

Us TOO International Webinar/Teleconference Transcript:

Estrogen Deficiency Side Effects Due to Androgen Deprivation Therapy 9.23.09

Pam Barrett: Hello, Everyone. Thank you for joining us for the Us TOO University Patient Education Webinar and Teleconference on *Estrogen Deficiency Side Effects due to Androgen Deprivation Therapy Treatment for Prostate Cancer*. My name is Pam Barrett, and I am the Director of Development with Us TOO International. I would like to recognize and give special thanks to our sponsor, GTX, for making this event possible, especially as this is the first time we are able to offer a Webinar in addition to an audio-only teleconference seminar. Dr. Taneja will discuss How ADT affects men; treating prostate cancer, the role of estrogen and testosterone in men, the deficiencies associated with ADT, estrogen deficiency side effects, and managing those side effects.

I am very pleased now to introduce our speaker for today's presentation, Dr. Samir Taneja. Dr. Taneja is an associate professor of urologic oncology with the New York University (Langone) Medical Center. He graduated from Northwestern University School of Medicine in 1990, completed his surgical and urologic training at the University of California at Los Angeles in 1996, and then joined the faculty of New York University where he completed a post-doctoral fellowship in the study of hormonal regulation of prostate cancer growth. He has been the director of urologic oncology in the Department of Urology at NYU Cancer Institute since 2000, Director of the Sherman Fellowship in Urologic Oncology since 2006, and Chief of Urology at the Veteran's Administration New York Harbor Healthcare System, Manhattan Campus, since 2008. In 2006, he was awarded an endowed professorship in urologic oncology. Dr. Taneja's clinical practice is focused in the care of prostate cancer patients. He has specific expertise in nerve sparing radical prostatectomy with clinical interest in prostate cancer diagnosis, prevention, and the management of high-risk and the advanced disease. He has been listed among *New York Magazine's* best doctors and (Cathel) and Connelly's America's Top Doctors for Cancer. Dr. Taneja's laboratory research focused on understanding how hormones regulate prostate cancer growth have been funded by the National Institutes of Health, the Department of Defense, and a number of private foundations. He also oversees a number of clinical trials of prevention and treatment. His most recent research interest is in developing strategies of mapping prostate cancer for focal therapy. Dr. Taneja has authored more than 150 articles and book chapters, edited two textbooks, and has lectured throughout the world on urologic cancer. Dr. Taneja is the host of the weekly men's health show on Sirius XM Satellite Radio. And now, for our featured presentation, Dr. Taneja.

Dr. Taneja: Ladies and gentlemen, thank you for joining me on this very important educational forum. We are going to be discussing a variety of side effects of androgen deprivation therapy for the treatment of prostate cancer, with a particular focus on the side effects of androgen deprivation therapy. I believe these side effects are typically under-recognized by most physicians, and most patients seem to be unaware of the potential long-term effects of androgen deprivation therapy in their treatment.

Currently prostate cancer is the most frequently diagnosed cancer in men. It is estimated that approximately 192,000 new cases of prostate cancer will occur in the United States during the year 2009. An average of 1 in 6 men will be diagnosed with prostate cancer at some point in their lifetime. Two million U.S. men are currently prostate cancer survivors. This illustrates the fact that after the diagnosis of prostate cancer, we are frequently very successful in our treatment, and men have a very prolonged survival under treatment, whether they have early-stage disease or advanced-stage disease at the time of diagnosis. Despite this, prostate cancer remains the second leading cause of cancer death in men. It is estimated that approximately 27,000 deaths will occur in the Year 2009 due to advanced prostate cancer.

At the time of diagnosis, most of you are aware, that various treatment options exist. This is often a point of tremendous confusion for patients in deciding how to proceed. Patients might be treated with surgery; various forms of radiation therapy, including external beam radiation, radioactive seed implants; or active surveillance if they chose not to have a conventional treatment. Androgen deprivation therapy is a treatment that is frequently used in men with advanced prostate cancer, that is cancer that may have spread to other parts of the body, or in patients with high-risk cancer in combination with conventional treatments. There are currently approximately 700,000 men in the United States receiving androgen deprivation therapy as part of their prostate cancer treatment.

Androgen deprivation therapy, also broadly called hormonal therapy, is really the standard of care for men with prostate cancer. This has been the case since the mid-1950s when a urologist by the name of Charles Huggins discovered that removal of testosterone from prostate cancer patients resulted in a regression of the cancer, a prevention of progression, and a stabilization of advanced disease. In doing so, it prolonged the survival of his patients. Previously androgen deprivation therapy was generally provided by removal of the testicles or bilateral orchiectomy. Subsequently a multitude of drugs have been developed which can suppress testosterone levels to castrate measurements. Examples of these drugs are drugs like Lupron or Xoladex by tradename. These are drugs that suppress the stimulus from the brain that provides testicles with a signal to go forward and make testosterone. So by suppressing that signal, the body shuts off production of testosterone.

Testosterone in the body is converted to estrogen by an enzyme in the peripheral fat called aromatase. As such, because men don't have ovaries, the only source of estrogen in a man's body is conversion from testosterone. Androgen deprivation therapy suppresses testosterone production and thereby decreases levels of testosterone by up to 95 percent and levels of estrogen by up to 80 percent. So in a patient receiving androgen deprivation therapy, the body has greatly reduced levels of hormone.

Estrogen in a man's body is the principle hormone responsible for maintaining bone integrity. Many of us recognize that women who are post-menopausal have a high risk of osteoporosis. That is because after menopause, the ovaries stop making estrogen. Similarly in men on androgen deprivation therapy, suppression of testosterone potentially

could result in osteoporosis. And likewise, as men age and their testosterone level declines, they may potentially see loss of bone density. Typically elderly men have higher levels of estrogen than women of similar age because most women of that age have gone through menopause. Illustrated in the graph on the right, you can see that men have about 3.5 times the level of circulating estrogen as do women.

The role of estrogen and testosterone in men is diverse. Estrogens have a multitude of functions ranging from regulation of temperature; cognitive function in the brain; providing some sexual desire or libido; cholesterol changes—estrogens are responsible for regulating cholesterol levels to some extent; providing bone health—as I mentioned estrogens are important in maintaining bone density; and interestingly, estrogens are important in maintaining prostate health as they may provide a signal for prostate maturation and stability of prostate cells, preventing them from unregulated growth.

Testosterone has a multitude of functions in the normal body, as well. It provides mental and physical energy to patients. This is in part through providing a stimulus for muscle strength. Body hair, male voice, and post-pubertal male characteristics are generally provided by circulating testosterone. Erections or erectile function are generally provided by testosterone, and removal of testosterone frequently will result in impotence. Also important in prostate health, at high levels of testosterone, the prostate develops following puberty. Much of its enlargement as we age is due to the presence of testosterone.

When estrogen and testosterone deficiencies occur in patients receiving androgen deprivation therapy, a multitude of side effects may arise. Hot flashes, also called vasomotor flushes, are due to the loss of estrogen. When estrogen signal is lost to the brain, there is temperature dysregulation, and men may experience short periods of a sensation of feeling very hot, flushed, sweating. Often that can be associated with a bit of racing of the heart. Men frequently complain of that while on androgen deprivation therapy. Men may also see breast enlargement and tenderness. We can note elevation of cholesterol, as well as a reduction of good cholesterol. There can be bone loss and fractures due to loss of bone density. And over time, there may be reduction in prostate size.

Testosterone deficiency can result in a multitude of side effects, as well. Men may develop a propensity for insulin resistance or diabetes. They may develop muscle atrophy and weakness. There can be body composition changes, with redistribution of fat to the axial skeleton around the torso and chest. There can be erectile dysfunction due to loss of testosterone. Finally, there can also be effects on prostate size. It is important to note that as men age, they may see a reduction in their testosterone levels to a milder degree than men on androgen deprivation therapy. Therefore, a number of the testosterone deficiency side effects are seen in the aging population.

In conclusion, key points on androgen deprivation side effects include the presence of fractures, which are highly prevalent in men on androgen deprivation therapy. Approximately 1 in 5 men will have a fracture in 4 years. Most men on androgen

deprivation therapy are not aware that they are at a higher risk for fractures. And I think many physicians who care for these men are likewise not aware. Hot flashes, breast pain, breast enlargement are highly prevalent and highly bothersome to patients on androgen deprivation therapy. Among my patients, hot flashes are probably one of the most common complaints that I hear. Breast pain and enlargement are not quite as frequent. But obviously when they do occur, they are very bothersome to the patient. Breast enlargement may become irreversible after the first year of treatment if it is not adequately attended. Finally androgen deprivation therapy can increase the risk for cardiovascular disease. This can occur through worsening of cholesterol levels, predisposition to obesity, predisposition to diabetes or insulin resistance, and direct effects on the blood vessels, reducing arterial compliance or stretchability such that high blood pressure and secondary effects on the heart may arise.

Let's first talk about increased fracture risk in men on androgen deprivation therapy. I can tell you from my own personal practice that 10 years ago we didn't even learn about the possibility of osteoporosis in men who were receiving androgen deprivation therapy. It has recently been recognized as an extremely important long-term effect of the treatment, and it has been addressed by a number of studies in the literature. I think part of the importance is that fractures are a tremendous cause of morbidity and a potential cause of mortality among aging men. They also pose a tremendous cost to our healthcare system.

We classify fractures in one of three ways: vertebral fractures, fragility fractures, or traumatic fractures. The importance of the classification is that patients will often say, "I don't think I know anybody who has a fracture." But some fractures are without symptoms, they occur due to loss of structural integrity within the bone, and they may over time cause deterioration of the skeletal frame and eventual morbidity. Vertebral fractures are typically determined by measuring the shape of the vertebral body on a simple x-ray. As the vertebral body collapses or fractures, its height may be lost and its shape may be altered. These types of fractures are often without symptoms, or they may result in back pain. Fragility fractures refer to fractures that are not due to acute trauma but may occur as the result of a simple fall from a standing height or less—someone slipping on the ice, someone slipping on the stairs, falling off of a chair. These may result in vertebral fractures, hip fractures, and wrist fractures. Certainly these are typically noticed by patients as a result of the trauma. Traumatic fractures arise from falls from a distance greater than the standing height of the patient or a fracture that occurs from some traumatic injury, for example a car accident or falling off a ladder. These fractures may occur in younger patients with strong bone density. But certainly patients with osteoporosis or reduced bone density would be at a higher risk of such a fracture. These are typically noted by the patient because they are associated with some form of significant trauma.

It is known that the risk of fracture increases with decreasing estrogen levels. As men age, their testosterone declines, and secondarily the estrogen level declines, as depicted on this graph. At a typical estrogen level in older men, over the age of 65, estrogen levels may decrease to the range of 20 picograms/mL. At this level, approximately 20 fractures

per 1000 person years are noted. When estrogen levels decline to below 10 in men on androgen deprivation therapy, this fracture rate appears to be nearly tripled by population incidence. One in 5 men receiving androgen deprivation therapy over 4 years will develop a fracture. As measured by a classical study in *The New England Journal of Medicine*, close to 20 percent of men had a fracture during 4 years of follow up. The most common of these types of fractures was in the hip. Hip fractures occurred in 4.1 percent of patients in the study. It is noted that this fracture risk persists not just when people start out on androgen deprivation therapy. Further studies have shown that by 7 years on androgen deprivation therapy, 45.5 percent of men would have developed a fracture. And by 15 years on treatment, close to 3 out of 4 men would have had a fracture. This exceeds the general fracture rates observed in the aging population.

Fractures in men on androgen deprivation therapy can significantly reduce survival. Among men with prostate cancer receiving androgen deprivation therapy, there is an average 3-year reduction in survival among men who have experienced a fracture as compared to those men without. It is well known among the medical community that hip fractures and spinal fractures among the aging population result in immobility, prolonged hospitalization, and potential for mortality in and of themselves.

The National Osteoporosis Foundation has recommended 5 simple steps to bone health. (1) Daily recommended amounts of calcium and Vitamin D should be taken by the patient. (2) The patient should engage in a regular weight bearing and muscle strengthening exercise regimen. The value of this is to provide impact to the bones as a stimulus for bone strength. (3) Patients should avoid smoking and excessive alcohol, both of which have been associated with osteoporosis in the aging population. (4) Patients should be active in talking to their healthcare provider about their own individual bone health. When appropriate, they should have a bone density test and take medication under their physician's guidance. (5) The National Osteoporosis Foundation has also created a guideline for medication treatment of osteoporosis. It is recommended that post-menopausal women or men over the age of 50 who have osteoporosis or who have had a prior hip or final fracture should be treated. Post-menopausal women or men with osteopenia, meaning not true osteoporosis but reduction in bone density, should be treated if they have a 10-year probability of hip fracture that exceeds 3 percent. Overall a 10-year probability of a major osteoporosis related fracture that is greater than 20 percent would also necessitate medical therapy. Interestingly men with prostate cancer who are undergoing androgen deprivation therapy typically meet that criteria. As I showed you in the earlier slides, the rate of fracture exceeds 3 percent in these patients and typically exceeds 3 percent by 4 years rather than 10 years. In *The New England Journal* study, 4.1 percent of men had had a hip fracture by 4 years. The vast majority of elderly men on androgen deprivation therapy have osteoporosis or osteopenia as measured by bone density studies. As such, medical therapy may very well be indicated in the majority of patients receiving prolonged androgen deprivation therapy.

As I said earlier, hot flashes and breast enlargement, breast pain, are very common sources of decreased quality-of-life among our patients on androgen deprivation therapy. Androgen deprivation therapy induces breast enlargement due to the fact that there is a

relative change in the estrogen to testosterone ratio. When men go on androgen deprivation therapy, you will recall that their testosterone level decreases by 95 percent while their estrogen level decreases by a lower relative proportion. As such, even though both are declining, the ratio of estrogen to testosterone increases. It is this ratio that potentially produces enlargement of the breast tissue, termed gynecomastia, or pain in the breast, termed mastodynia. Breast enlargement and pain is more common in men treated with Casodex or anti-androgens for complete androgen blockade. This is done in a subset of men, based on physician preference, to maximize the residual testosterone circulating in the blood stream. The natural progression of androgen deprivation therapy induced breast enlargement occurs slowly over the first 6 to 12 months. Patients may start to notice breast enlargement even within the first 6 months after treatment. If these changes persist longer than a year, scarring of the breast tissue will occur and this breast enlargement may become irreversible even with stopping the therapy.

Hot flashes are one of the most common and most distressing side effects of androgen deprivation therapy. They occur in 50 to 80 percent of men by report. But in my own personal experience, the vast majority of men will at some point have some hot flashes. Androgen deprivation therapy induces hot flashes by declining estrogen levels and declining estrogen feedback to the brain. Low estrogen alters the pituitary and brain feedback loop, and this stimulates the temperature regulatory centers of the brain. Abnormal stimulation of the temperature regulation center will eventually cause a hot flash. Hot flashes persist in 50 percent of patients on androgen deprivation therapy beyond 5 years. We often tell patients that hot flashes are worst at the beginning, but our data would suggest that they continue to progress for prolonged periods of time.

Increased risk of cardiovascular events in men on androgen deprivation therapy is perhaps the most newly recognized category of side effects. Medicare database results would suggest that men on androgen deprivation therapy have an increased risk of heart attack and sudden cardiac death. These men were at an 11 percent increased risk of a myocardial infarction and a 16 percent increased risk of sudden cardiac death as compared to men who were not receiving androgen deprivation therapy. Men on androgen deprivation therapy also have an increased risk of diabetes—that relative increase is 44 percent—and a 16 percent increased risk for coronary heart disease. As mentioned earlier, a reduction in testosterone is associated with body mass changes, body composition changes, and potential development of insulin resistance, Type 2 diabetes, and metabolic syndrome. Estrogen deficiency increases cholesterol. This may also secondarily affect the risk of cardiovascular disease over time. As such it is very important for men on androgen deprivation therapy to know risk factors for coronary heart disease.

Well recognized risk factors for heart disease include high blood pressure, high cholesterol, smoking, physical inactivity, obesity, diabetes, familiar history of heart disease; and women, for whatever reason, seem to develop coronary artery disease at a later age than men. Men on androgen deprivation therapy, therefore, should have a heightened awareness of their own risk factors and should be carefully monitored for

body composition changes, cholesterol changes, sugar changes, and overall changes in their blood pressure or cardiovascular risk.

In summary, it is exceedingly important for patients to recognize the long-term risks of androgen deprivation therapy. It is important to discuss these risks with your individual physician. It is important for the physicians to be aware of how to manage those risks as they arise. Men with prostate cancer therapy are at an extremely high risk for fractures and bone loss, resulting in increased risk of early mortality. Although the National Osteoporosis Foundation guidelines are not written specifically for men on androgen deprivation therapy, it is clear that these men have a sufficiently increased medical risk to warrant medical therapy and to fall into the high-risk definition in the National Osteoporosis Foundation medication guidelines. Early implementation of the five steps to bone health may be advisable for all men. And when noted to be on long-term androgen deprivation therapy, careful consideration to medication may be warranted by the individual physician. Men on androgen deprivation therapy should discuss heart failure, breast enlargement or breast pain with their physician early in their therapy. Prolonged breast enlargement beyond a year may become irreversible and would only be corrected by surgical therapy. Men on androgen deprivation therapy should be aware of their baseline cardiovascular risk and discuss their own lifestyle and risk factor modification with their physician. If at an increased risk coronary artery disease prior to androgen deprivation therapy, it becomes all the more important to institute early lifestyle and risk factor modification. Men should know their baseline lipid and sugar levels and ask about any changes in their cholesterol, lipid, or metabolic profile with their physician during each visit of their therapeutic follow-up. This good relationship between a physician and the patient, as well as the knowledge of androgen deprivation therapy side effects among patients, will surely reduce the potential long-term effects of the treatment. It is through early education and early awareness of side effects that much of the morbidity can be prevented.

I thank you for joining us. I hope it has been very informative to all of you, and I look forward to fielding any questions you might have.

Question & Answer Session

Welcome, everybody, to the question and answer session of our presentation this evening. I've been fielding a lot of interesting WEB questions from all of you, and I will certainly start by answering a few of these. First off, I want to thank you all for taking time out from your evening to join me. I hope that you found the presentation informative. Based on some of your questions, I think you're thinking right on about the relevant issues that are related to the presentation. I am going to try and get to a number of your questions, and we'll try to field as many as we can this evening.

One of the first questions that I think is a very good question is *Is estrogen replacement a way around the estrogen loss, or how about DES?* I think that is a great question because what we are saying is that the loss of estrogen from the body is causing all of these side effects. Why not put someone on estrogen therapy, much as you would a woman who has gone through menopause? The answer is that if you put a man on estrogen while he is on ADT, he will surely have fewer estrogen-related side effects. But the problem is that he will have a number of side effects potentially related to the estrogen itself. Although estrogens do good things in the bone and they give good feedback to the brain, they do have the potential to cause breast enlargement. So it may make it more likely that men would develop breast enlargement or breast tenderness, and we see that in men who are receiving estrogens or DES while on ADT or as a replacement for ADT. It used to be, before drugs like Lupron and Zoladex were developed, that patients actually got DES in order to suppress testosterone production. By overloading the brain with feedback from estrogens, the testosterone production in the body would actually shut down. One of the major side effects, though, of high-dose estrogen therapy and even low-dose estrogen therapy is the potential for cardiovascular and thromboembolic side effects. So patients would develop heart attacks, strokes, blood clots in the legs, which is another secondary side effect of unregulated amounts of estrogen. It is also the reason that many post-menopausal women are no longer put on low-dose estrogen. They are put on other drugs that mimic the action of estrogens, instead. So a big area of development, both for men with ADT and post-menopausal women, is to try and replace estrogens through a category of drugs called selective estrogen receptor modulators, which are drugs that are chemically similar to estrogens. But instead of acting like an estrogen in every location in the body, they are designed to block estrogen's function in some organs while stimulating estrogen's function in other organs. Thereby they can be used effectively in theory to address a lot of the side effects that one might experience.

I have a number of questions here about exercise while on ADT and whether this will help with bone density. They range from a question that says *Should I stop skiing?* One listener is asking if he will get shorter while he is on ADT. Another asks *What is the effectiveness of exercise in reducing fracture rates? And shouldn't more research be focused on eliminating ADT as a therapy?* So first, with regard to the issue of exercise—exercise is critically important for men who are on ADT, not only from the standpoint of maintaining bone density through impact and stimulation of the bone, but also in terms of maintaining muscle mass, which is a side effect of loss of testosterone. So I strongly encourage all of my patients who are starting ADT to be on a regular exercise regimen.

If they can afford to have a personal trainer, sometimes that is helpful because motivation for exercise is not always the greatest. But any exercise regimen that one can have is certainly going to help with bone density to some degree. Should you stop skiing? I don't think so. But if you are on ADT, I think it is important to be aware of your bone density. So it is critically important for patients on ADT to be monitored by their urologist using one of various tools, the most common being something called a Dexascan, which can measure bone density. If the urologist observes a reduction in bone density over time or your primary physician observes it, then that might be an indication that skiing might be a little bit dangerous for you. If there is osteoporosis or osteopenia, reduction of bone density, then you may be more prone to a fracture if you have even a light fall. So it is critical to monitor it. You shouldn't stop your life. Could you get shorter? Well, actually, if you are having vertebral fractures due to osteoporosis, you will get shorter. And this is one of the reasons that people often get shorter as they age. You remember in the slide I said there were three types of fractures, one being a morphometric fracture. Morphometric fractures are fractures that don't occur due to trauma or activity but instead they simply occur due to daily activity. So as a person is standing or walking, they may experience a morphometric fracture. And those are most common in the vertebral body. As they occur, the vertebrae compresses, and so the spine can shorten and people can actually get smaller.

Is it possible or is it desirable to replace ADT? I think there is some desire to replace ADT. There are ongoing research studies to see if there are other ways that we can selectively suppress the growth stimulatory effects of androgen on the body without getting rid of androgens all together. But for now, it remains the standard of care. I think the important take-home point is that although it causes a lot of side effects, it also saves a lot of lives. It is well shown that men with advanced disease do benefit from having androgen deprivation therapy. In a way, it is a necessary evil because it is helping our men with prostate cancer.

In fact, I have a number of questions over the Web Chatter tonight asking about specific clinical scenarios. I'm not going to run through all the specific clinical scenarios, but there are a couple of scenarios people have given me. One gentleman with a PSA of over 300 after radiation therapy who went on Lupron and Taxotere. He had a good response. He had a number of sites of cancer, and these appear to have regressed away so that a lot of his symptoms have gone away and he feels good. But he has noticed that he is starting to experience side effects from the hormone therapy. He is worried about fractures. His cholesterol has gone from 200 to 250. Another gentleman has a PSA of 46.8 and Gleason 9, aggressive prostate cancer. He is 75. And it sounds as though he is being treated primarily with hormone therapy alone. He developed a compression fracture of his L5 vertebral body, which is in the lumbar spine, and then was diagnosed with osteoporosis. Now he is scheduled to have his hormone therapy implant removed in February of 2010. What I would say is that stopping hormone therapy is certainly an option if someone is experiencing significant side effects, but it has to be vented on the clinical scenario. And what I mean by that is that if you have a PSA of over 300 and multiple bone metastases, I would argue that the risk of coming off hormone therapy or androgen deprivation therapy is far greater than the risk of side effects. What I really want you to take away from

today's talk is not that you should avoid ADT if you need, but instead you should be aware of the side effects. And if you are already worried about fractures, what that means is that you can be proactive by engaging in many of the guidelines we talked about tonight—having your physician monitor your bone density, starting you on medication if your bone density is low or he perceives your fracture risk to be high. If your cholesterol has gone up to 250, it sounds like it might be a reasonable time to consider anti-characteristic or lipid-lowering agents to help control that before it causes an increase in your cardiovascular risk. For the gentleman with Gleason 9 disease, I am not sure that I believe that hormone therapy alone is an appropriate treatment for someone with no evidence of metastasis or advanced disease. You may want to discuss alternative treatments with your urologist, perhaps radiation or cryotherapy or even in some cases surgery if it is appropriate. But to remove the hormonal implant and leave you alone simply because you have osteopenia leaves you very vulnerable to what sounds like a very aggressive cancer.

I have another question, which I think is a great one. It is radiation versus aromatase inhibitors for gynecomastia. Gynecomastia, just so you know, is enlargement of the breast, as we talked about. And as we mentioned, this is due to a hormonal imbalance, more estrogen on board than testosterone. This results because low levels of residual hormones that circulate in the body from the adrenal glands or from residual production by the testicles might get converted to estrogen. And the ratio of estrogen to testosterone remains high. So one way we can prevent breast enlargement is to give low-dose radiation to the breasts before someone goes on ADT. This is generally pretty effective in preventing breast enlargement, but we don't do it that much in clinical practice for a few simple reasons. One is that gynecomastia doesn't occur that often on ADT. It occurs in someone on just an LH-RH in about 15 percent of patients. So the relative risk of radiation and the secondary side effects of radiation may outweigh the relative benefit of avoiding gynecomastia in 15 percent of patients. Nonetheless, it is effective if given before the gynecomastia. It is not effective if given after. So if someone develops gynecomastia, typically 6 to 12 months after starting on ADT, and it persists for longer than 6 to 12 months thereafter, it is likely that that may be irreversible and radiation is not going to get rid of it. It may get rid of a little of the tenderness, but it won't get rid of the breast enlargement. In those circumstances, surgery is the only way that one can get rid of the gynecomastia reliably. Drugs such as aromatase inhibitors are designed to prevent the conversion of testosterone to estrogen. So the listener is asking a very intelligent question *If you get rid of the aromatase, thereby getting rid of the estrogen, will you reduce the likelihood of gynecomastia?* The answer is you very well may, but remember what we are talking about is low levels of estrogen causing bad effects on the body. So not only will you potentially get rid of the gynecomastia, but you will get rid of what little feedback your body has on the brain through low levels of circulating estrogen. You may also accelerate bone loss, etc. So I am not convinced that aromatase inhibitors are the best way of dealing with gynecomastia. I think other drugs in development, drugs that perhaps block estrogen receptors, may be a more effective way of selectively blocking the effect of the estrogen receptors in the breast without affecting the feedback to the brain and affecting the bone. Certainly there are a number of those drugs that

potentially are in development, and maybe it is worth talking to your physician about them.

Another good question: *What criteria do you use for therapy intervals, PSA line or PSA doubling time?* What this listener is talking about is the concept of intermittent hormone therapy. Intermittent hormone therapy is gaining popularity in the United States. It is the idea that if someone needs hormone therapy, give it to them long enough for the PSA to drop, and then stop it, let their PSA come back up, and give it again. And if you do that, you'll give them sort of a respite or rest period between hormone therapy periods or androgen deprivation therapy periods so that their testosterone can recover and maybe their body can be exposed to testosterone and estrogen. I will say that although that does appear to improve quality of life, it is not yet known if it will reverse these long-term side effects of continuous androgen deprivation therapy. So we don't know if men on intermittent therapy are less likely to suffer an increased risk of cardiovascular disease. We don't know what its effects on other parts of the body will be, although in theory it is appealing. If you believe in intermittent therapy, you probably believe in early androgen deprivation therapy, that is to say giving androgen deprivation therapy before people have a great deal of symptoms or evidence of disease spread. I am very reluctant in my practice to give intermittent therapy to high-risk patients, patients with bone metastases or symptoms at the time they are treated for fear that those symptoms might recur within the rest interval. And I think that is a general tendency among urologists who practice urologic oncology. So if you believe in early hormone therapy or early androgen deprivation therapy, then it is reasonable to consider it. There is no known fixed interval, and generally the interval is not based on time but instead on PSA. It is a bit arbitrary, but people will usually wait until the PSA reaches 10 or 20 and then restart the treatment. Usually that interval is about 4 to 5 months with testosterone recovered early in treatment.

I had another question that actually I was going to ask if one of you didn't, but one of you did. It's from a gentleman who says he is on a 2-month androgen deprivation therapy simultaneous with radiation. This is after a radical prostatectomy. *How long after the two months do people still have the side effects of androgen deprivation therapy?* This is an important question because a lot of people get androgen deprivation therapy in conjunction with radiation treatment. As a result, they're only on it for a short period of time. The short answer is your hormone levels will typically recover in a very short period of time for men who are younger. The older you are, the longer it may take. On average it is about 4 to 6 months. We don't know that those short periods of hormone deprivation produce any long-term side effects like osteoporosis, although they may affect cardiovascular risk, and we are still learning about that.

Let's take a couple of calls. We have a call from Leonard Fisher in Ohio. Leonard, thanks for calling in to our presentation tonight.

Leonard Fisher: Surely.

Dr. Taneja: What question can I answer for you?

Leonard Fisher: Well, I have been running about 25 miles a week for 50 years. I am keeping that up, with my doctor's blessing. And I just wondered does that actually keep you from losing your bone density?

Dr. Taneja: We think that running does because it is high impact and impact to the bone stimulates the cells in the bone that remodel. And so remodeling of the bone is what provides its strength. So if you've been running that much, I think it is going to have a lot of benefits for you. One in maintaining bone density and muscle mass, two in keeping some of the extra fat off that people tend to get when they are on androgen deprivation therapy, and three, in keeping your heart in good shape. So I think it is a great thing for you to keep doing, Leonard.

Leonard Fisher: Thank you.

Pam Barrett: Thanks to the callers for questions. Dr. Taneja, thank you so much for your time. For additional reading, I just want to remind everybody, that Us TOO has a number of education materials specific to hormone therapy and treatment of advanced disease including *Prostate Cancer Patients Guide to Hormone Therapy; What you need to know for Better Bone Health; What Now? Hope and Options when (Incomprehensible) see a Rise in PSA;* and *The Prostate Cancer Play Book for Prostate Cancer Recurrence, Rising PSA in Advanced Disease.* Again, they're all available for free on the Us TOO International Web site under the Helpful Resources Section on the right-hand side of the home page.

Also, if you want to continue the discussion amongst yourselves or in your support group meetings, I encourage you to do that. Also we have some on-line discussion communities called Prostate Pointers where you can interact with each other. There is one in particular called CHB for the discussion and support of combined hormonal blockade as a treatment of prostate cancer. And you can subscribe to that group on the Website. Again thanks to Dr. Taneja and to our sponsor, GTx, for making this event possible. And thanks especially to all of you for your time and interest. We hope you found the Webinar teleconference helpful to you and your family.