sustained over the study period.

Ibandronate significantly improved
- QOL,
- Patient functioning,
- Performance status (P<.05).

CONCLUSION: Nonstandard, intensive treatment with i.v. ibandronate seems to have a marked analgesic effect in patients with opioid-resistant bone pain from metastatic bone disease.

This study carries little statistical weight given the very small sample size, but the promising results in achieving rapid pain relief using high “loading-dose” ibandronate. Further studies are warranted.
Fig. Mean visual analog scale (VAS) bone pain score during study period (P values vs baseline). (*), $P < .05$; (**) $P < .001$; (***) $P < .0001$. SD, standard deviation.
Ibadronate

- 53 patients with urologic cancer and acute, moderate-to-severe bone pain.
- Treated with 6 mg ibandronate on 3 consecutive days followed by standard-dose ibandronate 6 mg every 3–4 weeks.
- Pain was assessed by visual analog score on a scale from 0 to 10.
- Maximum pain relief was achieved by day 3 and maintained for up to 20 weeks, with 80% of patients having at least a 3-point decrease and 25% becoming totally pain-free.
- This rapid pain relief was also accompanied by a marked improvement in patient functioning and mobility.
Ibandronate

- Preplanned pooled analysis of data from the two oral trials, ibandronate 50 mg PO in comparison to placebo.
- Pain relief and quality of life were looked at secondary end points.
- Significant pain relief was shown after 3 months in patients treated with oral ibandronate compared with placebo ($P=0.001$).
- Over the entire study period (96 weeks), pain intensity remained below baseline with ibandronate while increasing continuously with placebo.
- Analgesic consumption increased in both groups but significantly less so in the ibandronate group ($P=0.019$).
- Quality of life also decreased in both groups, the deterioration was significantly less with ibandronate ($P<0.05$).
- As in many other previous studies, reduced requirement for radiotherapy represented the largest single improvement in skeletal complications.
Ibadronate

Fig. Long-term effect of oral ibandronate on pain score in patients with breast cancer
Ibandronate

Fig. Long-term effect of intravenous ibandronate on quality of life parameters in patients with breast cancer
Clinical trial data on bisphosphonates in lung cancer and other solid tumors are more limited than for multiple myeloma, breast, and prostate cancer.

In a placebo-controlled randomized trial of 773 patients with skeletal metastases from cancers other than breast and prostate including non small cell and small cell lung, renal cell, thyroid, and head and neck cancers,

Patients who were randomly assigned to Zoledronic Acid had a significant reduction in the number of SREs (38 versus 47 percent) and a significantly longer time to the first event (230 versus 163 days). These benefits persisted with prolonged treatment and follow-up (approximately 21 months).
Summary

- Bisphosphonates have been shown to decrease bone pain, both short and long term.
- They are not recommended as substitutes for analgesics, radiotherapy, or surgery.
- Only a few studies have demonstrated significant improvement in quality of life, although this is always markedly affected by pain reduction.
- Analysis of the publications available to date has not revealed any great differences between individual bisphosphonates given at standard doses, but objective assessment is complicated by the differences in study design, measurement methods, and statistical analyses.
- In general more potent and IV formulations of bisphosphonates are considered more efficacious.
- It is recommended that bisphosphonates should be introduced at an early stage when bone metastases are diagnosed and not only when pain has become unbearable and skeletal complications are imminent.
Bibliography


- Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Rosen LS; Gordon D; Tchekmedyian NS; Yanagihara R; Hirsh V; Krzakowski M; Pawlicki M; De Souza P; Zheng M; Urbanowitz G; Reitsma D; Seaman J Cancer 2004 Jun 15;100(12):2613-21.


- Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. Clemons MJ; Dranitsaris G; Ooi WS; Yogendran G; Sukovic T; Wong BY; Verma S; Pritchard KI; Trudeau M; Cole DE J Clin Oncol. 2006 Oct 20;24(30):4895-900. Epub 2006 Sep 25.

- Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. Berenson J; Lichtenstein A; Porter L; Dimopoulos MA; Bordoni R; George S; Lipton A; Keller A; Ballester O; Kovacs MJ; Blacklock HA; Bell R; Simeone J; Reitsma D; Heffernan M; Seaman J; Knight RD N Engl J Med 1996 Feb 22;334(8):488-93.

- Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Berenson J; Rosen LS; Howell A; Porter L; Coleman RE; Morley W; Dreicer R; Kuross SA; Lipton A; Seaman JJ Cancer 2001 Apr 1;91(7):1191-200.