

MYELOMA BONE DISEASE CURRENT AND FUTURE TREATMENT

**A PUBLICATION OF
THE BONE AND CANCER FOUNDATION**



What Is Multiple Myeloma?

Multiple Myeloma is a cancer that results from a malignant change in a particular type of white blood cell which is found in the bone marrow. This cell is called a plasma cell and it normally helps fight infections.

Incidence in the U.S.

Multiple Myeloma is the most common cancer to involve bone, and it is the second most common cancer of the blood cells.

- Approximately 60,000 people have myeloma in the U.S.
- There are 16,000 new cases per year.
- And, it accounts for an estimated 11,000 deaths in the U.S.

Signs, Symptoms and Complications

Bone disease is a hallmark of multiple myeloma.

- The bone lesions are purely destructive in nature. Because of this, up to 60% of patients develop a fracture over the course of their disease.
- What is important to note is that myeloma bone disease differs from the bone metastases caused by other tumors.
 - Though both myeloma and other tumor bone metastases cause increased bone destruction, in myeloma bone repair does not take place.
 - Because of the severe bone destruction, patients can experience:
 - ♦ bone pain
 - ♦ fractures
 - ♦ too much calcium in the blood (hypercalcemia)
 - ♦ compression of the spinal cord (spinal cord compression syndromes).
 - These complications can be devastating for patients. They can have a major impact on the overall quality of life. And they can have an impact on expected survival.

How Myeloma Affects the Way the Body Works

What We Know

Bone Destruction in Myeloma Bone Disease:

What Happens in Normal Bone

- Normal bone constantly undergoes remodeling. This happens because there are bone cells (osteoclasts) that break down or remove bone and other bone cells (osteoblasts) that make and deposit new bone, at sites of previous bone removal.
- Hormones and other substances regulate the way these cells are formed and the way they work.

What Happens in Myeloma

- In myeloma, many different things interact to increase the process of bone destruction. These include:
 - the myeloma cells themselves
 - local cells in the bone marrow and
 - immune cells present in the marrow.
- Furthermore, growth factors released from the process of bone destruction also increase the growth of myeloma cells. This creates a vicious cycle:
 - Growth factors are released, as bone is destroyed.
 - This leads to the growth of myeloma cells.
 - The increased number of myeloma cells then leads to more bone destruction.

What We Are Learning

Bone Destruction in Myeloma Bone Disease

In addition to what we already know, recent studies have shown that there are several other substances that seem to play a role in the process of bone destruction and resorption. These substances which are produced by myeloma cells in patients include:

- the receptor activator NF- κ B (RANKL)
- macrophage inflammatory peptide 1-alpha (MIP-1a)

- Interleukin 3 (IL-3)
- Interleukin 6 (IL-6)

Problems with Bone Building in Myeloma Bone Disease:

Recent studies have shown that the bone that is destroyed is not being replaced by new bone.

- Multiple myeloma patients with bone disease have low levels of the substances that let us know that bone is being formed.
 - Bone scans cannot be reliably used to tell us the extent of MM bone disease. This is because bone scans reflect formation of new bone, but not bone destruction. So, bone scans underestimate the extent of the disease.

How We Can Apply What We are Learning

Targeting Bone Disease - Current Therapies and Future Direction.

Studies in the last few years have provided a better understanding of the causes of myeloma bone disease. In addition, these studies have identified several potential therapies for treating multiple myeloma bone disease. Forty-five percent of patients with myeloma suffer a fracture within the first year of diagnosis, and 65% will have a fracture over the course of their disease.

Treatment with bisphosphonates

- Therapy with intravenous bisphosphonates drugs (pamidronate, ibandronate, zoledronic acid) has become the cornerstone therapy for multiple myeloma bone disease, as well as for other cancer-related bone metastases. These drugs work by preventing the breakdown of bone.
- They prevent the breakdown of bone by killing or inhibiting formation of the normal bone removing cells (osteoclasts). In doing so, intravenous bisphosphonates have reduced the number of fractures, cases of hypercalcemia, surgery to bone and radiation treatment to bone by 50% over the first 9 months of treatment.
- Comparable results were obtained with all of the intravenous bisphosphonates if given on a monthly schedule.

Some side effects of bisphosphonate include kidney failure and protein in the urine.

- ♦ Osteonecrosis of the jaw (or ONJ) appears to occur in 4-6% of patients with myeloma treated with intravenous bisphosphonates.
- ♦ ONJ may increase with the use of more potent bisphosphonates and prolonged use of these drugs.
- ♦ However, so far, no studies have shown how this happens or if therapy with bisphosphonates clearly causes ONJ. **See the Bone and Cancer Foundation publication “Osteonecrosis of the Jaw: Information for Cancer Patients”**
- Many questions persist about the most appropriate length of treatment with bisphosphonates after the first year of therapy.
- There are ongoing clinical trials to determine duration of treatment with zoledronic acid in patients with myeloma.

[RANKLigand \(RANKL\) as a unique target for drug therapy of MM bone disease.](#)

- RANKL, a substance that is produced in the bone marrow, increases the number of bone destroying cells (osteoclasts). RANKL seems to play a role in the process of bone destruction and absorption. The drug Denosumab which blocks the effects of RANKL has been developed.
- Denosumab is currently being studied in clinical trials for myeloma and other diseases associated with bone destruction.

[Additional drug targets for treating myeloma](#)

Recent discoveries on the cause of myeloma bone disease have identified several additional potential drugs.

- **Bortezomib (Velcade®):** Bortezomib (Velcade®), a drug used to treat myeloma, appears to have excellent effects not limited to myeloma but also in myeloma bone disease.
 - Several studies have reported that patients on bortezomib have increased markers of bone formation in their blood. Blood tests also show that patients on this drug are forming more bone.

- However, it is unclear whether this new bone formation occurs in bones involved with myeloma or bones that are not involved with disease.
- Unfortunately, healing of previous bone lesions has not been observed consistently with Bortezomib therapy.
- **Anabolic (bone building) drugs:** Bone building drugs such as parathyroid hormone (PTH) may also be potential treatments for myeloma bone disease. However, there are concerns about PTH treatment because stimulating bone formation in myeloma bone lesions could also increase production of substances that increase myeloma tumor growth.
 - Side effects of PTH therapy, such as kidney stones, too much calcium in the blood (hypercalcemia), and problems with kidney function, could also pose obstacles for treating myeloma patients with PTH therapy.

Summary

As we learn more, there may be hope for new ways of treating myeloma bone disease.

- Recent advances in the understanding of what happens in multiple myeloma bone disease have identified several possible new drugs to treat myeloma bone disease.
- These new drugs should be entering clinical trials in the near future. We may then be able to use what we learn from these trials to help decrease the effects of this devastating complication of myeloma, extend survival of patients as well as improve their quality of life.

The mission of The Bone and Cancer Foundation is to:

- Provide information to cancer patients and family members on the causes and current treatment of cancer that involves the bone;
- Provide information and serve as a resource for physicians, nurses and other health professionals regarding the management of cancer that spreads to the bone.



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