THERAPEUTIC ADVANCES IN PROSTATE CANCER

Morgane Diven, PharmD, BCOP, Phoenix VA Health Care System
Robert Dreicer, MD, MS, MACP, FASCO, University of Virginia Cancer Center

MODERATOR All right. And welcome back, everyone. I hope you had a nice break. Our next session is on Therapeutic Advances in Prostate Cancer, so please join me in welcoming Dr. Morgane Diven of the Phoenix VA Health Care System and Dr. Robert Dreicer of the University of Virginia Cancer Center.

DR. DREICER So, good afternoon. I'd like to thank the organizer for their kind invitation. What I'm going to try to do in a relatively short period of time is talk about three areas in prostate cancer that's evolving, so it's new data, it's things that are happening, and trying to set the stage as you will see things change over the next couple of years.

So, what you see here is a timeline with drug approvals. And those of us of a certain age remember that prior to around 2004, the only approved drugs for advanced prostate cancer were mitoxantrone, which is a cytotoxic that many of you have probably never seen used, as well as older therapies; drugs that I refer as to sort of pseudo rat poisons. So, what's happened over the last 14 to 15 years is that almost every drug that you see there with one exception has been demonstrated to improve survival.

One of the challenges over the last couple of years has been sequence and how to optimize therapeutics. It's going to get more complicated because just as soon as people sorted out how to use the drugs that we have, all of them

are moving leftward and you will be seeing new drug approvals over the next couple of years with different classes.

So, let's start with biochemical failure or PSA-only disease. Remember that when a patient undergoes curative intense surgery or radiotherapy, the reality is about a third—maybe 30%, maybe higher—of patients will have a detectible rising PSA afterwards, especially if they've had a radical prostatectomy that they were not cured. But, also remember that most patients who have a detectible PSA after definitive local therapy don't die of prostate cancer, so therein lies one of the dilemmas about managing the disease.

One of the challenges since the advent of PSA—which was clinically available since around 1987—is the recognition that you weren't cured and, therefore, the desire to do something about a biomarker, right? PSA is something you can measure. People know that a higher number doesn't sound good and, therefore, there have been lots of folks treated with early—meaning in the nonmetastatic setting—androgen deprivation therapy. Recognize that there is no level 1 evidence to support that, but it's been done nonetheless. So, we'll talk about that and its implications for how the disease is now being managed.

So, of course, if you treat a patient with a rising PSA with androgen deprivation therapy, you will have that patient's testosterone decline, of course, on the basis of therapy. You'll also get a PSA response, but ultimately, that patient is going to have PSA progression. So, for definition purposes, castration-resistant PSA-only disease is a patient who has a testosterone that is less than 50 ng/dL, has a rising PSA, has no overt evidence of metastatic disease on

imaging using standard imaging, which is a technetium 99 bone scan and a CT of abdomen and pelvis.

Advanced imaging – PET/CTs, whole-body MRIs, etc.. As you get more sensitive assays, you pick up things that may be present, but the implications of how to manage patients are complicated. We don't really have time this afternoon to drop into that in any great detail, but the critical thing to remember as we start talking about therapeutic advances is that patients with a rising PSA, most of them don't die of prostate cancer, they die of other things.

All right, so how do you follow patients with a rising PSA in the castrate setting? So, this is a very interesting curve that came out of a prospective randomized trial of denosumab. This was done about 10 years ago where patients were randomized to receive denosumab or not in those patients with a rising PSA, castrate, nonmetastatic disease.

Interestingly enough, the denosumab trial was positive; it showed a 3-month delay in metastasis-free survival, but it was not approved. But one of the things that did come out of it – if you look at the PSA doubling time curve – and, remember, PSA doubling time is logarithmic equation, it's not something – well, I can't do it in my head. I'm guessing most people don't do logarithmic equations in their mind, so you use an online calculator and you usually need about three values.

So, you see that its PSA doubling time drops below about 8 months. You start seeing a much higher incidence of metastatic disease. And that is actually

not an unreasonable way to think about managing patients and it's relevant as we talk about the two trials that will come up.

So, at ASCO GU earlier this year, two very large phase 3 trials were presented. They were concomitantly within a couple of months also published in the *New England Journal of Medicine*. Apalutamide is a second-generation AR antagonist. It is a cousin to enzalutamide, so it has some of the same class effect agents. And, of course, enzalutamide as you know is a second-generation AR.

So, this is the two trials. One trial here – and, basically, they look the same because their eligibility and randomization was similar. So, this was the SPARTAN trial. To get on this trial you had to have castrate nonmetastatic disease, although it does allow you to have a couple of lymph nodes in the pelvis less than two sonometers, where the other study did not. And you had to have a doubling time – a PSA doubling time – of less than 10 months. You were randomized 2:1 to get apalutamide, an oral agent, versus placebo. Both groups, of course, maintained LHRH-agonist therapy.

This is metastasis-free survival of both studies. And what you can see is huge differences here. So, roughly speaking, both drugs led to 2 years of median improvement in metastasis-free survival. So, these are sort of, you know, hormone, grand-slam kind of differences. You look at the hazard ratios, it's in the 70% plus reduction of metastatic disease. So, these were strikingly positive trials for the primary endpoint. Overall survival is not demonstrated in either study and likely will never be demonstrated because of the nature of the population and the

fact that many of these patients will ultimately cross over ultimately to other therapies which can make people live longer.

So, this is the adverse events for the apalutamide study. I call your attention to a couple of things – and my colleague no doubt will talk about this in greater deal, so I will not dwell on it – you want to always look for at the fall and fracture rate for drugs in this class because of the cognitive dysfunction. So, one of the downstream impacts of that is fall and fracture rates. This particular compound also has an unusual rash that goes along with it, which can be annoying to patients, as well as hypothyroidism. That's not a class effect; you don't see that with enzalutamide.

This is the enzalutamide toxicity. And, again, enzalutamide has been around a long time; it has known CNS toxicity, as well as the associated fall and fracture rates. In this particular study there was a slightly higher – and somewhat disconcerting – cardiovascular morbidity rate. Again, this is a drug that's been around a long time, so what that ultimately means in the larger context of managing patients with this drug is not clear.

All right, so where we stand in 2018 is there was a press release about last week, darolutamide – which is another AR antagonist – similar trial to the two trials that I've shown you – press release suggesting it met its primary endpoint, which is metastasis-free survival. That study will either be published in a significant medical journal first or presented probably at ASCO GU, which happens in February.

So, assuming the data is similar, I would anticipate that yet another drug in this class will be approved. None of these drugs have been directly compared to each other. So, again, how to make selections is a more detailed discussion.

Let's move a little bit further down the disease course and talk about metastatic prostate cancer. This is hormone-sensitive metastatic disease. The number of patients who presented with de novo metastatic disease – meaning, they walked into clinic with metastatic prostate cancer – in 1982 was 30%. So, I started my oncology training a number of years later, but not that many years later, so I saw a lot of metastatic prostate cancer.

I work at a safety net NCI-designated center and I still see a lot of metastatic prostate cancer, but less, perhaps, than before. Whether or not the sort of change in the natural history of screening in the US has influenced that is unclear. What we know is that androgen deprivation therapy has been the standard of care for 80 years. There have been changes made to androgen deprivation therapy alone on the basis of randomized clinical. We know that if you start a patient on ADT, their nadir PSA is predictive of survival.

This is the CHAARTED study that was published now a number of years ago. Full disclosure: I am a co-author of this manuscript. This was done in the United States in patients who were considered either high volume or low volume metastatic disease. They were randomized to get androgen deprivation therapy with or without six cycles of docetaxel using standard dose and schedule. Patients were followed for survival and, in fact, there was a survival benefit that

was actually quite striking for this study, well more than a year and in a subgroup of patients about a year and a half.

This was a very striking finding. Remember that docetaxel has about a 2.5-month median improvement in survival in castrate metastatic prostate cancer patients. This is looking at both what we call high-volume disease in A, where you see the survival advantage has been maintained with longer follow-up patients with low-volume disease do not benefit. So, not all patients are appropriate candidates for docetaxel.

There was a similar trial called STAMPEDE, which is a trial done in the UK, which had a somewhat similar patient population, but also basically showed the same results. So, following the publication of both of those studies, the addition of docetaxel to many patients with hormone-sensitive metastatic disease became a standard of care.

So, let's fast forward to about 2 years ago. So, abiraterone acetate, which is a lyase inhibitor, which has been approved for castrate metastatic prostate cancer on the basis of two survival studies, was similarly studied in hormone-sensitive metastatic prostate cancer. So, one of the trials—a pharma-sponsored study—LATITUDE. And you see that the randomization is between androgen deprivation therapy in both arms, plus the addition of abiraterone plus prednisone using standard dose of abiraterone and prednisone. And, basically, this study also showed a striking survival benefit.

Now, to get in this study you had to have a little bit of high-risk disease; you had to have visceral metastases, a Gleason 8 or greater, or more than four

bone metastases. But, if you had that, you basically also showed about an 18-month improvement in survival.

A similar study called STAMPEDE again had another arm, which enrolled patients not only with metastatic disease, but locally advanced or node-positive disease similarly showed a survival benefit. So, following the publication of both of these studies, what we are left with were hormone-sensitive metastatic prostate cancer patients is the ability to improve survival on the basis of the addition of docetaxel or abiraterone.

So, the question, of course, is which one does one choose? There is no comparative data. There are differences in eligibility, so if this is a high-volume patient who could either meet the criteria for CHAARTED docetaxel or LATITUDE, then either therapy is reasonable. And this is a risk benefit discussion; we're talking about 2 years of abiraterone versus six cycles of docetaxel.

I will tell you that depending on where you are in the country, my colleagues that are on the New York or San Francisco sort of academic centers tell me that 80 to 90% of their patients opt for abiraterone. Again, I work at an NCI-designated, but safety net hospital and it's closer to 50/50 and I think it has to do with, you know, one, men hating to take pills, and, two, the reality is that it may be folks of a certain socioeconomic class are more interested in getting therapy over in a more rapid timeframe. Either way, we don't know what the right answer is.

There is a host of prospective trials looking at these questions and adding additional therapy – docetaxel plus an AR, antagonist, or abiraterone – to ask the question for very high-risk patients, does adding both of these therapies impact on outcome? As of today, that data is not available and, therefore, that should not be routine clinical practice; you make a choice, you discuss it with the patient, you press on.

And this is the toxicity profile. And those of you who use abiraterone recognize that it's relatively a well-tolerated drug. And if you mitigate the mineralocorticoid side effects with glucocorticoids, you really don't have much in the way of toxicities. Although, again, over a two-year period of time, issues like hypertension and fatigue can be an issue and, you know, a lot of these folks have cardiac disease as an underlying condition.

This is the STAMPEDE study; again, similar results. And failure from disease progression. So, again, these are really compelling changes in the natural history of the disease.

And this is looking at some of the characteristics of patients who are enrolled in CHAARTED, LATITUDE, and STAMPEDE, and it gives you a little bit of a chart like this when you sit with a patient, there are some patients who, again, have very low-risk disease who probably don't merit either agent given the toxicity and lack of benefit. Most patients will likely fit the criteria for one or both studies and this may give you some insight in terms of how to counsel a patient.

And this is just more data, including a couple of other studies, really looking at the high-risk patients. And what you see is high-volume, poor risk. If

you look at the hazard ratios, you're talking about 35 to 40% reduction in death. This is enormously impactful in solid tumor oncology where many of the studies that we have improve survival within a couple of months. This is approaching a year and a half of improvement in survival; it is really unparallel to most of what we do in medical oncology.

So, the initial management of patients with metastatic prostate cancer. Again, you see for high-volume patients, either abi or docetaxel given the lack of comparative data issues, like economics. And getting co-pays for patients with abiraterone is always a challenge depending on where you are and what time of the year you're trying to prescribe.

Duration of therapy, the toxicity, and the patient's world view. "My Aunt Emma had chemotherapy; I'll never have that, ever." So, okay, that patient's not likely to use docetaxel. Low-volume patients probably have less benefit from docetaxel and may be better choices for abiraterone or in some instances, no therapy in addition to androgen deprivation therapy.

So, in the last couple of minutes, let me just move to an area that is in rapid evolution and that is the genomics of prostate cancer. So, if I was doing this for you 2 years ago, I would not have even included a section in a short talk because I wouldn't have deemed it important. So, let's remember that when we think about genomics and our patients, that there are germline – comes from mom and dad – and there's somatic mutations that are inherited. We know that important mutations in prostate cancer are both germline, as well as somatic.

This graph shows a number of different what we call homologous recombinant repair mutations, the most common of which are *BRCA2* and *1*, *ATM*, and a couple of others. This was a study that was published in the *New England Journal of Medicine* now 3 years ago, which demonstrated that patients who had those homologous recombinant repair mutations – many of these patients were heavily treated with other therapies – had a very significant response to the drug olaparib, one of the PARP inhibitors targeted against *BRCA*. So, that led to a fair amount of excitement.

This is a very small study, but to get into the *New England Journal of Medicine,* it has to be a novel mechanism, a novel observation, and something that's new and different. All of those were the case, which is why a study that was less than 200 patients went on its way into the *New England Journal of Medicine*. And you can see all of this was not powered for survival, but you could see that those patients who got olaparib had a very significant impact. And this, again, is a very heavily treated group of patients.

So, with regards to germline, why is it important for our patients? Well, obviously, it speaks to family risk. It also probably impacts on treatment choices over time. What we've learned in prostate cancer is that anywhere from about 8 to 12% of our patients harbor germline homologous recombinant repair mutations. My practice has evolved to the point where if a patient walks in with de novo metastatic disease, right? This is not a patient who had a prostatectomy 7 years ago and evolved, it's, "I'm here for the first time, doc, and I've got

metastatic disease." I've essentially begun to do germline testing in almost all of these patients not only to define their risk, but to speak to their family's risk.

Somatic mutations are a different issue. And this is a series of data that comes from a number of different sources, including the Human Genome Project. We think about a quarter of patients with castrate metastatic prostate cancer have homologous recombinant repair mutations. The most common of those are *BRCA2*. So, *BRCA2, BRCA1, ATM* probably represent anywhere from 10 to 15% of castrate metastatic patients.

This is the inherited mutations. And as you see on the bottom, localized disease, so, as you walk backwards earlier in the disease course. We have less information with regards to the prevalence of germline mutations.

So, this is why DNA repair is a therapeutic target because PARP basically inhibits the ability for these double-strand DNA breaks to be repaired. That's why PARP inhibitors, as well as cisplatin or platinum because of the potential for it to hit the same place, may be drugs that have more activity, especially in prostate cancer where platinum is not routinely used, but platinum's in patients who express HRR mutations may have viable utility.

When you look at mismatch repair – all right, so prostate cancer compared to say, lung cancer or urothelial cancer has a lower mutational burden. Despite that, we know that patients who express MSI-high prostate cancer – and, again, this is mostly from the colon cancer literature – but, if you express that in prostate cancer – which is probably 2 to 3% of patients – you have the ability to receive pembrolizumab because of its pan-approval across solid tumor. So, again, MSI-

high testing is increasingly being thought of because of the potential to use the checkpoint inhibitor. The incidence, again, is relatively small.

So, this is, again, more data suggesting the prevalence. I will tell you that in my own clinical practice, I am now very commonly—as a patient evolves the castrate metastatic disease—doing somatic mutation testing. Remember that 70% of patients with prostate cancer have bone-only disease, so I tend to use liquid biopsies because of the difficulty of doing bone biopsies. Liquid biopsies, I think, are reasonable strategies and as the technology improves, that's probably how we're going to be testing almost everybody because of the inability to have available tissue. You know, if you've had a patient who had a radical prostatectomy 14 years ago, sending that tissue off for somatic mutation testing is probably not viable and, therefore, any number of commercial assays are available for liquid biopsies.

This is an interesting paper that was published earlier this year. This came from the West Coast Dream Team, which is a number of big academic centers. And this is about concordance. So, what they did was they took fresh tissue from a number of patients and they sent it off using a number of different commercial assays to do somatic testing. And they did the same thing in the same patient with liquid biopsies. And what this basically showed was there was pretty high concordance with the ability to identify homologous recombinant repair mutations with a liquid biopsy. So, while it isn't a definitive comparison, to me it is a viable comparison to suggest that I can spare my patients either bone biopsies or, frankly, even sticking a needle in nodes to get tissue.

So, among the things that we have sorted out – and this is a very rapidly moving field – there are at least 12 trials ongoing of four different PARP inhibitors in this space. It would not surprise me that within 12 to 18 months, one or two or three agents will be approved. Once PARPs are approved in prostate cancer, clinicians are going to start testing somatically because the reality is you will not be able to administer this drug probably without demonstrating the HRR. So, this is something that many clinical practices haven't really begun to do because, again, up until very recently, there wasn't a particularly good rationale to do it. So, this is something that will have to be discussed internally in all your practices and sort out how optimally to do that.

So, with that, I'm going to stop and try to give you back 2 minutes of your afternoon because I know it's Friday in Florida. Thank you very much for the invitation.

DR. DIVEN All right. So, I'm going to talk a little bit about the management of medication toxicities. And as Dr. Dreicer mentioned, so many of these are toxicities that we are pretty used to managing or evaluating in all of our cancer patients, especially in our prostate cancer patients. But I'm going to go through the medications.

Just to let you know, the way I arranged them was sort of by the oral agents first, so apalutamide, abiraterone, and enzalutamide and then docetaxel and then our niche market – you know, niche medications like olaparib and pembrolizumab. And after I go through the medications, I'm going to talk about some general side effect toxicity monitoring tips.

So, apalutamide is dosed at 240 mg once daily with or without food. I do think it's always important to remember for our patients whether medications need to be administered with or without food, especially I firmly believe that patients taking pills on an empty stomach makes them nauseous. It does for me, so I figure it does for most of my patients, as well. So, if I can have a patient take their medication with food, I think that helps them a bit.

It's important to remember apalutamide has not been studied in patients with a Child-Pugh class C, hepatic dysfunction, or an eGFR less than 29. So, there are pretty common side effects. You can see rash is in this, which isn't necessarily in some of the other classes of medications that we use. It is most commonly maculopapular rash. You can manage it with topical corticosteroids or holding a dose or a dose reduction if needed if it's problematic for the patient. Of course, there is the concern for falls and fractures, the thyroid dysfunction; both of those Dr. Dreicer talked about. And there is some concern for a QT prolongation.

Now, I work at the Phoenix VA where we have a national monitoring document that comes out based on the PI and national data. So, this is the monitoring as we do in our facilities.

Now, abiraterone we've all used for quite some time, so it's 1,000 mg daily with prednisone; 5 mg once a day in the castration-sensitive setting; twice daily in the castration-resistant setting. It's important to note there is a different formulation. The 1,000 mg daily is the Zytiga formulation, whereas there is a

Yonsa formulation that can be given with or without food, and the glucocorticoid with that is methylprednisolone.

Now, the abiraterone—the Zytiga formulation—are large tablets; they're film-coated tablets that patients have to take two or four of depending on the strength that you're using. The abiraterone—the Zytiga formulation—does need to be taken on an empty stomach, which means 1 hour before or 2 hours after food or other medications. So, this can get to be a little bit difficult for patients who are on other medications that need to be on an empty stomach. Sometimes a good hunk of my counseling with patients is spent organizing when they take all of their medications.

Most of my patients wake up in the morning, take their abiraterone, they wait an hour, they eat something, and take their prednisone because we do want our patients to take prednisone with food. But occasionally I do have patients who need to take their abiraterone at midday or in the evening; it just needs to still be on an empty stomach.

One thing I do tell patients about all of our oral agents is that the most important thing for me is for them to pick a time that they'll remember when to take the medication as opposed to is it better in the morning or the evening or the middle of the day. I want them to remember to take it as opposed to worrying about is it better in one part or the other. Abiraterone does need to be dose adjusted for hepatic dysfunction and there's no renal dose adjustment needed.

We're pretty familiar with most of the side effects that are seen in abiraterone and then I have the monitoring listed below. You will notice that we

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do every-2-week LFTs; that's because of the hepatotoxicity risk. I haven't had it happen often, but I have had a couple patients come back with hepatotoxicity 2 to 4 weeks after starting abiraterone. So, I work really hard to make sure our patients actually get their LFTs checked, although they're not always so happy about going to get their blood drawn that often.

Enzalutamide is four large gel capsules taken together once a day with or without food. They are pretty good-sized gel capsules if you haven't seen them. So, again, abiraterone—the Zytiga formation—is tablets, enzalutamide is gel capsules, so part of my counseling is always, "How do you do at swallowing pills?" Sometimes in my patient population that will sort of push us to use one medication over the other.

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Enzalutamide does have more CNS toxicities than abiraterone does. In my experience, I've had patients who have had severe dizziness, increased falls when they've been on enzalutamide, CNS confusion. These are things that when we stop the enzalutamide, it resolves. And if we rechallenge them with enzalutamide, it returns, so they don't get that medication. And I think it's something that sort of snuck up on a lot of us about the CNS side effects of enzalutamide, so it's always important to remember.

Docetaxel we've used for a long time. It does need to be dose adjusted or not used in certain hepatic dysfunction settings, but there's no renal dose adjustments needed. We do have issues with fluid retention, hypersensitivity reactions, peripheral neuropathy over time, and fatigue. And, of course, we need to check a CBC and a CMP prior to each cycle.

Now, as I mentioned, we are going to get into some of the more niche medications, so olaparib is dosed at 400 mg by mouth twice daily with or without food, but no grapefruit. And in my part of the world, that sometimes becomes a big issue for patients. I've had a number of patients who love grapefruit, have a bunch of grapefruit trees, and me telling them they can't have grapefruit—not with olaparib, but with other medications—is sort of a tough pill to swallow so to speak.

And I usually tell them a personal anecdote. My father-in-law loved grapefruit. He had a giant grapefruit in his backyard and he got put on a medication he couldn't eat grapefruit anymore and it just made him so mad to see his grapefruit tree with these beautiful grapefruit and he couldn't—we can't give it away in Phoenix—like no one takes it—so, he was just so upset.

So, finally, one day he went and he cut down his grapefruit tree. Yeah. But what he found was that when he had planted his grapefruit tree 40 some odd years ago, he had planted it in a corner of his yard that blocked the view of the mountains in Phoenix, so when he took it down, he had this beautiful view of the mountains in Phoenix that many people would just do about anything to get. So, I tell this to my patients as, "Maybe we'll find a silver lining for you not being able to have your grapefruit." I don't know, not all of them have found it, but –

The other thing that's important in my part of the world is these patients cannot take the olaparib if it's exposed to temperatures greater than 104 degrees Fahrenheit, which leads to some very intriguing ways of getting patients their medications when it's 122 outside. Most of my patients live very far away, but all

of our medications – or we have temperature explosion data, but it doesn't usually go up to 122 and it certainly does not cover the temperature that is in the UPS truck or the postal service truck while they're out making deliveries in that weather. So, we do a lot with sending our medications out UPS overnight with icepacks even if they're not refrigerated or having patients come to get them, if possible. So, with olaparib it's important to remember that temperature greater than 104.

So, the side effects and monitoring. You can kind of see the recommendations here and the most common and worrisome side effects. And pembrolizumab we have growing experience with, lots and lots. It is given every 3 weeks and in this indication it's for MSI-high tumors. And as Dr. Dreicer mentioned, it's sort of an exciting time in oncology because we have a drug that is not approved based on histology. So, it's not just prostate cancer or just colon cancer, it's a marker in the tumor.

It's important to know it's not been studied in moderate or severe hepatic dysfunction and the definitions are there. And there's no dose adjustment needed for rental dysfunction. We have lots of common side effects that freak out our patients when we go through the – these are the common ones and they sound a lot like they're really scary immune-related side effects, but part of that is just going through the side effects with the patients and letting them know when to give us a call.

Okay, so sort of the whirlwind for the specific medications. But, what I wanted to spend a little time on was the general side effect management that

wasn't – and I could have gone through fatigue for each of those medications, but that just wouldn't have been as much fun, I guess. So, I'm going to cover three big ones; I'm going to talk about hot flashes, fatigue, and bone health, which isn't necessarily a true side effect patients complain of, but it is something we get brought into helping manage.

So, as we know, hot flashes are common in our prostate cancer patients. We know it can affect a lot of their day-to-day lives and make them pretty miserable. There's a nonpharmacologic treatment or things patients can do at home, so avoiding alcohol, caffeine, cigarettes, heat – it's sort of tough for my patients – hot beverages, spicy foods, tight clothing.

I have a patient who has had horrible hot flashes kind of all along and he doesn't want to try anything to help with it – and we'll talk about pharmaco therapy options in a moment – but, eventually I convinced him to keep a log of when he got his really bad hot flashes. Well, he's from New Orleans originally and he really likes his spicy food.

So, sure enough, every time he had a horrible hot flash, it happened to be after he ate some of his good spicy food. And when we talked about, "Well, you could cut the spice out," he said, "No, I'm from New Orleans, I wouldn't do that." So, he's just mentally prepared that he's going to have hot flashes after he gets his food.

You can also do acupuncture, relaxation techniques, cooler room temperature, which is a really good option if a patient can and can afford to. So,

again, when it's 122 outside, cooling down the house can be quite costly and difficult and then they have to walk outside to go somewhere.

So, there are some studies looking at pharmacologic therapies for hot flashes. I'm going to highlight two studies. The first one was about 1,000 patients. They looked at venlafaxine versus medroxyprogesterone versus cyproterone, which I can say every other oncologic medication known to mankind doesn't trip me up, but cyproterone really does. Go figure. No matter how many times I've practiced. What they found is they all decrease hot flash scores from baseline and that cyproterone and medroxyprogesterone were better than venlafaxine, but cyproterone is not available in the United States.

Another study in about 200 patients looked at gabapentin 300 mg at bedtime versus gabapentin titrated to 300 mg three times a day versus placebo. And what they found was gabapentin did better than placebo in reducing hot flash scores. More was actually better in the gabapentin arm, so 900 mg a day was better than 300. And gabapentin was well tolerated with similar side effects seen to placebo.

So, just in summary, we do have some treatment options. Venlafaxine in the study they did use the ER formulation. I do end up transitioning to that with my patients, but typically we start with more of a short-acting version before we move up to the long-acting.

The most common side effects are nausea, appetite loss – which is not always a good a thing in our patients – and constipation. And it's important to remember venlafaxine is one of those medications you have to tell patients, "Do

not stop it cold turkey." It really can cause patients to have lots of issues and side effects if they don't taper off of the medication.

And another personal story. My mom was on a high dose of venlafaxine for hot flashes and she was getting tapered off of it. And she was about 3 weeks from being done and she just got frustrated and so, she just stopped it. And a few weeks later she calls me and she says, "You know, I've felt horrible. I've felt really horrible for the last couple of weeks. I'm irritable, I'm cranky, and I'm not sleeping well, and nah, nah, nah, nah, nah." And so, we talked through it and, finally, I said, "Well, how is your venlafaxine taper going?" She said, "Ah, I just stopped it." "Oh, that's why you felt so crummy." And she said, "Uh. Because I'm starting to feel better now, should I restart the venlafaxine?" "No. No, you've gotten through the worst of it, just power through the last little bit."

But, especially my patient population – you know, we'll have patients take medications and then some will just decide, "Ah, I don't want to take it anymore." So, I do spend a lot of time telling them on venlafaxine, "Do not do that. You need to call me first."

Gabapentin we titrate up. I tell patients that we use gabapentin first as an antiseizure medication. It didn't really work as well as we'd like, but we use it for other things now and we get to use it at lower doses. So, of course, as with all of our pharmacy dispensing, they get the nice, thick packet of every single potential side effect that might possibly happen. But, in gabapentin at the doses we use, it's really dizziness and drowsiness and that tends to get better after about 3

days, which is why we do the titration up. And then once they're on a stable dose, they tend to do pretty well.

And then you can take medroxyprogesterone, as well. You do get increased weight, but also can have vascular disorders. And in all honesty, in my patient population my most common agents are gabapentin and venlafaxine.

Fatigue. All of our cancer patients have it; it's rarely an isolate symptom. So, something I think we get so used to hearing that they're tired and we know chemotherapy or treatment for cancer makes them tired and we're kind of like, "Yeah, I know you're tired." But it's always good to kind of go back and make sure some of the other things that could be making them fatigued haven't changed since the last time we talked to the patient. So, it's rarely an isolate symptom. They can have emotional distress, anemia, sleep disturbances, poor nutrition, decreased functional status, medications, comorbidities that are all kind of contributing to that.

It's important to take a look at all of those potential comorbidities and other issues that could be going on and trying to get them under control. I think sometimes depression or anxiety sort of goes a little bit unnoticed. Patients don't always want to fess up to that, so spending a lot of time asking about depression type symptoms can help.

I tell all of my patients who get started on any type of oncolytic therapy the three best things to help with fatigue related to oncolytic therapy, which is to drink plenty of water. And if your patients are anything like mine, they say, "Oh, I drink a bunch." "Okay, how much do you drink?" "Three glasses this big." "No, that

doesn't work. We live in Phoenix, it's no humidity, we're dehydrated at the moment we wake up. You need to do more."

Also, resting when their body says to rest. A lot of my patients are all ex-military; a lot of them do powerful mind over matter. "I'll power through this, I don't need to take a rest." So, I use the example, "You have 10 things on your to-do list, you're at thing number five, you need to take a rest when your body says to take a rest. Don't do what I would do and push through those last five things thinking when it's all done, I'll take a rest. You need to do it then." And I usually spend quite a bit of time telling them, "It's okay. You might not get as much done, you may not get all of your to-do list done, but don't be discouraged. You actually need to listen to yourself."

The other thing, too, is the flip side of that coin, which is getting up and getting moving. And, you know, I tell patients, "We sit all day watching TV and we get to binge watch Netflix or something." I don't, but, you know, something exciting. And at the end of the day you stand up and you think, "Oh, I'm going to have so much energy, I'm probably not going to go to sleep." But we're all more tired.

It's the exact same thing in fatigue from oncolytic treatment, so getting up and getting moving – some of my patients, that may mean walking to the mailbox and back, so they may not go very far. But I have another patient who swims for 45 minutes in the morning and then he does, you know, a 2-hour walk in the evening and he's out gardening and, you know, he said, "Do I have to stop all of

this?" "No, you don't, but you may not be able to do as much, go as far, or go as fast."

And then there's pharmacologic treatments. So, unfortunately, though, what I tell patients is most of our pharmacologic treatments are less than exciting when it comes to fixing fatigue. So, methylphenidate has been evaluated in a number of trials. Two of them showed efficacy, but we had issues with appetite suppression, so if you have someone with baseline poor nutrition, that's not really great. Dextroamphetamine really didn't have any benefit. Modafinil did, but I don't have many patients that actually really have tried it.

And then the last of the kind of general topics is bone health. As we know, androgen deprivation therapy decreases bone mineral density and increases the risk of bone fractures in men with prostate cancer. There are some lifestyle preventions, so it's always a good thing to remind patients if there's things that they can do to actually help support their bones. And, of course, if they have bone metastases, you can consider bisphosphonate or denosumab.

What I will say is I know denosumab has statically significant data, but when you look at the four individual parts of the composite endpoint, the statistical significance was only in delaying the time to radiation, not in decreasing pathologic fractures, skeletal cord compression – or spinal cord compression, or time to surgery. So, in my practice we have most of our patients on bisphosphonate with very few on denosumab.

Now, between pamidronate—which doesn't get used very much—and zoledronic acid – zoledronic acid has a dose-dependent renal toxicity, so patients

do need to have their zoledronic acid dose adjusted for their renal function. And occasionally I get a patient who gets their zoledronic acid, they end up in the emergency room a few days later. And, of course, the emergency room blames anything and everything they can on the ONC Department, so, zoledronic acid becomes a fall guy for a whole lot of things. But, we do have patients that do get infusion reactions that kind of feel crummy, more run down, after they get zoledronic acid, but that's something that actually gets better with each infusion. And remember, too, we do have data for using zoledronic acid every 3 months now, so you can kind of space it out a bit.

The most important thing I would bring up is that I think using denosumab versus zoledronic acid is a discussion point. There is a significant cost difference, but in my world, I don't get insurance reimbursement. It's a little bit different than outside of the VA, so just important to remember.

I did list the calcium and vitamin D supplementation. I think it's something that sometimes gets forgotten in all the other things we're adding to patients as we're getting them started on therapy and so, just remembering that they do need calcium and vitamin D supplementation.

So, as I mentioned, I work at the VA and I do believe when all other things are equal, you look at cost. And I think when it comes to our oncolytic agents you also have to look at administration and other kinds of considerations. So, I put up a little chart here of the available medications that we talked about today and their up-to-date pricing. Now, I know, up-to-date, it's not always accurate; it's way

above what it usually is because we all have contracts and all that good stuff, but it's the most uniform pricing I can find.

So, Xenogen apalutamide is four tablets daily with or without food. Abiraterone is four or two tablets on an empty stomach. The Yonsa formulation is with or without food and the enzalutamide are the capsules with or without food. And you can see based on up-to-date pricing, all of those are in the pretty much similar cost per month.

Comment [KM4]: Left brand names

Docetaxel is by far our cheapest, about a little under $400 per dose. Olaparib is our most expensive, but in the right patient that's still a really good option. And pembrolizumab is actually right down there with docetaxel in terms of its price per cycle.

So, in summary, our current agents for prostate cancer are generally well tolerated with manageable toxicities. It's important to consider the patient when you're looking between the available agents. And I know I put oral here, but with all of them it's important to look at possible issues for each of them with a patient.

And then I always like to remind people that when they're not getting IV oncolytics, when they're getting oral oncolytics, patients kind of – hopefully they show up, we set appointments, say, "Come and back and see us," they may or may not. When they're getting IV oncolytics they're seeing us at the biggest distance; it's every 3 weeks – 3 or 4.

And so, that's when, you know, patients have everyone lay eyes on them. The nurses do, their providers do, social work, dieticians; everyone's in there and they kind of say, "Woo, that doesn't look so good, we need to make an

intervention." Whereas, if they're on oral oncolytics, we may not get to see that. And something we've worked hard in our clinic with is making sure all of our oral oncolytic patients are tied in with social work, our dietician, as well as the pharmacist – that's me.

So, I always remind people to utilize all the support that we have for cancer patients to help get them taken care of, and that includes primary care and specialists.

And about 7 minutes left in your afternoon, so –

FEMALE We have one question here.

DR. DIVEN Oh, yes. Okay.

FEMALE Hi, thank you for your talk. I know it's not FDA approved yet, but can you comment on the dosing of abiraterone at 250 mg per day with food?

DR. DIVEN The Yonsa formulation, it's a different as I understand it, and in all honesty haven't used it, but it's a microparticle formulation that allows it to be a slightly lower dose and be taken with food. But that's as best as I can understand it. Does that answer your question? No?

Comment [KM5]: Left brand name

FEMALE – not too long ago that had – we talked about using the 200 because the cost is so high –

DR. DIVEN Oh.

FEMALE – by taking it with –

DR. DIVEN With food because taking the –

FEMALE Take less of it?

DR. DIVEN Yeah, the abiraterone – taking it with food does increase the AUC, the regular Zytiga formulation, so there has been some hope with taking it lower dose with food. But, I haven't used that either at this point. I'd love to for our patients.

Comment [KM6]: Left brand name

FEMALE I have a question about bicalutamide.

DR. DIVEN Yes.

FEMALE Abiraterone was compared to ADT alone versus abiraterone plus ADT.

DR. DIVEN Mm-hmm.

FEMALE What about bicalutamide; is that too old? Could you comment?

DR. DIVEN I'll do my best. Oh, that's a good question. I don't think that bicalutamide is necessarily too old, I think they're just sort of looking at these subsets of patients for where you would use maybe something a bit stronger.

FEMALE It would be interesting to see the pricing of bicalutamide on your –

DR. DIVEN Oh, bicalutamide is way cheaper.

FEMALE Yeah. I think that's a really big jump. Like that should be there.

DR. DIVEN It is.

FEMALE That should be what abiraterone is compared to – abiraterone and ADT compared to bicalutamide and ADT.

DR. DIVEN Right.

FEMALE That doesn't make sense.

DR. DIVEN I would have loved to have seen that trial.

FEMALE I have a question. Thank you for your talk. It's kind of a little off point, but talking about the calcium and how you recommend it always, you know, taking calcium with the zoledronic acid or the denosumab, but at what point – talking about hypocalcemia and seeing hypocalcemia in these patients that are receiving this agent, at what point do you hold or delay a zoledronic acid or denosumab dose based on hypocalcemia?

DR. DIVEN That's a good question. In all honesty, I haven't run into an issue where the hypocalcemia has been the reason for holding or delaying a dose. Most of my patients tend to end towards hyper, so that's when we watch it a bit more with their calcium supplementation.

FEMALE Okay.

DR. DIVEN Yeah. Good question.

FEMALE I think that's it.

DR. DIVEN All right, thank you.

MODERATOR All right, really quickly. Thank you, Morgane, for the great talk.

[END]