Patient Guide

ASCO

Information for

People Living with Cancer

Bisphosphonates for Multiple Myeloma

Recommendations of the American Society of Clinical Oncology

Welcome

The American Society of Clinical Oncology (ASCO) includes over 19,000 medical professionals worldwide and is a respected authority on the practice of clinical oncology, the care of people with cancer. To help doctors give their patients the best possible care, ASCO asks its medical experts to review the latest research on issues in cancer care and develop recommendations called clinical practice guidelines.

To help patients understand their cancer care, ASCO has created this patient guide, based on the guidelines ASCO's experts have developed to help people with multiple myeloma.

As you read this guide, please keep in mind:

- Every person treated for cancer is different. These recommendations are not meant to replace your or your doctors' judgment. The final decisions you and your doctors make will be based on your individual circumstances.

- These recommendations do not apply to clinical trials (research studies). Many of the drugs here continue to be studied in clinical trials. If ASCO does not recommend a drug or practice, it is often because there is not enough information to provide such recommendations, not because they are useless or harmful.

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What is multiple myeloma?

Myeloma is a cancer of the plasma cells in the bone marrow. Plasma cells normally act as part of the body's immune system, producing antibodies that help the body fight infection. If these cells change (*mutate*) and grow unregulated by the processes that normally control cell division and cell death, they can form cancerous tumors called *plasmacytomas* or myeloma. Myeloma is most often called *multiple myeloma* because most people (90%) have cancer in many different sites in the bone marrow by the time it is discovered.

Multiple myeloma causes increasing damage to the bones and bone marrow. Normally, people have balanced levels of cells called *osteoclasts* and *osteoblasts* that work together to shape and maintain healthy bones. Osteoclasts destroy old bone, and osteoblasts help to build new bone in its place.

People with myeloma have abnormally high levels of osteoclasts. When osteoclasts break down and absorb old bone faster than new bone is formed, fractures (breaks), bone pain, osteoporosis (thinning of the bones), and *hypercalcemia* (high levels of calcium in the blood) can result.

What are bisphosphonates?

Bisphosphonates (pronounced *biss-FOSS-fuh-nates*) are drugs that work by inhibiting the activity of osteoclasts. In theory, when osteoclast activity is inhibited, people should experience less bone pain, fewer fractures, and slower loss of bone mass. Bisphosphonates are already used to treat hypercalcemia in people with cancer, Paget's disease of the bone, and osteoporosis in postmenopausal women.

There are currently seven bisphosphonate drugs. Of these, pamidronate and zoledronic acid have been approved by the U.S. Food and Drug Administration (FDA) for use in multiple myeloma.

- Etidronate
- Clodronate
- Tiludronate
- Pamidronate
- Alendronate
- Ibandronate
- Zoledronic acid

Since bisphosphonates are used to treat other bone diseases, they have also been studied to see if they help relieve symptoms in people with multiple myeloma. ASCO's panel of experts reviewed the available evidence on the use of bisphosphonates in multiple myeloma. The goal of their recommendations is to present all the available evidence and to help health-care providers and their patients make informed decisions about treatment.

About the Expert Panel

ASCO's panel of experts met twice to develop this guideline. The members included medical, surgical, and radiation oncologists, health services researchers, statisticians, and pharmacists. A patient receiving bisphosphonates for multiple myeloma was also on the panel.

As they evaluated research, they considered studies that measured the effectiveness of bisphosphonates in different ways:

- Number of bone fractures per year (also called skeletal related events or SREs)
- Time to first bone fracture after beginning bisphosphonate treatment
- Number of bone fractures that needed treatment with radiation therapy
- If patients who take bisphosphonates live longer than those who don't
- How bisphosphonates are given (by mouth or intravenously)
- If patients who take bisphosphonates have less pain than those who don't
- If patients function better overall on bisphosphonates than not (performance status)

The panel worked together using the evidence and their own expertise, and formed their opinions by *consensus* (agreement from everyone in the group).

What are the recommendations?

The recommendations of ASCO's panel are listed below in their original form. In **bold** is a brief description of each guideline.

1. *Lytic disease on plain radiographs:* For multiple myeloma patients who have on plain radiograph(s), lytic destruction of bone, intravenous pamidronate 90 mg delivered over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended.

For people with multiple myeloma who have bone loss or fractures visible on an x-ray, intravenous pamidronate or zoledronic acid may be recommended.

2. *Monitoring:* In patients with pre-existing renal disease and a serum creatinine < 265 umol/L or < 3.0 mg/dL, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates in patients with worse function has been minimally assessed.

   Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided.

   The panel recommends intermittent evaluation (every 3-6 months, via urine analysis) of all patients receiving chronic pamidronate or zoledronic acid therapy for the presence of albuminuria and azotemia. In patients experiencing unexplained albuminuria (defined as > 500 mg/24 hours of urinary albumin) or azotemia (defined as an increase of ≥ 0.5 mg/dL in serum creatinine or an absolute value of > 1.4 mg/dL among patients with normal baseline serum creatinine levels), discontinuation of the drug is warranted until the renal problems are resolved. These patients should be

reassessed every 3-4 weeks (with a 24-hour urine collection for total protein and urine protein electrophoresis) and pamidronate re-instituted over a longer infusion time (≥ 2 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline.

People who have kidney disease and whose blood tests show high creatinine levels (indicating kidney damage) before beginning bisphosphonate treatment may take bisphosphonates as recommended.

Each treatment of pamidronate should be at least two hours. Each treatment of zoledronic acid should be at least 15 minutes.

People taking bisphosphonates should be monitored regularly to check for albuminuria (protein in the urine) and azotemia (high levels of nitrogen in the blood), tests that may indicate the drugs are causing kidney damage. If either is detected, bisphosphonate use should stop until the problems are identified and resolved. Side effects of bisphosphonates can include flu-like symptoms, anemia, or joint and muscle pain.

3. *Duration of therapy:* The panel suggests that, once initiated, intravenous pamidronate or zoledronic acid be continued until there is evidence of a substantial decline in a patient's general performance status. The panel stresses that clinical judgment must guide at what point the potential palliative benefits of pamidronate or zoledronic acid are less than the inconvenience of receiving this intravenously administered drug. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.

Since the best length of treatment has not been established, patients taking bisphosphonates may take them until the inconvenience or cost is greater than any other benefits the

drugs provide. Patients and doctors should decide together how long to continue bisphosphonate treatment.

4. *Myeloma patients with osteopenia based on normal plain radiograph or bone mineral density measurements:* It is reasonable to start intravenous bisphosphonates in multiple myeloma with osteopenia but no radiographic evidence of lytic bone disease. Note: patients with non-lytic lesions have been included in selected trials but have not been 1) the primary focus of the trial and 2) never of sufficient number to be separately analyzed.

Patients with lowered bone density or bone mass may take bisphosphonates, even if bone lesions are not yet visible on an x-ray.

5. *Patients with solitary plasmacytoma, or smoldering or indolent myeloma without documented lytic bone disease:* Starting bisphosphonates for patients with solitary plasmacytoma or smoldering or indolent myeloma is not suggested.

Most people with myeloma have more than one tumor, so it is called multiple myeloma. People with one myeloma tumor, or who have other types of myeloma, may be advised not to begin bisphosphonate treatment. There has not been enough research to determine if bisphosphonate use would be helpful.

6. *Patients with monoclonal gammopathy of undetermined significance (MGUS):* Starting bisphosphonates for patients with monoclonal gammopathy of undetermined significance (MGUS) is not suggested.

Patients with MGUS (abnormal protein in the blood that may lead to myeloma) should not take bisphosphonate treatment. There has not been enough research to determine if bisphosphonate use would be helpful.

7. *Biochemical markers:* The use of the biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care.

For women with osteoporosis or breast cancer, bisphosphonate treatment is sometimes given if blood or urine tests show evidence of bone loss or weakness. These methods are not recommended for people with multiple myeloma since they have not yet been adequately studied.

8. *Pain control for bone involvement:* Intravenous pamidronate or zoledronic acid is recommended for patients with pain due to osteolytic disease and as an adjunctive treatment for patients receiving radiation therapy, analgesics or surgical intervention to stabilize fractures or impending fractures.

Bisphosphonates may be useful for preventing pain and progression of bone disease. For people who are already experiencing pain from bone lesions, bisphosphonates may help when given along with standard methods to relieve pain: radiation therapy, pain medication, or surgery for bone fractures.

Areas for further research

The panel recommended that more research on the following will help to further determine the best use of bisphosphonates to help people with multiple myeloma:

- When to start and stop treatment
- How bisphosphonates should be combined with other treatments for bone disease
- How bisphosphonates should be used in multiple myeloma patients who do not have bone involvement visible on x-rays
- If bone fractures or involvement that do not cause symptoms should be treated the same as those that do
- How the benefits of bisphosphonates compare to the costs

Where can I get more information?

The original guidelines were published in ASCO's *Journal of Clinical Oncology* (*JCO* Sep 1 2002: 3719-3736). For a copy of the original guidelines, visit www.asco.org or call 703-299-0150.

For more information about cancer, visit People Living With Cancer at www.plwc.org, ASCO's website for patients, families, and the public.

For more information about bisphosphonates, patients should speak directly with their doctor.

Resources

International Myeloma Foundation
12650 Riverside Drive
Suite 206
North Hollywood, CA 91607
800-452-2873
www.myeloma.org

Multiple Myeloma Research Foundation
3 Forest Street
New Canaan, CT 06840
203-972-1250
www.multiplemyeloma.org

The Leukemia and Lymphoma Society
1311 Mamaroneck Avenue
White Plains, NY 10605
800-955-4LSA (4572)
914-949-5213
www.leukemia-lymphoma.org

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THE ASCO FOUNDATION

The American Society of Clinical Oncology (ASCO) is the world's leading professional society representing medical professionals of all specialties who treat people with cancer. ASCO's more than 19,000 members from the United States and abroad set the standard for patient care worldwide and lead the fight for more effective cancer treatments, increased funding for clinical and translational research, and, ultimately, cures for the many different cancers that strike 1.3 million Americans every year. ASCO publishes the semi-monthly *Journal of Clinical Oncology (JCO)*, the foremost peer-reviewed journal focusing on clinical cancer research, and produces the award-winning website People Living With Cancer (www.plwc.org), which provides oncologist-approved cancer information to help patients and families make informed health-care decisions.

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

1900 Duke Street, Suite 200, Alexandria, VA 22314
Phone 703-299-0150 Fax 703-299-1044
Toll Free 888-651-3038
www.asco.org www.plwc.org

February 2003