

Restoring Quality of Life: Managing Side Effects/Palliative Care

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I. Bone Metabolism and Osteoporosis

Dr. Slovin

Bisphosphonates, including Zometa or zoledronic acid, will delay skeletal related events (SREs) and will delay myeloma, renal cell, prostate, and breast cancer associated with delaying any sort of skeletal event. Denosumab is a monoclonal antibody which can delay SREs, has not been shown to affect survival in prostate cancer patients, and does cause osteonecrosis; it has limited effect on bone health.

I apologize for using the phrase bone metabolism and osteoporosis in elderly patients, because quite frankly, what is the definition of the word elderly? The ARP guidelines call anybody over 55 as older people; I think 65 is still ridiculous; an 86-year-old patient of mine recently had a penile implant.

This is what we want to avoid: a cord compression. A goal in metastatic prostate cancer is to prevent further progression of the disease, and also preventing additional aspects of pain. There is a yin-and-yang of bone consumption and bone making. The bone consuming cells are osteoclasts, which are stimulated by RANK, or receptor activator of nuclear factor kappa-B, which is usually stimulatory for cells that are in the predevelopmental stage of becoming osteoclasts. On the other hand, osteoblasts are the cells which make bone. Urine tests can tell whether or not a person is losing bone.

Estrogens inhibit the activity of osteoclasts. When women go through postmenopausal changes, they start losing bone mineral density, making them more prone to fractures. Women need to start taking care of bone through exercise and extra calcium supplements and vitamin D.

The precursor of the osteoclast, which is stimulated by RANK, exist in a complex interaction between RANK and RANK ligand. When RANK and RANK ligand come together, they will induce the formation of osteoclasts. Can we prevent this? Yes, we can prevent it through a number of different ways, including through denosumab, which inhibits RANK ligand from binding to RANK and promoting osteoclast factor.

Conversely, Zometa binds to the hydroapatite, which makes up the bone, making it so slippery that the osteoclasts themselves just slip right off the bone.

This illustration depicts the complex interplay between estrogens, androgens, bone break, bone formation, and with the idea that there are just so many different molecules and co-stimulatory molecules that are involved in making bone and destroying bone. Androgen deprivation therapy (ADT), whether via surgical orchiectomy and removal of testes, or hormonal therapy either continuously or intermittently, will cause bone loss, not particularly substantial. As we use hormonal therapy increasingly with metastatic disease, or disease where PSAs are doubling or tripling very rapidly and you want to just grab onto those PSAs, or someone who is getting it for a big fat gland in the neoadjuvant setting prior to radiation, we are still going to see some bone loss, even if it is very limited.

The number of prostate cancer survivors fortunately is in excess of two million, and one-third of them are receiving ADT. About 45% of androgen deprivation naïve patients, without metastatic disease, already had osteopenia, and about 35% had osteoporosis. What causes this? Contributing causes including smoking, sedentary lifestyle, certain drugs such as Tegretol, anticonvulsants, not exercising enough to really maintain good bone health, diet poor in calcium, and lack of sun. Following androgen deprivation, we see more bone loss; after ten years, nobody has a normal bone mineral density. Bone decreases significantly at the level of the spine and the hip, particularly during the first year of ADT, then 4-5%, respectively, both in lumbar spine and the total hip.

The green in this slide represents osteoporosis or bone loss. In patients who have been on ADT for many years, within the first two years, compared with baseline, there definitely is an increase in the amount of osteoporosis relative to osteopenia. The amount of osteoporosis markedly increases in the four-, six-, and eight-year periods, such that patients are at greater risk for skeletal events. There is 2.2-fold higher risk of having vertebral body or hip fracture in patients who have undergone orchiectomy, which is usually the VA population where this is very popular. One study showed a history of fracture since diagnosis of prostate cancer decreased median overall survival from 160 to 121 months.

An NEJM article addressing prevalence of fractures in men with prostate cancer determined that those who received less doses of a GnRH agonist such as Lupron showed a greater survival benefit than a man who had surgical removal of the testes, or someone who took Lupron for greater than nine doses.

Osteoporosis and osteopenia are largely underdiagnosed, which leads to the question, should every man who comes in with prostate cancer have a baseline bone mineral density? Should they have specific gold standards like the DEXA scan? Should they have a CT of their lower lumbar spine to really get an assessment of where their baseline is? I think it is a good idea for anybody over the age of 50 to have that, particularly postmenopausal women. The reality is it is not done. Factors such as smoking, alcohol, sedentary lifestyle, and obesity tend to complicate the scenario, and therefore, patients have other reasons why they are losing bone.

This study looks at veterans with prostate cancer who received ADT; 34% of those without evidence of disease had received any sort of recommended screening, prophylaxis, or therapy.

Zometa was the first FDA approved drug for use in men who had prostate cancer as well as patients with myeloma and kidney cancer and breast cancer. This slide shows the impact of Zometa on SREs. While many other cancers are lytic diseases which make holes in the bone, prostate cancer is mainly a bone making cancer, meaning it makes new bone which is apparently weaker, and therefore not strong.

Among markers of bone turnover, indications that the bone is getting stronger, is the N-telopeptides which can be measured in the urine. Zoledronic was shown to reduce the urinary telopeptide, suggesting that it impacts directly in osteoporosis. Men who had been on a GnRH agonist did much better on zoledronic acid in terms of percent change in their serum N-telopeptide levels and the bone alkaline phosphatase level, indicating that there was a distinct benefit to both of these.

Preliminary studies with denosumab suggested there were fewer events regarding osteonecrosis of the jaw, but this year's ASCO meeting revealed presence of osteonecrosis. We do not know why this is site specific. Denosumab is a monoclonal antibody which works on RANK ligand, and through a completely different mechanism than Zometa. Zometa makes the bone slippery; denosumab actually blocks an interaction of a particular molecule such that the osteoclast does not develop, ergo, it will not be as virulent. In men receiving ADT for prostate cancer, lumbar spine and total hip were markedly improved in terms of rise in bone mineral density, suggesting that bone was regained with denosumab. Another study showed a marked reduction in vertebral body fracture while on denosumab. Across the board, regardless of age and other factors, there was a definite advantage with denosumab treatment; the effects on bone turnover and fracture risk were positive.

What does this mean for patients with metastatic disease in bone? Algorithms are available, yet much is dependent upon family genetics, physical activity, and diet and calcium and vitamin D supplements.

Cord compression is accompanied by pain. Often as a man ages, there is a balance between pain from prostate cancer with pain from degenerative arthritis. A bone scan is nonspecific and will light up whether you have degenerative arthritis or disease. MRI will show bad spinal stenosis and spurs, but when you see cancer, you will know it is the real thing. How do we do this? Pain from degenerative joint disease (DJD) is usually migratory and improves over time, as opposed to cancer related, which is unremitting, usually in one area. Both types of pain respond to NSAIDs. Pain with DJD improves with increased activity, but cancer related pain can inhibit activity.

One option in treating pain is to use bone seeking radiopharmaceuticals, such as Quadramet, which targets the bone and helps patients in terms of pain. Pain palliation can be achieved with a shot of radiation, but this has a side effect of drying bone. A drug called Radium, which treats pain in rheumatologic patients, is now in clinical trials. Bisphosphonates and combination analgesics can be used. Physical therapy is extremely important.

In conclusion, androgen ablation impacts on bone health; early intervention is important; there is a role for exercise and bisphosphonates in health maintenance; and novel agents will improve QOL and pain.

II. Surgery Perspective

Dr. Krongrad

I work at the other end of the clinical spectrum from what you just heard about. One regret I have regarding bone loss is that about 20-25 years ago, we observed that patients who were on DES had normal or better than normal bone density as compared to patients who were on Lupron or those who had received orchiectomy. One big miss from a pharmaceutical perspective is that we were unable to adapt the DES to eliminate the thrombotic events such that we could still achieve the hypogonadal state yet preserve bone density. It is almost as if we invent one drug to make up for the deficits of the other.

Today we talked about the cultural biases that we face at the physician-patient interface, as well as how to communicate with your doctor or with your patient. As we talk about possible side effects of treatments for early stage prostate cancer, for example, after surgery or radiation, the question becomes how complete are we in our communications? How special are patients' needs and how do we talk about it with our doctor? One example in real practice involves a patient of mine: a year-and-a-half after surgery, he was very happy when he came to the office; he brought his girlfriend with him. They wanted to have a baby. First of all, that would be hard to do the natural way, and secondly, I thought to myself, what is your wife going to think? How do we talk about that with the girlfriend sitting there?

Daryl pointed out this morning an interesting solution, which could have been useful in this case, to ask to speak with your doctor alone without other people around you, to perhaps raise issues that you may not want to bring up, or your doctor, out of consideration for you, does not want to bring up. I said to my patient, I have a referring doctor to send you to; he is a specialist in infertility at the university. I sense this woman really needed to have a baby with this guy for her own reasons.

I run an online social network called The New Prostate Cancer Info Link, which has got 2000 members and climbing. It is commerce-free. Our members include patients, doctors, wives, ministers, researchers, and activists and advocates. I thought the topic of complications of surgery would be great to have on the website, so I put it on; most of what I got back was a lot of snickers. But one member is a world class medical ethicist who took the position that was completely unexpected: men have reproductive rights, just like women; in a situation like this, the wife has no rights at all. Ethics and practicalities can put you in situations where you try to preserve dignity, discretion, confidentiality, and it is really up to the patient to decide where the limits of confidentiality are, not the doctor.

The communications aspects are increasingly obviously public. Why? Because people are tweeting about their experiences, patients and doctors. Recently there was a situation where doctors were tweeting from the OR about an 18-hour complex hand operation.

General reactions to those who reacted publicly was that was a really bad idea. Why? Because the tweeting in no way serves the patient's interest and provides absolutely no health value; obviously, it is distracting for the surgeon. Some communications should be shut down right away because they are bad for the patient.

What about patient initiated communications with the doctor, such as email, cell phones, and beepers? Online communication potentially in these circumstances can be an extremely valuable tool in the sense that they make things really efficient, but they are not really being embraced. The doctor is, at least based on my personal observations, as well as the literature that I have read on it, are not really doing it. Is that a good idea to not do it? Probably not: studies now show that electronic communications can actually help patients get answers to their practical questions regarding treatment complications. I would like to know about how you as a group or individuals have handled your communications in regards to the side effects of treatment with your physicians, and do you have any suggestions or desires in terms of ways that that could be improved? A tiny minority of you use email to communicate with your doctors. How about the rest of you: why don't you email your doctors if you have blood in the urine, for example?

Male Participants

Most people do not have access to their email, or do not have the physician's email address.

Dr. Krongrad

Have you ever discussed that with your doctors, using email? What was your argument: how did you explain that you thought you should have his email address?

Male Participant

It was early on when I was still in shock following diagnosis, and our conversation got sidetracked.

Male Participant

I email all my doctors, and I do not think I would have a doctor who I could not email. My doctors respond to me. One oncologist does not always respond, but her nurse practitioner responds.

Dr. Krongrad

Does it take a long time to get a response? Are the responses on point, do they help you?

Male Participant

No, response does not take a long time. Yes, the responses help. I think it has to do with what we talked about this morning: the doctor has to understand that you may have questions and need answers.

Dr. Krongrad

The overall question becomes nothing is black-and-white; there is an area of gray and the question is one of balance and dose. The doctors with whom I speak about this seem to be afraid of two things: number one, lawsuits and lawyers; and secondly, they worry about their time if they are busy. From personal experience, the timeframe that you were talking about, which is immediately after diagnosis when you felt in emotional turmoil with distress, that is the period where you most need that sort of support. You do not necessarily need somebody to write War And Peace back to you, just a short bullet point that puts your mind at ease, has immense practical value for relatively little effort.

Female Participant

But you can make an argument that we can prophylaxe that by letting the patient know what the possible sequelae might be.

Dr. Krongrad

Exactly right, and we do. The point was that if we give an informed consent and we say, for example, you can have blood in your semen after your biopsy, that that will obviate the need for those phone calls. The reality, of course, is that patients forget, and patients need clarification.

Male Participant

I have been going to the VA for 30 years. They keep changing their position, like a teaching hospital. In private practice, there is no record, while in the VA, everything is computerized. Doctors in private practice pay, for example, \$150,000/year for malpractice insurance.

Dr. Krongrad

Yes, I have never seen any studies looking at the liability issue for the doctor if he answers a patient initiated email about something like blood in the urine. I cannot imagine that if he is answering an email like that, that he is exposed. I do not see what the argument would be there. From a practical point of view, I find that email correspondence helps me as much as my patients: first, I do not have to retrieve messages from my secretary, and secondly, it is actually very fast, as with a Blackberry. Some patients need a reminder that there is a limit to how many questions you should be asking, but most patients are not abusive. The patient expectation of digital communication with physicians is relatively new; the demand for the doctor to use email in regards to treatment side effects is a new thing.

Male Participant

The efficacy of email communication is mindboggling; all my doctors communicate by email. Before email, I may or may not receive a returned call to my message I left for my doctor. My doctor responds to my email, maybe between patients or while sitting on the train; 99.9% of the time, I get an answer within three or four hours.

Dr. Slovin

In the course of a day, a physician could be deluged with emails. That is not an excuse; it is an observation. One of the biggest concerns we have had at Memorial is what if there is an emergency and I am in clinic for God knows how many hours, and the person needs immediate help? That is why we tell people, call the office. We now have a portal system where the patient can communicate via email, and we pick up the message the next day and get back to them. One big concern of mine is that very often, it is very hard, for instance, while on a cruise, where on a bad day, I would like to throw the Blackberry into the ocean as the questions do not end. I have a very good memory, but that does not mean I remember every nuance for every patient.

Male Participant

One of my doctors whom I emailed simply told me later that he does not answer emails.

Mr. Simons

In sum, there is a need for communication, and there is also a mandate that we try to communicate. The key thing is that we must initiate much of it because we are the consumer, we are ultimately buying their service, and if the service is not acceptable, we need to find another provider.

Dr. Krongrad

We are talking a bidirectional relationship here, and we should really examine what the obligations are on both sides. Confidentiality: obviously, we are all obliged to honor that if somebody requests it, and you have to assume it if they do not otherwise say so. In terms of the discourse, the public discourse is a good example. Mark's book cover showing two fists, along with an April Men's Health article depicting an image of a handgun and empty bullet casings, suggest violence; we recently had a surgeon at Johns-Hopkins shot by an angry patient. Patients want a good outcome, and doctors really want a good outcome. The best way this can happen is if the communication is transparent and nonjudgmental and open; we have to be careful with our connotations, like two fists or a handgun and bullet casings.

Dr. Slovin

A man came in for recent consultation with no less than three pages, typed single-spaced questions. I went through every single one, but understand, my office is not a Well Baby office. People have cancer; people are sick. It takes time to answer questions, and if I am running behind, I will answer what I consider to be the most pivotal questions, and tell the patient we will address the other questions at our next visit. People have got to understand we all hold doctors to a very high authority, but we too are human beings. We all want to give the best cancer care but we want to be fair. There is a priority: somebody coming in with three pages, where I just have to address these, is very different from the man who thinks he is going to die two doors down and needs to go on his umpteenth chemotherapy. My own feeling is that I beg indulgence for that. There are people who are sicker, and others not so.