Transcript Details
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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Preventing Skeletal-Related Events in Patients with Multiple Myeloma

Announcer:
Welcome to ReachMD.

This medical industry feature, focusing on "Preventing Skeletal-Related Events in Patients with Multiple Myeloma" is sponsored by Amgen. This program is intended for physicians.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
It's widely known that multiple myeloma puts patients at risk for bone complications, also known as skeletal-related events or SREs, which is defined as radiation to bone, pathologic fracture, surgery to bone, and spinal cord compression. This risk continues throughout the course of a patient's disease. On today's program, we'll explore the latest information around an available treatment option intended to reduce SREs in these patients.

This is ReachMD and I'm your host Dr. Jennifer Caudle, and joining me is Dr. James Berenson. He's Chief Executive Officer at Berenson Cancer Center, as well as Founder, President, Chief Executive Officer, and Medical and Scientific Director of the Institute for Myeloma and Bone Cancer Research in West Hollywood, California. Dr. Berenson, welcome to the program.

Dr. Berenson:
Thank you for having me.

Dr. Caudle:
To start us off Dr. Berenson, can you share the extent to which bone complications are associated with multiple myeloma?

Dr. Berenson:
Sure. Approximately 60% of multiple myeloma patients experience pathologic fractures over the course of their disease[1]. Most of these pathologic fractures occur in the spine and ribs[1]. We also know that in multiple myeloma, one fracture can lead to another. Patients with a prior bone complication are at least seven times more likely to experience a subsequent fracture[2]. But despite these risks, an ongoing challenge is that the majority of multiple myeloma patients still remain untreated with a bone-targeting agent or BTA at three months following their diagnosis and treatments often get initiated only after a bone complication has occurred[3]. That's why it's important to follow the NCCN guidelines, which recommends starting a BTA in patients receiving therapy for symptomatic multiple myeloma regardless of documented bone disease[4].

Dr. Caudle:
So, clearly given the scope of this issue, early detection of the underlying disease is a must. But how does multiple myeloma most commonly present and what clinical features do we need to keep in mind?

Dr. Berenson:
I'll walk through the current definition of active multiple myeloma since this incorporates its most common clinical features. We define multiple myeloma based on fulfilling two criteria [5]. The first is clonal bone marrow cells in greater than 10% or biopsy-proven boney or extramedullary plasmacytoma [5], and the second is any one or more myeloma-defining events, which group into two sets of features[5]. One set is called the CRAB features based on the acronym for the four criteria, which include[5]: hypercalcemia, defined as a serum

calcium greater than 11 mg/dL,[5] renal insufficiency with serum creatinine clearance less than 40 mL/min or a serum creatinine greater than 2 mg/dL[5].

Next is anemia, defined as a hemoglobin value more than 20 g/L below the lower limit of normal or less than 100 g/L[5]. And lastly, bone lesions, which is to say one or more osteolytic lesions seen on skeletal radiography, CT, or PET/CT.[5]

The other set of features are known by the acronym of SLiM and these include[5]: the presence of 60% or more clonal plasma cells on the bone marrow examination[5], a serum involved to uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved free light chain is at least 100 mg/L[5], and more than one focal lesion greater than 5 mm each detected on MRI, much in keeping with the CRAB feature, centered on bone lesions [5]. An important note here is that approximately 70% of patients at diagnosis present with bone lesions, which often lead to bone complications.[1,6]

Dr. Caudle:
Thanks for putting that into context for us, Dr. Berenson. Now let's dive deeper into what's thought to be going on at the molecular level. Can you take us through the mechanism behind lytic bone lesion development in multiple myeloma?

Dr. Berenson:
Yes. A key factor in the cycle of bone destruction is called RANK ligand, or RANKL, which can lead to excessive bone reabsorption and therefore represents an important therapeutic target to reduce the risk of bone complications[7,8]. Here's what we understand about this cycle: Excessive RANKL released by myeloma cells drives increased osteoclast activity [7,8]. This unbalanced activity causes bone lesions to develop and weaken bones by extension, which increases their risk of bone complications.[7,8]

Dr. Caudle:
Now, with this background in mind, let's examine the available treatment option in focus today: Uh, the bone-targeting agent, XGEVA®. First, let's first review some important safety information.

Announcer:
XGEVA® is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.

XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently. Additional important safety information will be provided later in this program.

Dr. Caudle:
So, Dr. Berenson, coming back to the mechanism of disease involving RANK ligand, where does XGEVA® factor in breaking the cycle of bone destruction?

Dr. Bereson:
XGEVA® is the first and only BTA that specifically blocks RANKL to prevent bone complications [9]. XGEVA® binds to and inhibits RANKL, which inhibits the formation function and survival of osteoclasts, leading to decreases in bone reabsorption[9]. So, this represents a unique mechanism of action with XGEVA® that helps to break the cycle of bone destruction[9].

Dr. Caudle:
For those of you who are just joining us, this is ReachMD. I'm Dr. Jennifer Caudle and today I'm speaking with Dr. James Berenson about preventing bone complications in patients with multiple myeloma, focusing on the treatment option of XGEVA®.

Dr. Caudle:
Now, what were some highlights within this study design in methodology that led to this evaluation for XGEVA®, specifically?

Dr. Berenson:
XGEVA® was studied over a four year period in the largest international trial ever conducted in multiple myeloma for the prevention of bone complications[9,10]. The study included over 1,700 newly diagnosed patients from a broad range of demographics and characteristics, including patients with ECOG levels 0, 1, or 2, autologous stem cell transplant or ASCT-intended or non-intended, those receiving doublet and triplet therapies across international staging system levels, and those with varying types of previous SREs[9,10]. It's

also important to note that the majority, approximately 73% of patients in the denosumab arm had normal renal function, defined as a creatinine clearance at or beyond 60 mL/min [11].

Dr. Caudle:
Now let's examine the evidence supporting this treatment's efficacy for preventing bone complications. What can you tell us about that?

Dr. Berenson:
Sure. It was found that XGEVA® provides nearly twenty-three months of prevention, meeting the primary endpoint of non-inferiority to zoledronic acid, or ZA, with 22.8 months median time to first on-study bone complication versus 24 months in the ZA arm.

Dr. Caudle:
And staying with that clinical trial, what was uncovered regarding XGEVA®'s safety and tolerability profiles?

Dr. Berenson:
The safety profile of XGEVA® in multiple myeloma was consistent with its known profile in solid tumors [9]. Rates of adverse reactions were similar in both XGEVA® and ZA groups [10,12], and in an ad hoc analysis, acute phase reactions were reported in fewer patients with XGEVA® than with ZA, though this finding wasn't powered for statistical significance[10,12,13]. The most common adverse reaction leading to discontinuation of XGEVA® was osteonecrosis of the jaw or ONJ.[9,12]. Rates of ONJ were 4.1% for XGEVA® and 2.8% for ZA[9,12]. A majority of the cases of ONJ in this study were either grade 1 or 2[10], and almost 60% of these patients had known risk factors, such as invasive dental procedures during the study period [9]. Fewer XGEVA® patients experienced renal AEs versus ZA patients[10] and it should be noted that patients with creatinine clearances less than 30 mL/min were excluded from the phase 3 study[9]. Also, the risk of hypocalcemia increases with decreasing renal function[9].

Dr. Caudle:
Now, let's stay on those last points for a moment because I understand that renal clearance is actually a point of distinction for this treatment option. What's the significance of that? And how does it impact dosing and administration?

Dr. Berenson:
Well, this brings out an important treatment distinction for XGEVA® in that XGEVA® is a monoclonal antibody and the only bone-targeting agent that isn't cleared by the kidneys[9,10]. This enables us to treat to prevent bone complications using a consistent dosing across patients[9,10]. Another important differentiator here is that XGEVA® is the first and only BTA that can be administered subcutaneously[9,13], which may compliment the route of administration of primary treatments with its convenient administration and keep patients out of the infusion chair just for their BTA[9].

Dr. Caudle:
And Dr. Berenson, before we close, I'd like to follow up on your comment about the subQ administration route. How does this factor into your BTA considerations?

Dr. Berenson:
80% of multiple myeloma patients today receive their primary treatment as either oral or subcutaneous administration[12], which is very different than what multiple myeloma looked like in the past. This makes the subQ route of administration for XGEVA® consistent with the evolving multiple myeloma treatment landscape[9,12]. And when I choose XGEVA® for these patients, they can avoid the IV infusion chair to get their BTA[9].

Dr. Caudle:
Well, those are great, practical take-aways for us to come away with as we close today's program. I'd like to thank my guest, Dr. Berenson for helping us better understand the role of XGEVA® in preventing bone complications in patients with multiple myeloma. Dr. Berenson, it was great speaking with you today.

Dr. Berenson:
Thank you for giving me the opportunity to talk about XGEVA®.

Dr. Jennifer Caudle:
I'm your host, Dr. Jennifer Caudle and before we go, let's take a moment to review some important safety information.

Hypocalcemia

- Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. XGEVA® can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Concomitant use of calcimimetics and other drugs that can lower calcium levels may worsen hypocalcemia risk and serum calcium should be closely monitored. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.
- An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

Hypersensitivity

- XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently.

Drug Products with Same Active Ingredient

- Patients receiving XGEVA® should not take Prolia® (denosumab).

Osteonecrosis of the Jaw

- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving XGEVA®, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with cancer, the incidence of ONJ was higher with longer duration of exposure.
- Patients with a history of tooth extraction, poor oral hygiene, or use of a dental appliance are at a greater risk to develop ONJ. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections.
- Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA® and periodically during XGEVA® therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA®. Consider temporarily interrupting XGEVA® therapy if an invasive dental procedure must be performed.
- Patients who are suspected of having or who develop ONJ while on XGEVA® should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture

- Atypical femoral fracture has been reported with XGEVA®. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.
- Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone (GCTB) and in Patients with Growing Skeletons

- Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in XGEVA®-treated patients with GCTB and in patients with growing skeletons within one year of treatment discontinuation. Monitor patients for

signs and symptoms of hypercalcemia after treatment discontinuation and treat appropriately.

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

- Multiple vertebral fractures (MVF) have been reported following discontinuation of treatment with denosumab. Patients at higher risk for MVF include those with risk factors for or a history of osteoporosis or prior fractures. When XGEVA® treatment is discontinued, evaluate the individual patient's risk for vertebral fractures.

Embryo-Fetal Toxicity

- XGEVA® can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA® is expected to result in adverse reproductive effects. Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of XGEVA®. Apprise the patient of the potential hazard to a fetus if XGEVA® is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA®.

Adverse Reactions

- The most common adverse reactions in patients receiving XGEVA® with bone metastasis from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation were osteonecrosis and hypocalcemia.

Announcer:
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