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Approaches to Utilizing Bone-targeting Therapies in mBC

Dr. Chalasani:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me today to talk about bone-targeting therapies in patients with metastatic breast cancer is Dr. Gabriel Hortobagyi. He's a Professor of Medicine in the Department of Breast Medical Oncology in the Division of Cancer Medicine at the University of Texas, MD Anderson Cancer Center in Houston.

Dr. Hortobagyi, thanks for being here today.

Dr. Hortobagyi:
Pleasure to join you today.

Dr. Chalasani:
To start with some background, can you tell us about bone metastases in patients with metastatic breast cancer, frequency on the biologies, and the incidence or the prevalence?

Dr. Hortobagyi:
Yes. So bone metastases are the most frequent site of metastatic spread for breast cancer, especially for the luminal subtypes, which are the most frequent types of breast cancer. And autopsy studies show that patients who develop metastatic breast cancer in about 75 percent of cases have bone metastases. And I believe the figure is even higher for the luminol subtypes. So this is a huge problem. It is estimated that worldwide about one and a half million women develop bone metastases from breast cancer. So it is a common public health issue. Bone metastases can cause a number of complications, or what is commonly called skeletal-related events, including pain, pathological fractures, spinal cord compression, and often require other interventions, such as radiation therapy, orthopedic correction of pathological fractures and of course, systemic therapies to address the source of their metastases. And bone is a very favorite source of growth factors for the metastatic cancer cells, and bone metastases create what we call a vicious cycle because bone metastatic cells, they release from the bone structure growth factors that enhance the growth, and similarly, the release of these growth factors of course, makes metastatic cells proliferate and spread further. It is thought that bone metastases start in metastatic niches within the bone marrow, and then it creates through activation of osteoclasts, lytic or lytic and mixed blastic metastases, which then result in the complications that we have mentioned.

Dr. Chalasani:
So how do patients typically present with bone metastases, and what kind of workup do you recommend for further evaluations when you're suspecting bone metastases?

Dr. Hortobagyi:
Patients who present with already known metastases of some other type, lung or local recurrence or some other site of metastases, obviously undergo a structured metastatic workup that includes a bone scan, CAT scans, or magnetic resonance imaging that will reveal existing bone metastases if they are there. In patients who do not have known bone metastases, our current guidelines do not recommend monitoring with the imaging, unless there are symptoms or other abnormalities that suggest that metastases might be an issue, in which case, the first line of imaging would be even today a bone scan. Although, magnetic resonance imaging is an even more sensitive approach to imaging for screening for bone metastases. So in someone who does not have symptoms, does not have known metastases, one would not actively seek for bone metastases but in someone who has a suspicion or who has known metastases elsewhere, then imaging would be the first line of screening.

Dr. Chalasani:

So you briefly touched about this earlier, but can we talk a little bit more about the skeletal-related events that we are concerned as a complication of bone metastases? I know you briefly alluded on the biology or how it can cause, but what are the most frequent skeletal-related events that the patients present with?

Dr. Hortobagyi:
Before the development of bone-targeting agents, the most frequent complication was pain, followed closely by the occurrence of pathological fractures. Pathological fractures obviously occur at the sites of metastases since a bone metastases weaken the bone strength by destroying bone structure, the trabecular pattern within bone, and especially in areas that are weight-bearing, such as the long bones, the femur, and the humerus, it is frequent to find pathological fractures. And common sites of bone metastases include the entire spine, especially the lumbar spine, and ribs, and in all of those areas, pathological fractures can occur. They can be quite disabling, and they create functional problems for patients. Less frequent manifestations of skeletal-related events include spinal cord compression, which is usually the consequence of a pathological fracture of the vertebra, which then expands, and with the addition of its soft tissue component, compresses the spinal cord or nerves that start from the spine and the spinal cord. So that's a less frequent manifestation of skeletal events. Another form of skeletal-related event, although we don't usually include it as a direct manifestation is hypercalcemia. Some 30 years ago, hypercalcemia used to be present in 15, 20 percent of patients with metastatic breast cancer. Today, it is much less common to a large extent because of the use of bone-specific or bone-targeting agents.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Gabriel Hortobagyi about bone metastasis in metastatic breast cancer patients.

So on that note, switching gears to treatment. Can you tell us about the bone targeting agents and their role as an adjunct or supportive treatments for the system management too?

Dr. Hortobagyi:
So bone metastases, or clinically relevant bone metastases, developed by osteoclasts, whose role is to resorb bone exceeding in their activity, the activity of osteoblasts, which function to build bone. So bone-targeted agents target osteoclasts and inhibits the bone resorptive activity of osteoclasts. And in the case of bisphosphonates, cause apoptosis of osteoclasts. In the case of RANK inhibitors, or RANK ligand inhibitors, it's a slightly different mechanism upstream from there. So the two most common types of bone-targeted agents are bisphosphonates on the one hand, and then there are the RANK ligand inhibitors. So the two most commonly utilized bisphosphonates in North America are pamidronate and zoledronic acid, also called Zoledronate. Both are administered intravenously about every three to four weeks, and they are well-tolerated agents that can be administered chronically for a fairly long period of time. They decrease the risk of skeletal-related events by about 30 percent. And in the case of zoledronic acid, which is slightly more potent than pamidronate, they can essentially double the time to first skeletal-related event compared to placebo. So they are fairly effective, although they are not universally effective. Denosumab, which is a monoclonal antibody against RANK ligand, is another well tolerated agent administered subcutaneously about once a month. It is also well tolerated, it is considered slightly more effective than the bisphosphonates, although that has not translated in the case of metastatic breast cancer to an effect on overall survival. So the slight improvement is in the delayed skeletal-related events and perhaps the delay in some other complications.

Dr. Chalasani:
So I'm going to ask you a few clinical questions we frequently come across as we are using the bone targeting agents. First, for example, if we have a patient who is on zoledronic acid and tolerating it well, but if they notice disease progression in the bones especially, do you recommend or is the data to switch bone-targeting agent for disease progression? And the second thing is if they were to have a skeletal-related event on one agent, is there any benefit in switching to the other?

Dr. Hortobagyi:
That is a very important question and an important question that we face in many other aspects of managing breast cancer, especially with these targeted agents. The answer is not completely clear. The accepted philosophy is that chronic suppression of osteoclast activity is important to maximize the benefit for patients with bone metastases. It is also not considered that progression during a bone-targeted agent is necessarily a manifestation of resistance to that agent. So it is not completely clear whether changing to a different agent would derive greater benefit or if it is simply by continuing suppression with whatever existing agent you're using is of similar benefit. I have done both depending on the circumstances. And I can tell you that after dealing with these agents for about 35 years, I don't know the right answer to this. Another important aspect for all of these agents is to consider the benefit-risk ratio of long-term administration versus the emergence of adverse events.

Dr. Chalasani:
When we are starting, or you recommend starting the bone targeting agents, is there any standard recommendation in terms of patient

needs to get dental clearance or evaluations? Because the guidelines are one thing and practical reality is another one for us in terms of the timeline. So I just wanted to get your opinion on, I mean, what the guidelines would suggest and what you do in practice.

Dr. Hortobagyi:
My approach to the utilization of these bone-targeted agents is to initiate their use as soon as I detect the presence of bone metastases. And in the absence of complications or adverse events, I continue with these agents. It used to be indefinitely, but that was at a time when the median survival for patients with metastatic breast cancer was around two years. Today, for the hormone receptor-positive, it exceeds five years for the HER2-positive subtypes, it approaches five years, and five years after bisphosphonates or denosumab, is associated with an increasing risk of developing complications. So I tend to reevaluate the benefit-risk ratio after the first two or three years because that's the period for which we have solid, clinical trial-based data. The second part relates to what one should do to minimize the occurrence of the most common side effects of a complication of bone-targeted agents, which is osteonecrosis of the jaw. And it has been fairly well established that patients who start with poor oral hygiene or with abnormalities in dentition are at a higher risk for developing osteonecrosis of the jaw and developing that at an earlier stage than those who do not have such pre-existing condition.

Dr. Chalasani:
With those key insights in mind. I want to thank my guest, Dr. Gabriel Hortobagyi, for discussing bone-targeting therapies in treating metastatic breast cancer with me today.

Dr. Hortobagyi, it was a pleasure speaking with you.

Dr. Hortobagyi:
Equally, a pleasure to speak with you. Thank you.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series. Visit Reachmd.com/project oncology where you can Be Part of the Knowledge. Thanks for listening.