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Preventing Bone Complications in Breast Cancer Patients with Bone Metastases

Announcer
Welcome to ReachMD. This medical industry feature, titled “Preventing Bone Complications in Breast Cancer Patients with Bone Metastases” is sponsored by Amgen. This program is intended for physicians.

Here’s your host, Dr. John Russell.

Dr. Russell:
This is ReachMD, and I’m Dr. John Russell. Joining me to discuss bone complication prevention in breast cancer patients with bone metastases are Dr. Fadi Braiteh and Dr. Jacob Kettle.

Dr. Braiteh is a practicing medical oncologist and Director of the Translational Oncology Program, or TOP-Phase I, and the GI Malignancies Program for Comprehensive Cancer Centers of Nevada in Las Vegas, Nevada. Dr. Braiteh, thanks for being here today.

Dr. Braiteh:
Thank you for having me.

Dr. Russell:
And Dr. Kettle is an oncology clinical pharmacy manager at the Ellis Fischel Cancer Center at the University of Missouri Health Care in Columbia, Missouri. Dr. Kettle, welcome to the program

Dr. Kettle:
Thank you for having me.

Dr. Russell:
Starting with you, Dr. Braiteh, can you define bone complications also known as skeletal-related events or SRE’s, specifically in how they relate to breast cancer patients with bone metastases?

Dr. Braiteh:
Sure. So solid tumors, such as breast cancers with bone metastases, are stage four diseases. Unfortunately, for the most part, they are incurable and laced with potential problems, like bone complications, which are the four events shown in the slide here.

My goal as a medical oncologist is to try to protect my patients from the potential dreads of bone complications[1-3], also known as skeletal related events, which are [defined as] spinal cord compression, pathologic fracture, the need for radiation, and the need for surgery to bone.

For most breast cancer patients who’ve developed bone metastases, it's likely just a matter of time before they have a bone complication. And the risk for more increases once a patient has experienced a bone complication. In one study, after the first complication, almost 7 out of 10 patients had another one[4]. So, time really is of the essence.

Dr. Russell:
Turning to you Dr. Kettle, now that we know that there’s a risk of bone complications in breast cancer patients with bone metastases, why is prevention so important?

Dr. Kettle:
For these patients, the risk of bone complications with bone metastases is immediate and continues to increase over time.

In one study of 47,000 patients with solid tumors and bone metastases who never had a bone-targeting agent before, 25% of patients developed a bone complication within one month of diagnosis[5]. And then within 3 months, the number jumped to 33%[6], and as you might've expected, about 50% of patients experienced at least one bone complication within 2 years, and this was regardless of prior bone complication status[6]. It's important to note that the risk increases over time with treatment as well but it's even higher without treatment.

And as Dr. Braiteh had mentioned earlier, for our patients with bone mets, time is of the essence. Once they develop bone mets, SREs are a real risk. So, after the first one, we know there's an increased risk of having another skeletal-related event.[4] And as you can imagine, we want to do all we can to help patients reduce their risk of suffering a pathological fracture or a spinal cord compression. When patients experience SREs, they can be complicated and severe, carrying some morbidity along with them. So, we can try to prevent the bone complications from occurring by starting these patients on a bone-targeting agent.

Even though bone complications can be painful, bone mets themselves may or may not be painful, but as we will see, the risk still exists even without pain.

Dr. Russell:
And Dr. Braiteh, if we dig deeper into the use of BTAs to prevent SREs in breast cancer patients with metastases, would your treatment plan change based on a patient who shows to have one bone metastasis versus a patient who has many mets?

Dr. Braiteh:
Great question, and I want to make a very important point here is that even a single bone metastasis carries SRE risk in itself. Regardless of the number of mets or where they appear, whether they're in weight-bearing bones or non-weight-bearing bones, BTAs must be started immediately upon diagnosis.

I want to talk about pain as an indicator for the risk of bone complications. One study in men with bone mets from prostate cancer found that the risk of developing a bone complication was basically the same regardless of whether or not they had pain at baseline[7].

Now having a bone complication is another story. 86% of patients who experienced a bone complication also experienced pain in a different study[8]. So we know having a bone complication, like a pathologic fracture can be painful, but we should not use pain as a predictor of a patients risk for a bone complication.

We want to intervene with a BTA before they experience their first bone complication.

Dr. Russell:
So, Dr. Kettle, we know that bone-targeting agents are key in preventing SREs in our breast cancer patients with bone metastases, so let's zero in on a specific agent called XGEVA. But before we go further, can you review some important safety information with us?

Dr. Kettle:
Sure. XGEVA (denosumab) is indicated for the prevention of skeletal-related events in patients with multiple myeloma and patients with bone metastases from solid tumors[9].

XGEVA is contraindicated in patients with pre-existing hypocalcemia and clinically significant hypersensitivity to XGEVA[9]. XGEVA can cause severe symptomatic hypocalcemia, and fatal cases have been reported[9]. Osteonecrosis of the jaw and atypical femoral fracture have been reported[9]. Clinically significant hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone and patients with growing skeletons have been reported[9]. Multiple vertebral fractures following discontinuation of treatment have been reported[9]. XGEVA can cause fetal harm[9].

Dr. Russell:
Thank you for sharing that with us, Dr. Kettle. There will be additional important safety information provided later in this program.

So, Dr. Kettle, coming back to you, how does XGEVA work to break the vicious cycle of bone destruction, and how does it differ from zoledronic acid?

Dr. Kettle:
So, if we start by taking a look at how XGEVA works, XGEVA inhibits osteoclast formation, functions, and survival by binding to RANK ligand[9,10]. XGEVA prevents the maturation of osteoclast, which helps to decrease bone resorption and break the vicious cycle of bone destruction[9,10].

I'd also like to point out that XGEVA is a monoclonal antibody[9] and is not cleared by the kidneys[9,11-15]. This is very important to note because it means that there's no need to adjust, delay, or withhold treatment due to renal function. I should note that patients with CrCl < 30ml/min were excluded from the phase 3 study and the risk of hypocalcemia increases with decreasing renal function[9]. We've actually used zoledronic acid for decades to prevent complications from bone metastases, but with XGEVA, we have another option for breast cancer patients that have bone metastases. An option with demonstrated superiority in delaying time to first bone complications versus zoledronic acid. Here we have the results from the head to head study in breast cancer patients. As you can see, the median time to first bone complication was 26.4 months for ZA, but at 27 months, the study end, 60% of the subjects on XGEVA were still free from their first on study bone complication and in this integrated analysis of the three head-to-head pivotal trials for XGEVA vs. zoledronic acid, which included patients with bone mets from breast prostate, and a range of solid tumors, XGEVA delayed the time to first bone complication by 8.2 months longer than zoledronic acid[16]. And we should highlight that, in patients with breast cancer and bone metastases, XGEVA demonstrated superiority by reducing the risk of bone complications by 18%[9,17] vs zoledronic acid which could be meaningful to our patients.

So, we talked about XGEVA's superiority in delaying time to first bone complication in patients with bone mets from solid tumors. Being diagnosed with bone mets is a milestone, and when you hit a milestone like that, it forces you to look at all of your patients' treatments and make new decisions about what's the best therapies based on their treatment goals. If a patient has had a bone-targeting agent whether in an adjuvant setting or the neo-adjuvant setting and now is in the metastatic setting with bone metastases, we need to be vigilant to their treatment needs for skeletal-related event prevention. This is so important and cannot be missed, because when your breast cancer patient has bone mets, regardless of prior bone-targeting agent use in the adjuvant setting, XGEVA should be considered.

Dr. Russell:
For those just joining us, this is ReachMD.

I'm Dr. John Russell and today I'm speaking with Dr. Fadi Braiteh and Dr. Jacob Kettle about XGEVA and its role in preventing SREs in breast cancer patients with bone metastases.

Now Dr. Braiteh, if we continue our discussion about XGEVA, once the decision has been made to start XGEVA, what are some monitoring parameters that we should keep in mind?

Dr. Braiteh:
It's important to note that XGEVA can cause severe symptomatic hypocalcemia, so you'll need to check your patient's calcium levels, and if there's pre-existing hypocalcemia, correct that before starting XGEVA[9]. Patients on calcium lowering drugs and those with reduced renal function should be monitored more frequently[9].

Now the incidence of hypocalcemia does increase in patients without oral calcium and Vitamin D supplementation[18]. So, when you do initiate therapy with XGEVA, start a regimen of calcium and vitamin D supplementation. I typically recommend over-the-counter calcium and vitamin D product that includes at least 1000 mg of calcium and 400 international units of vitamin D. I suggest they take it twice a day while on the therapy. I also check calcium levels before each dose.

Dr. Russell:
And Dr. Kettle, are there any instances when you'd consider stopping XGEVA treatment?

Dr. Kettle:
So, for patients with bone mets, I typically keep the patient on XGEVA for the duration of their care but having said that, I do consider the risk of osteonecrosis of the jaw, since it increases with a longer duration of use[9]. But that doesn't lead to stopping XGEVA automatically, I look at the patient's situation and their specific benefit to risk ratio to determine the next steps. To help mitigate this risk, it's important that your patients discuss any invasive dental procedures they're planning and that they maintain good dental hygiene since about 80% of patients who developed osteonecrosis of the jaw had a history of tooth extraction, poor oral hygiene, or use of a dental appliance[9].

Dr. Russell:
Finally, Dr. Braiteh, what are some essential take-home messages about XGEVA that you'd like to reiterate for our listeners?

Dr. Braiteh:
First of all, we must remember that SREs are complicated and can be devastating, which is why we need to be vigilant and proactive in preventing them from the first time, if possible. So, when treating a breast cancer patient with bone mets, bone-targeting agents like

XGEVA can go a long way in helping them.

SREs, for our patients, often end up equating to an increased risk of subsequent SREs. And as we said previously, SREs are often painful. On that note, in a post hoc analysis of time to progression of bone pain by tumor type, the median time to moderate to severe pain was 9.7 months for patients taking XGEVA versus 5.8 months for patients taking zoledronic acid. That's a difference of 3.9 months[19-22]. I think we need to put ourselves in our patients' shoes and consider what having something like a pathologic fracture would mean for them.

Dr. Russell:
And how about you Dr. Kettle, would you like to share any closing remarks for our listeners?

Dr. Kettle:
Yes, I'd like to remind our listeners that it's extremely important to keep to the XGEVA dosing of once every 4 weeks[9].

Dosing per the approved label is going to give you the best chance of seeing the kind of results we saw in the phase 3 studies. Remember that an integrated analysis across the three pivotal trials in patients with bone mets from solid tumors found that XGEVA was superior at delaying the median time to first bone complication with 27.7 months for XGEVA vs 19.5 months for zoledronic acid, that's 8.2 months longer compared to zoledronic acid[16], so it's very important to stick with that interval.

Dr. Russell:
That's a great thing for us to keep in mind as we come to the end of our discussion.

I want to thank my guests for helping us better understand the importance of preventing bone complications in patients with breast cancer and bone metastases. Dr. Braiteh and Dr. Kettle, it was great speaking with you both today.

Dr. Braiteh:
Thank you for having me.

Dr. Kettle:
Thanks so much.

Dr. Russell:
I'm Dr. John Russell. And before we close, let's take a moment to review some important safety information.

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

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.

For multiple myeloma patients receiving XGEVA®, the most common adverse reactions were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache. The most common serious adverse reaction was pneumonia. The most common adverse reaction resulting in discontinuation of XGEVA® was osteonecrosis of the jaw.

Please see full Prescribing Information for XGEVA® available with this presentation.

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Announcer:
This program was sponsored by Amgen and Novartis. To revisit any part of this discussion, please visit ReachMD.com. This is ReachMD. Be Part of the Knowledge.