



Maintaining Your Bone Health After Breast Cancer

November 1, 2008

Generosa Grana, MD

LINDA RINALDI:

Good morning, everyone. My name is Linda Rinaldi. I am a Survivors' Helpline volunteer for Living Beyond Breast Cancer [<http://www.lbbc.org>]. I'm a ten-year survivor; ten years and six months today. [Applause]

Let me introduce our speaker, the person you're all here to see. Dr. Generosa Grana is the director of the Cancer Institute of New Jersey at Cooper [University Hospital; <http://www.cooperhealth.org/content/cancer/>] and is an internationally recognized expert in the field of breast cancer. She is a well-known authority and speaker on the genetic factors of breast cancer, and she has pioneered important new treatment options for patients.

For over a decade, Dr. Grana has been the director of the Comprehensive Breast Care program at Cooper. In this capacity, she has emphasized genetic testing to identify those women at high risk, and she has stressed the importance of expert counseling and detection services. Dr. Grana is also a strong advocate of a multidisciplinary approach to cancer diagnosis and treatment. A respected educator in the field of hematology and oncology, Dr. Grana is an associate professor of medicine at the Robert Wood Johnson Medical School [<http://rwjms.umdnj.edu>] at Cooper University Hospital, and she's also an adjunct assistant professor at the Coriell Institute for Medical Research [<http://www.coriell.org>] in Camden.

Without further ado – Dr. Grana.

[Applause]

GENEROSA GRANA, MD:

Thank you. I see a lot of my patients in the audience. I think that's a problem. [Laughter]

[A discussion of] bone health and breast cancer would have been very different 10 years ago than it is today. Ten ago we were talking about metastatic disease to bone and how to manage it.

Today we're going to start our discussion by talking about osteoporosis and why that is an issue in regard to early stage breast cancer, and then we're going to [talk about] some of the treatments for early stage breast cancer and how that field is evolving. Then we can open it up to talk about metastatic disease and all of the things that are out there. I hope to give you a feel for the importance of bone health in the first 20 to 25 minutes, and then to answer any and all of your questions.

I thought this was cute. These are two puppies looking at a bone. We need to start with some humor in this situation. We're going to talk about normal bone physiology and what happens to bone as we age. We're going to talk about bone health and what we know about vitamin D deficiency. You guys have heard a lot this year, after the ASCO meetings, about vitamin D deficiency: potentials, risk factors, management of it. Then we're going to talk about some of the drugs that are being used and their side effects. Many of these toxicities have gained a lot of media attention over the last year, and I think [that these reports] are scaring women away from using very effective drugs.

I'm not [trying to make] scientists out of you here today, but you'll hear terminology such as this, so I want to give you a feel for it. This is a bone spicule; if you do a bone marrow biopsy, you're going to find areas like this. The two cells that are important in regard to normal bone development are osteoblasts and osteoclasts. These are osteoclasts; [these,] right at the periphery, [are] osteoblasts. What's important is the fact that normal bone is not a static structure. Normal bone is constantly forming and resorbing, and it's that balance of constant formation and resorption that helps us maintain healthy bones. If one of these [processes] takes over – if one of these is overly active compared to the other one – then we start getting bone disease, such as osteoporosis or other diseases.

[It's vital that our bones maintain these] continuous processes of resorption and formation or remodeling as we age. And, [to a great extent, the maintenance of a healthy balance of these processes] depends on [what's happening] in the woman's life. How much calcium and vitamin D intake you have? How much exercise do you do? [There are] hormonal factors – estrogen is one of the drivers of this process.

[We'll also] talk about other diseases [and factors] that can affect bone health and the process of resorption: thyroid disease; parathyroid disease; steroid therapy; et cetera.

Why are we interested in [bone health] in women with early stage breast cancer? Several things happen to women when they get diagnosed with breast cancer. Many of the treatments that we give to premenopausal women render them [prematurely] postmenopausal; chemotherapy often makes women go into early menopause. And you lose estrogen when you go through menopause. That lack of estrogen actually accelerates the bone loss that we normally see in women.

In the last five to ten years, a new group of drugs, the aromatase inhibitors, have been used in postmenopausal women. As you go through menopause you lose bone, and the aromatase inhibitors cause increased bone loss – not just bone pain and arthritic pain, which we'll talk about – but bone loss. As we look at bone loss [that's caused by chemotherapy-induced menopause, and] at bone loss that's caused by the aromatase inhibitors, the importance of thinking about that as it relates to therapy [becomes clear].

I think bone health must be managed if you want women with early stage breast cancer to do well. And there's a lack of data yet as to how to do that well.

Osteoporosis: Why is it an issue? I see a lot of women with breast cancer, and they obviously understand the importance of having breast cancer;



the fear of recurrence; the fear of death. But I think very few people have a real appreciation of the severity of osteoporosis. And it is a very important health issue for women. About four to six million women in the United States have osteoporosis and are therefore at risk for hip fractures. It primarily affects Caucasians and Asians because of low bone mineral density. African-Americans have a little bit lower risk. And about 1.5 million fractures occur annually.

The other important factor is down here: 300,000 hip fractures [occur] each year. The important thing is that, of those women who get hip fractures from osteoporosis, 20 to 25 percent will die from the complications that arise as a result of the hip fracture – from blood clots, bedsores, infections and everything else. Clearly, osteoporosis is an important issue in terms of women's health. [Of the women who survive hip fractures,] 25 percent get confined to long-term-care facilities because of the impact on their mobility, and 50 percent have long-term loss of mobility. We are not talking about a health issue that's mild in nature. We're talking about a huge problem for women.

And this is not [just] breast cancer patients. [Osteoporosis, hip fractures and resulting loss of mobility or death occur more frequently] in breast cancer patients, but it's [an important issue] for women in general. I think the media hasn't paid enough attention to this. We've scared women about breast cancer. We've talked a lot about heart disease. But this is an evolving need.

This is what osteoporosis looks like. This is a woman who was straight as a rod in her youth. [Now] she has several of the features that we see for osteoporosis. As you start to get these compression fractures in the spine, you get the dowager's hump and a lot of pain that comes with those fractures; the effect on mobility that comes from those fractures. Look around at your acquaintances that don't have breast cancer – you'll probably see a lot of women that have this type of look, [albeit] maybe not as extreme as this.

The problem is that, [even though] women [and men] start out life with similar bone mineral density, because we have estrogen and not androgens we never quite achieve the same amount of bone density that men achieve. And we begin to lose bone earlier and lose it faster. This is normal bone mineral density over time for men and women. You can see here – this is by age – that our peak tends to be in the 30s, and we tend to

peak about here. Men peak [at a] much higher [level] because of androgen and muscle. We start to lose bone with menopause. Men [who have hit their peak] also lose bone as they age. There are certain men who are at risk for osteoporosis either because they lose androgens as a result of treatment for prostate cancer or because they're [calcium] deficient. But, again, women lose bone much more quickly and at a younger age.

There is some big concern in the United States now because it seems that we are seeing many more women entering menopause with poor bones. The amount of bone that we achieve by age 30 is really determined by the things that we do in our teens and 20s – how much calcium we take in; how much vitamin D we take in; how much exercise we do. If we're living in a country in which some of those things are not optimized – the fear is that many more women will not achieve their ideal bone mineral density and will therefore start menopause with a much lower level [of bone mineral density than that of women in the past], putting them at a greater risk for fractures.

This gives you a sense of the risks that we're talking about. [Here are the] lifetime risks of [incurring specific] fractures if you're 50 years of age: hip fractures – about 17 percent; vertebral – 15 percent risk; [and there are] other fractures, meaning [fractures of] small bones or other [things like that]. Now, the interesting thing is that wrist fractures are a mobility issue; [it's] not a terrible thing. Vertebral fractures tend to be very painful, and they're the ones that lead to that dowager's hump. But it's hip fractures that have those complication rates that I spoke about. [This shows data on] Canadian women – again, [we see] vertebral fractures in about 23 percent [of that general population].

What happens, then, to the population as we age? The greatest loss of bone occurs in women as we enter menopause. That first year of menopause – that lack of estrogen that we see in menopause is the greatest. And you can see that, in the first year after menopause, we have an 8 percent decrease in bone mineral density in the spine and a 3 percent decrease in the forearm. And, as you know, if we're making you postmenopausal at 35 or at 40, we're beginning this process much earlier.

Now, forget that first year. Let's look at the years after that, when you become postmenopausal and live in your postmenopausal state. There continues to be an ongoing decrease of 1 to 2 percent per year. Now, if you're a lucky woman –

if you started with very good bone mineral density and you're not on an aromatase inhibitor, which causes more bone loss, and you're physically active and you're taking your calcium . . . plenty of women die of other things [before they develop poor] bone health. But, again, it is an ongoing loss.

Many women say, "Well, I went into menopause. I stopped." You go into menopause and you stay in menopause. Menopause is a lifetime event. [Laughter] And you continue to lose this bone each year of menopause. So, again, this is an important issue.

How do we monitor bone mineral density? Most places are now doing a combination of DEXA scans, which measures bone density – DEXA [stands for dual energy X-ray absorptiometry] – of the spine and hip. Some people are doing heel scans. When we start looking at those other parameters, I'm not sure that [the] validity [of the tests] is the same.

This is what a DEXA unit looks like. No injection is required. It's actually a very easy test. And the recommendations have been well defined: women should have this at the start of menopause or [earlier,] if they've had an unusual number of fractures. The frequency with which you get additional scans depends on the bone mineral density you have at your most recent scan. [For example,] if your first scan shows that your bone mineral density is normal, you can get another scan in three to five years, assuming you don't have anything else going on. In my breast cancer population, I tend to do second scans at two years for those whose first scans show normal bone mineral density; if it's not normal, I might do a second scan sooner.

What does bone mineral density tell you? I'm going to show you because I think it's important for you to understand what we look at when we look at bone mineral density. We get a report that tells us a T score. Your T score tells us how your bone mineral density compares to that of a woman at her peak, young age. The T score allows us to predict risk of osteoporosis. We can follow a woman's T score from year to year as it changes.

This is normal. Minus one to minus two standard deviations is [labeled] osteopenia. Minus two and a half is osteoporosis. Much of anything [under two and a half], [especially in a woman who's had] fractures, is severe osteoporosis. [Let's look at this in terms of] risk of hip fractures – this is for white women, because they have the highest risk – risk of hip fracture goes along with that T score.



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Look at a woman who has normal bone. She still has a 10 percent lifetime risk of fractures. But this is her baseline risk. Now look at a woman who has a T score in the osteoporotic range. If she's 50, she's got about a 50 percent risk of future fractures. Now look at a woman with a T score standard deviation of 1.5. This is the beginning of osteopenia here. She's got about a 20 percent risk of fracture. You can see that it's important to know what your T score is and how your T score is changing [over time], because we use that as the marker of risk, and we now have drugs that allow us to intervene and stop this process [of losing bone mineral density].

What this shows is how quickly you see an increase in fracture risk. This is the relationship between bone mineral density and risk of fractures. When we get a report back – if you ask for a copy of your DEXA report, not only do you get the T score and the Z score [Editor's note: the Z score compares the density of your bone to the average bone density of other people your age and gender] – and there's a whole other piece of data that comes with that – but you also get a printout, like this, that shows density change over time. Each time you change one of these standard deviations – you can see how much your rate of fracture increases. When you're in the severely osteoporotic range, you have a markedly increased risk of fractures.

What are the risk factors for osteoporosis? Gender – [generally speaking,] you have to be a woman. Men can get it, but that's less common. Heredity – Caucasian and Asian women are more at risk. Look at your mother; look at the other women in your family. There clearly is a hereditary component. If osteoporosis is common in your family, that's what you're looking at [for yourself]. Body frame – petite, small-boned body frames tend to have a higher risk. Estrogen levels – and, in particular, your estrogen levels when you went into menopause and subsequently. And age is important. These are things that you're not going to be able to change very much. You can change estrogen levels by taking estrogen [as a] hormone replacement. But you're not going to be able to change many of these other things. So what can you change? You can change the amount of exercise you're doing. You can make some better health choices in terms of calcium, vitamin D, et cetera. And you can choose drugs that may be effective.

When I see a woman with osteopenia, I don't necessarily focus on sending her for an

endocrinologic evaluation. But if I see a woman with osteoporosis, I always send her for one because, rather than just beginning treatment for osteoporosis, you want to know whether or not there are contributing factors that have led to this that need to be treated.

Who treats osteoporosis? Some family physicians are very good at doing the evaluation. I tend to refer women to the endocrinologist or the rheumatologist because it's their expertise that really is important. They do a series of studies that involve blood work – they look at vitamin D levels; thyroid levels; steroid hormone levels; parathyroid hormone levels. There's a whole assessment. Then they look at urinary tests to see if you're spilling calcium in the urine.

There is a whole host of things that need to be evaluated when you see a woman; you can't just give her a drug. If she has hyperparathyroidism, for example, she basically has a history of kidney stones; a history of fractures; her bone mineral density is poor. She is producing too much parathyroid hormone in these glands that we have in the neck. Yes, I can give that woman medicine for her osteoporosis. But unless we do something about these glands, things are not going to settle down very well. So, again ... you want to seek expert care.

Let's talk about vitamin D deficiency. It's actually a very interesting process. Vitamin D is part of the process of normal bone formation. There are a lot of data that suggest that vitamin D deficiency is common. This is [vitamin D deficiency in the] general population – studies show that, in women with breast cancer, [vitamin D deficiencies] are even worse than this ... you can see that a large number of women in the US population are vitamin D deficient. You can give these women lots of calcium, but they may not necessarily utilize it well. Now when we give calcium, we give calcium plus vitamin D. But if you're at these very low levels of vitamin D, you need more vitamin D than what we're giving you in a routine calcium pill.

This was a study that was presented this year at [the 2008 meeting of the American Society of Clinical Oncology]. It's very important because it was done in a breast cancer population, and there's a suggestion that, if you look at a breast cancer population, you may actually find that you have a bigger problem than you think you have. Goodwin et al. did this study in Canada [<http://www.asco.org/ASCOv2/Meetings/Abstr>

acts?&vmview=abst_detail_view&confID=55&abstractID=31397]. The idea was to look at how common vitamin D deficiency was, to see if any relationships between vitamin D deficiency and other factors could be teased out and to see if a correlation could be made as to how vitamin D deficiency impacts breast cancer survival. Does it make a difference in how you do with breast cancer?

They broke down vitamin D levels into deficient, insufficient and sufficient. What is deficient? For them, deficient was less than 20. Insufficient was 20 to 30. Above 30 was normal; sufficient. Many of our local labs break it down into these categories, as well. What they found in the study is very important. About 70 percent of women fell into the deficient or insufficient category. As you can see here, 37 percent of women were deficient; 38 percent were insufficient. Only 24 percent of the women in this large Canadian study of breast cancer patients had sufficient vitamin D levels.

So, is this duplicable? Can we say that this is the case in the United States? Maybe not. We live in areas that have a slightly lower altitude. We get a little bit more sunlight than they do in Canada. I think that a lot more work is needed to see if [these findings are] applicable worldwide. But I think that this study is very impressive, and many people are now looking at patients' vitamin D levels to make recommendations.

What are the recommendations? If you are in the deficient range, the first recommendation is to figure out why. The second recommendation is to give these patients 50,000 units each week. It's a prescription; you can't buy this. If you're in the insufficient range, we give you 1,000 units a day, which is higher than what you're getting in many of your supplements. If you are in the sufficient range – above 30 – we tell you, "Take your vitamin D." Take anywhere from 800 to 1,000 [milligrams a day] and you'll be fine. So, the [deficiency level determines the way in which] we supplement it.

The first question asked in the study was this: Is vitamin D important and common? The answer was yes. The second question that was asked was this: Does vitamin D level relate to breast cancer prognosis? Unfortunately, in this study it did. If you look at deficient/insufficient groups versus the sufficient group, you can see that, at five years – this is disease-free survival; you may want to look at this, which is overall survival. But here, at five years, 87 percent in the deficient group were alive versus 92 percent in the group that had normal



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vitamin D. At 10 years, it was 74 percent versus 85 percent. In this study, something as simple as a vitamin supplement made a tremendous difference in terms of survival at 10 years.

What does this study allow us to say? We can say that the woman's level at start of the study correlated with her outcome from breast cancer. What we don't know – and, unfortunately, that's where future work needs to be done – is what happens if I replace your vitamin D; if you're deficient and we replenish it, will that change your prognosis? We don't know. Studies are being done to try to answer that.

[Let's talk about] treatment and prevention of osteoporosis: We know a lot about exercise, calcium and vitamin D. [For women with osteoporosis,] I think the important thing is to rule out pathology; get a good endocrinologic evaluation – thyroid; parathyroid; steroid therapy; other things. Next, we need to start looking at drugs. The drugs that we use depend on the patient's history. I think we're going to recommend different things for the breast cancer population than we might for the regular population.

Raloxifene: Raloxifene is Evista. It is a reasonably good drug – it's not the strongest or the best drug for osteoporosis, but it's a reasonably good drug, and it has been shown to lower risk of breast cancer in high-risk women. [A study was done on women who had] a family history of breast cancer but who didn't have breast cancer [themselves]. The study compared tamoxifen to Evista. Both drugs were shown to decrease risk of breast cancer by 50 percent. So, if I have a high-risk woman who also happens to have osteopenia, I want to give her Evista to lower her risk of breast cancer, and Evista's going to help her bones.

The problem is that there is no data in women using Evista to treat breast cancer. I often get women saying to me, "I don't want tamoxifen. I want Evista." Or, "I don't want Arimidex. I want Evista." There is no data, in the published literature, of Evista as treatment for breast cancer. The only data is for osteoporosis and for prevention of breast cancer. So, again, raloxifene is an active agent [in preventing breast cancer].

Tamoxifen is a SERM [selective estrogen receptor modulator]. Tamoxifen also is a good drug. If you're postmenopausal, tamoxifen stabilizes and improves bone.

Now, the bisphosphonates. The problem with the bisphosphonates – and we have to talk a lot about this – is that they come in a variety of

formulations, and the toxicity that you get depends on what you use. They come as IV, oral and subcutaneous formulations. Boniva also comes as a subcutaneous agent. They come in daily dosing; weekly dosing; monthly dosing. And now we have Reclast, which is Zometa that's given intravenously once a year for osteoporosis. So, again, we have a variety of ways of giving these drugs.

Which way should you go with first? What you should first use is a pill, if you can tolerate it. On the other hand, if you try the pill and you can't tolerate it, then you go through the other routes. [But] there are some things to be said for taking a pill rather than putting yourself through an IV infusion or other procedures.

What drugs are there? In the United States, Fosamax, Actonel and Boniva are FDA approved for treatment of osteoporosis. In Europe, clodronate is FDA approved for treatment of osteoporosis. And then we have Reclast, which is approved for intravenous treatment of osteoporosis. How do you choose among these? I've seen a lot of endocrinologists discussing this topic, and the decision-making process is rather less than perfect. There are [studies] that have shown that all of these agents improve bone mineral density, improve T scores and decrease incidences of fractures. The problem is that these studies have not compared these agents head-to-head, so most endocrinologists can't really say [which is the best choice, and I think they sort of choose [on their own]]. There's no great dogma to this.

Actonel probably has a little bit better GI toxicity profile. And monthly dosing is sometimes a little bit better because you face the toxicities only once a month for a few days. So there are ways to choose based on tolerance rather than on how active these drugs are.

Let's go back to bone health. That's osteoporosis. Let's go back to bone health and breast cancer and why [their relationship] important. How do these two go together? We know that women who have low bone mineral density have a lower risk of breast cancer. How do we know that? Plenty of data show that that is the case – if you have low estrogen levels [and] low bone mineral density, you have a lower risk of breast cancer. How does vitamin D affect that picture? All low levels of vitamin D increase risk of breast cancer. I don't think we understand that process in and of itself. [But] keep that in the back of your head.

Bone loss is rapid at the onset of menopause. Early menopause due to chemotherapy causes [rapid bone loss]. Hormone therapy is associated with bone loss. We need to think about that as we go forward.

What studies of these drugs in early stage breast cancer are currently out there, and what have these studies tried to show? The most interesting study was one done in Europe, probably seven years ago now, in women with early stage breast cancer, not metastatic disease. The idea was to give these women clodronate – not to treat their osteoporosis; not to prevent their osteoporosis – but to see if it could be used to prevent recurrence of breast cancer. Why would [researchers] think that it would happen? Because there's actually some interesting data that show that the bisphosphonates strengthen bone and make it less hospitable to attack. And the most common place for breast cancer to go is to bone. If you avoid that – if you make that bone environment inhospitable to attack – you might prevent the spread from the bone to other areas.

The Europeans said, "Well, let's see if bisphosphonate does that." In the study, they gave women clodronate every day for, I believe, two and a half years. They were able to show a decreased risk of breast cancer recurrence – not just recurrence in bone, but recurrence everywhere – and an improved survival. That was the first of the studies that were done to show that.

These studies have been going on for ten years now. We have a study in the United States that's looking to duplicate that European study; it hasn't been published yet. It [looked at] clodronate versus a placebo in early stage breast cancer. The second study done involved Zometa versus placebo in early stage breast cancer. And we have had a series of studies of various forms of Zometa, the intravenous bisphosphonate. We have data that shows that clodronate can decrease recurrence. We now have data that shows not only that Zometa can prevent the bone loss that you get with chemotherapy, but that it also may prevent recurrence in women who are treated with hormonal therapy.

I'll walk you through these slides quickly – I think the concepts are interesting. This is data from a European study that included 1,800 premenopausal women. The Europeans love the concept of using ovarian suppression in premenopausal women – taking a premenopausal woman whose breast cancer is hormone sensitive,



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suppressing her ovaries and giving her a hormone – and that may be enough.

[In this study,] they did just that. They basically gave goserelin. Some of you have heard of this drug – [its brand name is Zoladex] – which blocks the ovarian function. I could do the same thing by removing your ovaries; if you're a young, healthy, premenopausal woman with breast cancer, I could give you Zoladex or remove your ovaries. [In the study, they then] gave the women either tamoxifen or Arimidex. So, they basically made the women postmenopausal and then gave them either tamoxifen or Arimidex.

Then they said, "Okay. Now let's look at the addition of Zometa," which is the intravenous bisphosphonate. "Let's give it every six months, or not, and let's see what happens." So we basically have four groups of women. We have a group that had their ovaries suppressed and were given tamoxifen and a group that had their ovaries suppressed and were given Arimidex. And then, [within each of those groups,] we have [groups that were or were not given Zometa].

There's a lot of data from that trial that show that, if you give a premenopausal woman ovarian suppression but not Zometa, they lose a tremendous amount of bone – that's clear – and that, if you do give those premenopausal women Zometa, [regardless of] whether they're also getting tamoxifen or Arimidex, you block their bone loss.

That's fine; wonderful. But remember, that's not what the study was looking at. The study was looking at whether or not recurrence could be avoided. This is what was presented this year at the cancer meeting. Forget the secondary malignancies. This is opposite-breast cancer. Interesting. This is the group that got Zometa. This is the group that didn't. Six here; 10 here – not a big difference, but a little bit of a difference. Distant recurrence: This is what we're worried about – [recurrence in] bone; lung; liver. Twenty-nine in the group that got Zometa [experienced distant recurrence]; 41 in the group that didn't [get Zometa experienced it]. That is significant.

This is local recurrence. Local usually means breast/underarm; local, regional disease. Again, [the results were] 10 versus 20. If you add these together you have about 46 versus 70, which is very significant. This is the first real study [of a significant number of women] that shows that the addition of a bisphosphonate [in the treatment of] early stage breast cancer in women who are getting hormonal therapy lowers risk of recurrence locally and distantly.

WOMAN:

I just want to clarify: that was based on [women who were] estrogen positive?

GENEROSA GRANA, MD:

This [involved women who were] estrogen receptor positive. And these were women who got hormonal therapy – no chemotherapy – and who either did or did not get Zometa. The other data that's out there also involves women with estrogen receptor-positive breast cancer, although, in that study, they were given Femara. That data shows that, if you give women with estrogen receptor-positive breast cancer Femara plus Zometa, they do better than those who receive Femara but not Zometa.

Your question is good. Does this also work for women with estrogen receptor-negative breast cancer? There is a suggestion that it does, because the clodronate study didn't pick out estrogen receptor positive [as a group].

What happens, though, when you give these drugs? This is the data on Zometa. Earlier somebody asked me about fibromyalgia. This is [a] different [study]. Arthralgias are joint pains – pain in the joints; bones. [Among the women who received] tamoxifen plus Zoladex, about 14 percent of had bone pain, [compared to] 33 percent of the women who received Arimidex plus Zoladex. Why do you think it's so much greater with Arimidex plus Zoladex?

WOMAN:

I think that's what the side effects –

GENEROSA GRANA, MD:

Exactly. The aromatase inhibitors give you arthritic symptoms. Therefore, the addition of Zometa increases arthritic symptoms, regardless of whether you're getting tamoxifen or Arimidex. But Arimidex itself gives you a fair amount of arthritic symptom.

Again, 20 percent of the group that got tamoxifen experienced bone pain; 29 percent of the group that got tamoxifen plus Zometa experienced it. Twenty-eight percent of the women who got Arimidex had bone pain. Forty-one percent of the women who got Arimidex plus Zometa. [It's clear] that, when Zometa is part of the treatment, its side effects – arthritic symptoms; bone pain – need to be taken into account.

[I want to mention] febrile syndrome [as well. This is] a flu-like syndrome that can last a few days after receiving Zometa – usually after the first

infusion of it. It tends to occur only after the first treatment with Zometa; it doesn't tend to recur over time.

WOMAN:

The difference between Zoladex and Zometa – are they two different drugs?

GENEROSA GRANA, MD:

Zoladex was used in this study. Zoladex is an intramuscular hormonal drug that's given once a month to shut down the ovaries. Zoladex should be used only in premenopausal women . . . Zometa is once – in this study it was given every six months. It's given intravenously. Zometa is the bone drug.

The authors of the study concluded that Zometa has an antitumor benefit and that it improves outcome above and beyond the effects of the hormone therapy alone. But also they concluded that the optimal dose, the optimal schedule and the length of time for which it should be continued have not been clarified. There are studies looking at giving Zometa once a month for six months, every three months, every six months and once a year. I think we still have a lot of questions as to how to use Zometa in early stage breast cancer. And it is by no means the standard of care.

I'm just going to highlight this study to show you the other thing that we [learned at] the ASCO meetings. If you take premenopausal women – I told you that, if we give them chemotherapy, they lose bone. If we make them postmenopausal they lose bone. By giving these women Zometa, we can block that process. Let me walk you through this interesting slide, which is too complex for words. [Laughter]

This is what happened in the group of women that got chemotherapy but no Zometa. It doesn't take a rocket scientist to see that they experienced a drop in bone mineral density. When you make a woman postmenopausal, she loses bone quickly in that first year. On the other hand, if you give her Zometa, she doesn't lose it; she actually gains a little bit of bone. Again, this applies to tamoxifen and Zometa as well. This study shows that, if you give women a bisphosphonate during chemotherapy, you can block the bone loss. The study looked at the question of whether to give it early or to wait a year. We don't have answers to that question yet.

What else is going on now? There's an interesting study going on right now; they're recruiting women for it. A placebo is not used in



this study. It's looking at [the effects of] giving women, during chemotherapy or after chemotherapy, clodronate or Boniva – both of which are pills that they take every day – versus Zometa. In this trial, the Zometa is being given once a month for six months and then every three months thereafter. Everybody gets drugs for three years. We hope we'll get an answer from this study [as to which, if either, is the better choice]. In this study, women can be ER positive or ER negative. There's no selection for either.

Some other interesting compounds are being tried; these are not bisphosphonates, and they may not have some of the toxicity of the bisphosphonates. There is a lot of information out there about the toxicity of these drugs. When you talk about bisphosphonates, you can't help but discuss the GI toxicity of the oral bisphosphonates. About 10 percent of women end up not tolerating Fosamax, Actonel or Boniva because of the GI toxicity. You have to take them on an empty stomach, first thing in the morning, with a full glass of water. And, despite following that rigid schedule, about 10 percent of women have to stop them because the GERD-like symptoms are intolerable.

But, besides that, the arthralgias, the bone aches are real. Then there's osteonecrosis of the jaw. Most of [the information we have on] that comes from the data on women with metastatic or advanced breast cancer who've been getting Zometa every month for a long, long time. [In that situation,] we see osteonecrosis of the jaw. But there also have been case reports about osteonecrosis of the jaw in women who were given Fosamax for osteoporosis. Any woman who is getting a bisphosphonate for any reason right now should have education about what this is. She should have dental exams every six months, and she should really inform her dentist that she's on this drug so that, if a tooth needs to be extracted, the dentist is aware that she's on it – because, in at least in 80 percent of the cases, osteonecrosis seems to be related to an extraction and failure to heal following an extraction.

That's my take on bone health. Again, I think it's an important issue for the general population of women. I think it's [particularly] important for the breast cancer population, not only because you go into menopause earlier, but also because you have untreated menopause. We're not going to give you hormone replacement, so you're going to have more ongoing bone loss. Actually, some of the

drugs we're going to be giving you in menopause will add to your bone loss. Furthermore, I think it's interesting [to consider] all this new data that's evolving; [data that] suggests that, maybe, by giving you bone strengthening agents, we may alter your outcome from breast cancer. That's where, I think, the future is headed.

And now, questions.

WOMAN:

I've learned recently, [as a result of having had] a tooth extraction – people who [have] osteopenia [or] osteoporosis [due to] bisphosphonate, don't even consider implants; it's not a good idea. At least my dentist wouldn't [consider] it. And I think that's pretty common across the board.

The other thing is that Fosamax just went generic. Is the generic okay?

GENEROSA GRANA, MD:

[Regarding] dental implants and osteonecrosis of the jaw – osteonecrosis of the jaw . . . was first reported in the breast cancer world probably three years ago; a report out of Long Island reported 60 cases of osteonecrosis of the jaw. The common factor [among those cases] was bisphosphonates for treatment of metastatic breast cancer or metastatic prostate cancer, although there were a couple of cases in which Fosamax had been used for osteoporosis.

Usually – 80 percent of the time – [osteonecrosis of the jaw involves] extractions of teeth that don't heal. Instead, you get this necrotic piece of bone that doesn't cover over and doesn't heal. And, in a certain number of women, if you extract enough teeth, you actually have a whole ridge that's sort of denuded and necrotic and that may need to be debrided, and it can be really problematic.

How often do we see it? I can't tell you how many women with metastatic breast cancer I take care of. And, in my practice, I think I've seen four or five cases of it. Now, you could argue that, in the past, we might not have recognized it or appreciated [its seriousness]. It's seen in people with other forms of cancer as well. Osteonecrosis of the jaw is very common in patients who've had radiation for head and neck cancer. So there are other conditions. But [in women with breast cancer], it seems to be the bisphosphonate that's playing a role.

Why might that be? In order for you to heal after a tooth is pulled, you need that process of bone resorption and bone formation.

Bisphosphonates bind to your bone matrix and sort of make it very rigid, so there's not a lot of formation or resorption and you don't heal. There is some concern, in the bone community, that the bisphosphonates may also [cause] trouble late[r]. Another important issue: It seems that, for bone health; for vertebral health, you need to have a certain number of small fractures and healing that's constant. The bisphosphonates may give you this steady bone but not a lot of that [fracturing and healing], so the bone may not be of the best quality. We need 20-year studies; 30-year studies.

My message to women is this: Your dentist should be aware that you're on a bisphosphonate. The problem is that we don't know whether or not stopping the bisphosphonate prior to your tooth extraction will help. You may still have the same problem because these bisphosphonates hang around forever. If a woman needs an extraction, I do tell her, "Let's hold off for three to four months if we can." If you can't do that, then you become aggressive [in fighting infection]; your dentist manages it aggressively. Some of the studies seem to show that you can actually culture infectious agents out of the socket, so better antibiotic coverage and better local care may be important. But it is an issue. I wasn't aware that it was an issue in regard to implants, though.

WOMAN:

Alendronate [inaudible].

GENEROSA GRANA, MD:

Alendronate – [with] all of these agents, the concern is that we don't have good data that say that these are single-drug specific. We clearly see a lot of reports in which Zometa [is a factor]. A lot of the reports have been about cases of metastatic disease in which Zometa was given intravenously. In the European study, they didn't see any cases of osteonecrosis of the jaw when it was given for early stage disease every six months. But, again, the fear is there also with Fosamax and Actonel. The cases are rare. I would tell you that it's probably more important to not be so fearful of these drugs and to be active because osteoporosis is a big problem also.

WOMAN:

My question is specific to me, but I think there's enough that you can take out of it to generalize. I've had both hips replaced due to arthritis. The tamoxifen had brought me back into the normal range. I had been osteopenic before. I've now been on Femara for the last two and a



half years, and I'm osteopenic. However, the last time I had my DEXA scan done, they couldn't do the hips anymore, so they did my forearm. The forearm is showing osteopenia. The lumbar spine is normal —no osteoporosis, no osteopenia.

Who do I talk to? Do I talk to my nurse midwife, who I go to for gynecologic care? Do I talk to my medical oncologist? Do I go to my internist? Or — I heard you say to go to a rheumatologist or an endocrinologist? At this point, I don't know. Do I need to have the forearm treated?

GENEROSA GRANA, MD:

That's a dilemma. You bring up several very important points. Number one is an interesting thing about tamoxifen. Tamoxifen, like Evista, is a good bone drug. I don't think we had these problems in the past because women were on tamoxifen. It's a dichotomy, though. Tamoxifen in premenopausal women causes bone loss. Tamoxifen in postmenopausal women causes bone gain. Then you switch from tamoxifen to Femara, and you have bone loss. Typical. Aromatase inhibitors cause bone loss.

The encouraging thing, though, that you need to take away from this is that, in the ATAC trial, which looked at Arimidex versus tamoxifen, the women who had normal bone density never became osteoporotic. Some of the women who had osteopenia at start of therapy became osteoporotic. So I think the reassuring thing for you is that you were normal when you started, so the likelihood that, within the five years of therapy, you'll become osteoporotic is less.

Who deals with this? It's anybody's guess. I've had patients for whom I was very fanatical about ordering the bone density scans and I've told them, "Go talk to your primary [care doctor]"; and the primary [care doctor] comes back and says, "If you order it, you deal with it." So I find that oncologists are dealing with this a lot now. The American Society of Clinical Oncology has actually put out guidelines, and the guidelines are not necessarily to start treatment [for] osteopenia unless [you have several other risk factors for bone problems]. If you know you're going to be on Femara for a long while, maybe it's worthwhile. If you've had fractures, maybe it's worthwhile. But the other option is to just repeat [tests] and try to optimize exercise; try to optimize vitamin D and calcium. Check your vitamin D levels.

If, the next time around, despite all attempts

to optimize, your [bone mineral density has continued to decrease], then think about starting. But I think it's a toss-up as to who to go to for the management of this. I think the oncologists are doing it much more [than they had in the past].

WOMAN:

In 2001 I developed a cancer that required me to have a Whipple operation, and I developed all the malabsorption-type issues. In 2005 I developed breast cancer. I went through the mastectomy; chemo; radiation. Now I'm finding that I have osteoporosis. I'm on 50,000 units of vitamin D three times a week. I'm on Zometa. I'm taking vitamin E and vitamin A, and all those levels continue to be deficient. I'm getting overwhelmed by all of this. I don't know what my prognosis is. I'm just at a loss as to what I should do.

GENEROSA GRANA, MD:

How often are you taking the Zometa?

WOMAN:

Once every three months — and I've had horrible side effects from that. I was on Arimidex and I couldn't stand the bone pain. They switched me to Aromasin, and I'm still having quite a bit of bone pain. I don't know if it's from the Aromasin, the Zometa or what.

GENEROSA GRANA, MD:

I don't have an answer for you, unfortunately. But I think you highlight several important things. Again, I think that, if you have a woman who has bone loss, you need to look for explanations. In your case, the [most likely] explanation is your malabsorption. That's why I like sending women to endocrinologists. If your endocrinologist — there are other things besides the bisphosphonate, besides Zometa, on the horizon now. There is a fluoride. There are a couple of other drugs that can be used. Are you being seen by an endocrinologist?

WOMAN:

Not anymore. There was an issue — my general internist had put me on Actonel and things like that. The endocrinologist felt that I didn't need that because of the type of bone issues I was having.

GENEROSA GRANA, MD:

I would probably say to get another opinion from another endocrinologist. And see if you can find an endocrinologist that can work with you, because I think your issues are very specific. Or go to a rheumatologist. These issues are dealt with

mainly by those two specialties. Again, if I see a woman who has bone issues, my first thought is to send her to someone; oftentimes you'll find reasons, like yours, that have led to the problem with bone.

Now, the other interesting thing: You're getting a lot of vitamin D replacement. One study that was presented last year said that we know that bone pain is [an issue with] the aromatase inhibitors. About 50 percent of women that are on an aromatase inhibitor will have some bone pain. [In situations that are similar to yours,] I tend to do what [your doctors] did with you. If a patient has bone pain on Arimidex or Femara, I switch her to Aromasin; sometimes you can get away with it.

But there was an interesting suggestion that women who were vitamin D deficient had more arthritic [issues when on] the aromatase inhibitors. Those of you who are having arthritic symptoms, think about that and bring up the issue when you see the oncologist.

You're getting a lot of Zometa. I would [ask whether or not there were other drug or dosing options]. I don't know that changing the Zometa dosing is going to give you any benefit, but it's worthwhile talking about it. There are newer drugs. There's a parathyroid type of compound that I've seen used. Forteo is another compound that's now on the market. So I think it's time to go back and discuss these issues again with someone.

WOMAN:

You mentioned the importance of exercise. Are there any specific types of exercise that you recommend or any that you don't recommend?

GENEROSA GRANA, MD:

I wish I could give you an answer to that. Just last week a study was published that suggests that exercise is important in terms of breast cancer risk — that information doesn't help those who already have breast cancer, but it is important for our daughters to know. There was a suggestion that you need exercise from adolescence on in order to lower risk of breast cancer.

But there's also data that suggest that exercise and diet may help prevent recurrence. How much exercise? That's [what everyone wants to know]. Any amount is better than none. The more you can do the better. The suggestion is that you need at least three to five encounters [with exercise] a week, and they should be somewhat more intensive than you anticipate. A combination of weight-bearing exercise and aerobic exercise is probably best.



There is nothing that I would avoid. [Women who have] had lymph nodes removed or who have lymphedema [need to be cautious when exercising]. Even for those women, though, we still recommend exercise and weights. We just caution them to use smaller weights – five pounds; whatever – and to perform fewer repetitive exercises of the upper arm. [In general, though], the more the better, but I think the jury is still out on whether or not any particular exercise or combination of exercises is best.

WOMAN:

When a woman is diagnosed as being premenopausal and is forced into menopause by chemo, at what point is she considered postmenopausal? And – does salt intake have an impact on the bones?

GENEROSA GRANA, MD:

Hmm. I don't know if there's a relationship between salt intake and bone. I've never heard of it, but I'm not a bone expert. Regarding the first question – when is a woman who goes into chemotherapy-induced menopause considered postmenopausal? That's a very good question, because oftentimes we use that determination to decide what hormone to give. The definition of menopause is no period for one year. In women who've gone into menopause due the chemotherapy, I use that same definition: no period for a year.

But you have to have extra caution because some of those women may not have a period but may still have higher levels of estrogen than you would anticipate – they're not making enough estrogen to have a period, but they may still be above that threshold. And some of those women, especially if they were very young when they went into menopause, may resume their periods. It's rare that they'll resume after a year, but you don't want to get burned with that.

If I'm making the decision, I put those women on tamoxifen for about a year or so. Then, if the year has gone by and they haven't had a period, I'll check LH, FSH and estradiol. Your estradiol should be very low. Your LH and FSH are the pituitary hormones that are whipping your ovaries – basically, the ovaries stop working; the pituitary senses that and whips them with LH and FSH [in order to try to get them working again]. So you should see low estradiol and high LH and FSH. If a woman is not in that range, I keep her on tamoxifen – because the worst thing you could do would be to switch her over to an aromatase

inhibitor, which may not be fully effective if she's not fully postmenopausal.

WOMAN:

My question is regarding the vitamins D and C. What are the appropriate number of milligrams to take per day?

GENEROSA GRANA, MD:

The optimal amount of vitamin C – well, no, I shouldn't say that. We don't know anything about vitamin C. We think it's about 1,000 milligrams, but who knows? There's no idea. There has been a concern about – some people believe we should take much higher amounts of vitamin C. Linus Pauling, who won the Nobel Prize, would say that you need megadoses of vitamin C. I have patients who are getting vitamin C infusions at one of the local places. There is, unfortunately, no data that says that that is beneficial or safe or anything else. But, so be it. I would say that the information on vitamin C is not clear.

Vitamin D: We need somewhere around – the recommendations for the population are 400 to 800 milligrams. But, based on the data that we're seeing, I would argue that you should have your level checked if you've had breast cancer because you may be deficient, and you need much higher levels if you're deficient.

The recommended amount of calcium is about 1,500 milligrams per day, and it should be taken in divided doses because if you take it all as a single dose you won't absorb it. Most of the calciums on the market are calcium-plus-vitamin D combinations . . . some women get constipation, gas or GI distress with one form but may not with another form.

The other option you have is to look at your diet. Some of the cookbooks that are out there tell you how much calcium is in a cup of cottage cheese; how much calcium is in a cup of yogurt; how much calcium is in a cup of broccoli. So, if you're really intolerant of calcium [supplements], see how you can integrate 1,500 milligrams of calcium into your daily diet. You can do it; I think it can be done.

WOMAN:

And what forms of the calcium? Bicarbonate or –

GENEROSA GRANA, MD:

There's no data. The only difference may be – I've seen some patients who have been doing a special kind of calcium.

WOMAN:

Coral?

GENEROSA GRANA, MD:

Coral calcium. There is absolutely no data that shows that the type of calcium you take alters absorption or outcome. But there can sometimes be differences in tolerance. Now, there are people who have had kidney stones who do need to take different kinds of calcium. If you've had a kidney stone, you should talk to your family doctor because there may be testing that you need to have done that may guide you in choosing the type of calcium to take.

LINDA RINALDI:

I have a question back here. In a woman who's had a bilateral mastectomy – actually, two single mastectomies performed years apart – and who has lymphedema in one arm and one arm is atrophied, do you have any suggestions for how that – what is next? How do you treat that? How do you not get atrophy in the other arm?

GENEROSA GRANA, MD:

I think the key is really upper extremity exercise. In the past, we used to keep women away from exercise, thinking that weights and such were going to increase risk of lymphedema. That's not true. There are a couple of really good experts in the area on lymphedema. There's a woman, Linda Miller, who lectures a lot. She's a big proponent of weight training programs for women who have lymphedema.

Again, use light weights – you don't want to lift 20 or 30 pounds. But you want to use light weights and to perform other upper body exercises. The belief is that, by building the musculature in the arm and chest, you're actually improving the flow of lymph back to the body. That's the only thing I can think of.

WOMAN:

Atrophy –

GENEROSA GRANA, MD:

The only thing you can do for the atrophy is exercise. There's nothing else. There's no –

WOMAN:

[Inaudible]

GENEROSA GRANA, MD:

Exercise; weights and exercise. That's the only thing you can do to try to recover some of the muscle that's been lost. Exercise – using light weights – is helpful both for the lymphedema and for atrophy.



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WOMAN:

What's the difference between Zometa and Reclast?

GENEROSA GRANA, MD:

Good point. Purely marketing and packaging. [Laughter] We live in a wonderful world called America. Zometa is Reclast. But I have no idea – maybe an endocrinologist could tell you. Zometa, when given for osteoporosis, for bone density issues or for metastatic breast cancer, is usually given in doses of 4 milligrams intravenously over 10 minutes. Reclast is given in 5-milligram doses. They basically got around [the naming issue] with different packaging and a different FDA approval. Reclast is approved for once-a-year dosing. Zometa is also approved for once-a-year dosing, but we actually can use Zometa for more frequent dosing. So it's purely a marketing and packaging. But there is a 1-milligram difference in dose.

WOMAN:

I don't know if you've had patients who've been on Zometa for a number of years, but I have been. [If you have,] do you recommend any diagnostic tests – for example, do you tell them to get a DEXA scan? If they're doing okay, do you still think that they could benefit from having an endocrinologist looking at their calcium levels or anything? Or do you just let them keep going?

GENEROSA GRANA, MD:

The questions that have to be answered before that are why the patient is on Zometa and whether it's for osteoporosis or for metastatic disease. If a patient is on it for osteoporosis, I leave her in the world of her endocrinologist. Often the endocrinologist will tell me when to stop – they often start and stop drug usage. In women with metastatic breast cancer, the dogma – these drugs have been around. It started with Aredia, then Zometa. Aredia is still used, and it's given via a two-hour infusion. Zometa's a little bit better, and it's given over 10 minutes.

These drugs went on the market about 14 years ago. Until the osteonecrosis stuff [came up], we were keeping patients on these drugs forever. We'd only stop it if the patient's renal function – because Zometa can affect renal function – was changing. We weren't monitoring bone mineral density because we weren't using it for bone mineral density. We were basically putting them on the drug and leaving them on it. And there was nothing else to monitor.

Since all of this started, the oncology community has sort of sat back and said, "Well, now what do we do?" We don't have any data, because the studies didn't go out 10 years. I have had patients on Zometa for 10 years. So I think we're in a period of uncertainty. Zometa is used for metastatic breast cancer, metastatic prostate cancer and multiple myeloma, all diseases of bone destruction. In the myeloma community, what's happening now – there's actually a study that will address this – is that, once people get to their two-year mark, their dosing schedule is changed to every other month or to every three months. But [currently] there's no data.

I'm doing the same thing, on an individualized basis, with some breast cancer patients now. If they've been very stable for two years and their bone is good, I may switch their dosing to every two months or every three months – but they need to understand that there is no data and that this is being driven by our fear of osteonecrosis.

WOMAN:

But do you still have them get DEXA scans?

GENEROSA GRANA, MD:

I don't, because what am I going to do with it? I'm not using the Zometa to improve their bone density. And their bone density should be phenomenal because they've been getting it. So, no, I don't monitor anything else.

WOMAN:

My question is about once-monthly Boniva versus Actonel. Is there a difference in the toxicity? For example, do you reduce the risk of GI issues if you take the drug less frequently? But, because it's more at one time, is there a greater risk for the osteonecrosis?

GENEROSA GRANA, MD:

There's very little data on that. Remember these drugs have not been compared head-to-head, which would be the ideal. If you gave a woman a monthly dose versus a weekly dose versus a daily dose, are there differences? I think the GI toxicity may be a little bit less. I am seeing women who are having a little bit less in terms of the heartburn/GERD kind of things. There is no data out there to say that it's more effective or less effective; that there are more or fewer cases of osteonecrosis. There's just no data.

WOMAN:

You mentioned that, for vitamin D deficiency, some of the doctors, endocrinologists, are giving 50,000 units once a week. Is there a certain toxicity level or a time at which you would stop that? Or is it okay to continue to do that?

GENEROSA GRANA, MD:

Again, I'm telling you what I'm seeing done, because most of these are being diagnosed by the endocrinologist. The endocrinologist I work with tends to give 50,000 units once a week for three months and then [checks your vitamin D] level at three months. If the patient's vitamin D level is then fine or sufficient, she may lower the dosage to 1,000 units a day.

Is there a downside to vitamin D? I think there is. There is toxicity; I honestly can't tell you that I know what it is, but there is toxicity. Vitamin D overload does have toxicity. I want to say [that it involves the] liver, but I may not be completely correct. I just don't deal with this often enough. But, yeah, they tend to do it for three-month periods.

WOMAN:

My sister's a 24-year cancer survivor. And, after 24 years, it came back in her bones. Is it possible that that cell could have been lurking around there all this time and, because of low bone density – is that how it could have made a comeback?

GENEROSA GRANA, MD:

Possibly.

WOMAN:

Am I at risk, in terms of [family history], of getting that?

GENEROSA GRANA, MD:

I think that you have just highlighted what's probably the biggest fear that many of the women in this room have. I think that, in the past, we did women a disservice because we told them, "Five years, and you're cured," and women went on their merry ways. Now we know that, depending on the kind of cancer you have, the rates of recurrence vary. Dr. Alapati talked about the triple-negative basal cancers. Interestingly, those cancers tend to either recur early or not recur. So, once you get through the five years, for those patients it's great. It's rare that those cancers recur after the five years.

The ones that are a problem are the estrogen receptor-/progesterone receptor-positive cancers. These are hormonally dependent cancers. If you



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look at the curves, [you can see that] the biggest rates of recurrence are in the first two to four years or so. Then the curve drops and drops, but it never becomes zero; you have women who have recurrences at 10 years; at 15; at 20. Although something recurring at 24 years is so rare that you'd want to make sure that you've looked — that there was no cancer in the opposite breast; nothing else — I would buy that as a late recurrence.

What can we say about a late recurrence? Actually, the prognosis is better. The fact that it recurred in bone is better. Women that have bone-only disease have a very good prognosis. Late recurrences have much better prognoses. But it's still the thing that we miss.

Your other question — are you at risk? I think you need to look at two things to determine if you're at risk. How old was she when she was diagnosed the first time around? And is there any other family history, besides hers, of breast or ovarian cancer? Who?

WOMAN:

My mother.

GENEROSA GRANA, MD:

Okay. That's your answer: Yes, you are at risk. Genetic testing should be done, and it should start with your sister or your mother, whichever of the two of them is still living. If you find a genetic abnormality in her, then you can be tested. [But, whether or not you] find a genetic abnormality in them, you're still at increased risk, and you still should be screened differently.

WOMAN:

Is my risk any higher because I have had a recurrence? I've had breast cancer; 10 years later I had a recurrence. Is my risk of getting it in the bone any higher, given that recurrence?

GENEROSA GRANA, MD:

No. I think you bring up an interesting point. You have a mother with breast cancer and a sister with breast cancer, and you, yourself, have had bilateral breast cancers?

WOMAN:

No.

GENEROSA GRANA, MD:

One?

WOMAN:

I've had [one] twice.

GENEROSA GRANA, MD:

Twice. Okay. In a family like yours, genetic testing is very important for the other women in the family. It's also important for you in terms of what to do with your ovaries. But genetic testing doesn't tell you anything at all about the chances of cancer spreading to bone or other areas. All genetic testing tells you is this: What is your risk of getting breast cancer the first time? What is your risk of getting a cancer in the opposite breast? What is your risk of getting ovarian cancer? And what are your daughters' and sisters' risk? It doesn't tell you anything at all about prognosis once you've had the breast cancer.

The other thing is this: Why did the breast cancer recur at 24 years? Has it been lingering for 24 years? We think so. We think that these cells have been latent. And then, for whatever reason — is it an immune system change? Is it osteopenia? Maybe. We don't know.

The Europeans have done some interesting studies looking at bone marrow biopsies in women with early stage breast cancer. At the time of their lumpectomies or mastectomies, they did blind bone marrow biopsies of stage I and stage II [cancers]. In about 30 percent of the women, they found cells that are identical to their breast cancer cells already in their bone marrow.

So this is a situation of very early breast cancer and some cells in the bone marrow. But the very interesting thing is some of those women who had cells in their bone marrow will never develop metastases. Why not? Is it that their immune systems are better? Is it that those cells are not functional? We don't know.

WOMAN:

Is it a normal thing [that] she's not in any pain at all?

GENEROSA GRANA, MD:

Well, that's fortunate. It's not normal — the one problem with bone metastases is that it can be painful, although we now have great ways of treating bone metastases. But it's a lucky thing.

WOMAN:

With respect to your choice of calcium or vitamin D, are the store brands at CVS okay?

GENEROSA GRANA, MD:

Absolutely fine. Again, see how you tolerate what you're taking. Some women have a lot of gas and constipation with one brand, and they'll switch to another brand and will be fine. I like those

chewable candies just because you — my problem is remembering to take them. I just never remember to take the stupid things. But the chewable ones are great. They come in different flavors.

WOMAN:

Do you recommend the Fosamax plain or the Fosamax with D? Also, knowing that they're showing that, if you take a bisphosphonate and you develop a fracture, it takes longer to heal, are you recommending a honeymoon from the drug —

GENEROSA GRANA, MD:

Well, that's —

WOMAN:

— in a period, you know, before you develop the fracture.

GENEROSA GRANA, MD:

Do I recommend Fosamax or Fosamax D? I think that, if you're getting enough D in your diet and in your calcium supplement, I don't think Fosamax plus D is adding anything else. So I don't care which one you take if you're getting enough D.

But you bring up another issue. Remember that I said that the endocrinologists and rheumatologists who manage this are concerned that the quality of the bone that is being formed on these bisphosphonates is not perfect; it's not normal — that you need the microfractures that are normal to have strong, healthy bone. That's they've just started to talk about drug holidays. I don't recommend that because I don't know what to do with it. And I would tell you that the endocrinologists don't know what to do with it.

There is a real concern that we need to study this better because it may not be productive to keep a woman on a bisphosphonate for 10 years. It may be better to have periods of being on and off. But I don't know the answer.

WOMAN:

Do they say to take calcium with food for the purpose of absorption or just so you don't upset your stomach? Do you have to take calcium with food?

GENEROSA GRANA, MD:

You don't have to take calcium with food. The bisphosphonates have to be taken without food. The calcium can be taken with or without food; it doesn't matter. I think it really hinges on your tolerance of these things.



WOMAN:

Are there any side effects of raloxifene?

GENEROSA GRANA, MD:

There are side effects of raloxifene. Interestingly, they're very similar to the side effects of tamoxifen. Raloxifene and tamoxifen are SERMs. They block the estrogen receptor. What does it mean to block the estrogen receptor? If you give women tamoxifen, what [side effects] do they typically get? Hot flashes; night sweats. Raloxifene does that as well. Vaginal dryness is common. That tends to be the major thing.

Raloxifene may be different than tamoxifen, or a little bit better than tamoxifen, in that there tend to be fewer blood clots and less uterine cancer than we see with tamoxifen. Tamoxifen – that's its major concern. In the big prevention study of tamoxifen versus raloxifene, breast cancer prevention was found to be equal, bone was similar – both are good bone drugs – and hot flashes and night sweats were similar. There was a little bit of a suggestion that more genital, sort of sexual, symptoms were experienced with raloxifene, but clotting and uterine cancer were a bit less.

WOMAN:

[Inaudible]

GENEROSA GRANA, MD:

I never use raloxifene in a woman who's had breast cancer because, again, it's not a drug that's approved for the treatment of breast cancer. It's used for osteoporosis. The only exception I [might] make to that is if you're estrogen receptor negative, I haven't given you tamoxifen, I haven't given you Arimidex and your bones need treatment – then raloxifene is not a bad choice.

WOMAN:

[Inaudible]

GENEROSA GRANA, MD:

Yeah. Raloxifene's not a bad choice. But what I see happening – and I'm a little uncomfortable with this – I see people, often gynecologists, give raloxifene to a woman who's on tamoxifen or Evista. That's not a good choice. Or I see raloxifene given to a woman who's been on tamoxifen or Arimidex – again, not a good choice, because they've already had their hormonal treatment for their breast cancer. Look for other drugs to treat their bones. We have plenty of other drugs to treat their bones.

LINDA RINALDI:

Any other questions?

GENEROSA GRANA, MD:

Two more, back there. She has a question about the drug Forteo, and I can tell you I know nothing about Forteo.

WOMAN:

[Inaudible]

GENEROSA GRANA, MD:

The question is in regard to bisphosphonates and a drug holiday. That's anybody's guess, because we just don't have the data.

WOMAN:

[Inaudible]

GENEROSA GRANA, MD:

I guess the first question is about this drug Forteo. I know nothing about it. That's why I send patients at this level to an endocrinologist or a rheumatologist – because I think there is other stuff that can be done. If your bone mineral density is declining despite good calcium, despite good vitamin D and despite bisphosphonate therapy, there are other things.

Now, what I didn't even talk about is a drug that was described this year at the breast cancer meetings. It's called dasatinib. It's a totally different compound. It's not a bisphosphonate. It appears to be dosed similarly to dosing of the bisphosphonates – it's given via IV. It doesn't seem to produce the arthritic symptoms of the bisphosphonates. And it's now being tested in osteoporosis. The study that was presented was in metastatic breast cancer where there was activity. So I think we're just beginning to have other options besides the bisphosphonates.

LINDA RINALDI:

Okay. Our time is up.

[Applause]

GENEROSA GRANA, MD:

But not FDA approved, just being tested.

LINDA RINALDI:

Thank you so much, Dr. Grana.

GENEROSA GRANA, MD:

All right. Thank you.

[END OF TRANSCRIPT]