Podcast Episode Title: Shared decision-making in nmCRPC: Treatment considerations to maintain quality of life

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This GU NURSES CONNECT programme is supported through an independent educational grant from Bayer is an initiative of COR2ED.

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Transcript

Brenda Martone
Hello and welcome to this podcast discussing 'Shared decision making and non-metastatic CRPC: treatment considerations to maintain quality of life'. I'm Brenda Martone and I'm a nurse practitioner at Northwestern Medicine in Chicago, Illinois, and I am delighted to be joined today by Dr. Alicia Morgans. Alicia, would you like to introduce yourself?

Dr Alicia Morgans
Thanks so much, Brenda. My name is Alicia Morgans, and I'm a GU medical oncologist at Dana-Farber Cancer Institute in Boston in the United States. And I'm so excited to be here today. Full disclosure, I used to work very closely with you at Northwestern, so I'm really excited to reconnect and talk about patient care with you.

Brenda Martone
Me too. So, to get started we know that shared decision making between the patients and the physician is key. The patient needs to understand they have choices, and by understanding the implications of each treatment, they are more likely to be able to adhere to the treatment plan. As a nurse, it is essential to have an up-to-date knowledge on the disease and common symptoms, key data and studies, treatment aims and options as well as potential side effects and how we can proactively manage these. So, with this in mind, perhaps we should start off by understanding what is non-metastatic CRPC and how these patients present.

Dr Alicia Morgans
Sure, I agree. That's a great place to start, Brenda, because I think there's a lot of misclassification of non-metastatic castration resistant prostate cancer in our day to day practice. And a lot of discussion around this. As with any situation where we have castration-resistant prostate cancer, there's a rising PSA in the setting of castrate levels of testosterone during treatment with androgen deprivation therapy. And typically castrate levels of testosterone are considered 50 nanograms per decilitre. There also has to be no evidence of metastatic disease unconventional radiographic imaging, and that would be bone scan and CT scans or MRI scans, if you prefer to use those rather than CT scans.

This does not include no evidence of metastatic disease by PSMA or other PET imaging strategy, and I really want to emphasise that - that's no radiographic evidence of metastatic disease by conventional, traditional imaging. Usually, these patients are asymptomatic and some of the biggest decisions we make are when do we actually treat these patients? The ones at highest risk are usually the ones that need to have treatment. And those are, again, patients who are still receiving androgen deprivation therapy, but have this rising PSA with a PSA doubling time that is ten months or less. And these patients are at highest risk for developing metastatic disease or dying from their prostate cancer and are typically the ones that we really want to make sure we target when we're using treatment.

Brenda Martone
Thanks, Alicia. As you've said, and I see in my clinical practice also, our non-metastatic CRPC patients are relatively asymptomatic and it's important for us as providers and physicians and nurses to understand what the patient goals of treatment are when making treatment decisions. And there are several things that we've seen in clinical practice as well as in clinic. Different things may actually influence patients' decisions. Some patients may be less focussed on longevity due to their age. And may opt not to begin of treatment for non-metastatic CRPC.

Maybe they're really concerned about maintaining a quality of life right now and looking at that side effect profile, the risks and the benefits of treatment lend more towards their decision to continue off treatment due to their quality of life. And kind of keeping that in mind, they may be focussed on being well enough to attend a family event, such as a wedding or seeing a new grandchild. So, asking patients sometimes when we do present the options and they defer to begin treatment, asking them if they would share what kind of led to that decision so we can understand what their thinking is and be supportive of them. They may have concerns regarding their other health issues and how these treatments and side effects may impact them. And always the patient's goals and preferences may change over time.

So, it's important for us when we're seeing patients in the clinic, both you and I know, to continually touch base with that patient and find out where they are today. And with that, we can help them decide, you know, treatment goals, benefits, treatment management strategies, just because a patient made a decision regarding starting a treatment or not, in the past doesn't mean that that's not where they are today or that's not always where they are today. So again, just revisiting that so we can help our patients make the best decisions and provide our patients with the best outcomes. Alicia, I'm interested to hear your thoughts about this and how the goals of treatment may differ from a physician's perspective.

Dr Alicia Morgans
Well, I think that you just went through such an important list of what patients might think about, what their families might think about. And those are always going to be the primary things that we need to sort out and talk through. But physicians are also thinking about other aspects of treatment that are going to, I think, affect the treatment decision. Certainly, we want to try to help our patients live longer and we want to delay the time until metastases occur again by those conventional radiographic imaging strategies that we use. Of course, when those metastatic sites do occur, patients tend to have a poor prognosis, especially if they're associated with the development of pain. And that's been demonstrated time and again in multiple clinical trials.

Additionally, when metastatic disease occurs in the bone, patients can develop skeletal related events that can lead to a shortened life expectancy, but also can cause a lot of pain and limitations in terms of mobility and the ability of patients to take care of themselves and quality of life considerations, in addition to disease control considerations, are of utmost importance to physicians, just as they are to patients. I think we always want to balance the risk of benefit with risk of harm. And I would say importantly that the treatments we have for non-metastatic CRPC generally seem to maintain or improve patient related quality of life or patient reported quality of life during treatment. So that's so important too because we can feel confident that we might be using a more intensive treatment combination against the cancer, but the patient himself actually will probably feel at least as well, if not better.

And finally, from a physicians perspective, and you know this well, Brenda, we also have to think about drug:drug interactions and patient co-morbidities so that we can try to be sure that whatever we're prescribing is actually going to be tolerable for the patient. And we're still going to be able to manage the co-morbid diseases that the patient is dealing with. And having a clearance in terms of drug:drug interactions when we're prescribing medicines is always really critical.

Brenda Martone
Some great points there, Alicia. As you know, the treatment of non-metastatic CRPC has changed significantly over the past few years and we have the introduction of multiple second-generation AR inhibitors, which are androgen receptor inhibitors, and these include enzalutamide, darolutamide, and apalutamide. Could you perhaps give us an overview of the available treatments, the key data that nurses should know, or it would be important for nurses to know so that we can support our patients' discussions and support them through side effect management.

Dr Alicia Morgans
Absolutely. So, the three drugs that you mentioned were tested in three phase 3 registrational clinical trials. Apalutamide was assessed in SPARTAN, enzalutamide was assessed in PROSPER and darolutamide was assessed in ARAMIS. And these three trials all had very similar designs and really very similar outcomes. The primary outcome of each trial, which included patients with non-metastatic castration resistant prostate cancer was the development of metastasis or metastasis-free survival. So, all of these patients were enrolled and were randomised to continue treatment with ADT or placebo versus ADT and apalutamide, darolutamide or enzalutamide depending on the trial. And metastasis-free survival was prolonged in all of these studies with the addition of apalutamide, enzalutamide or darolutamide to the ADT backbone as compared to ADT alone. So that combination strategy really prolonged the time to the development of metastasis by about two years, which is hugely important, as we've already talked about.

Also importantly, though, patients who are on the control arm, which again was ADT and placebo, actually very commonly crossed over at the time of progression to treatment with an androgen receptor targeted type agent. So essentially crossed over to the other arm in many, many, many cases. But despite that crossover, the initiation at a later time point of a really highly effective treatment for their prostate cancer, overall survival was actually prolonged in all of these trials. And patients who had the earlier start of intensified treatment with apalutamide, enzalutamide or darolutamide had better survival. That's the bottom line. So I think importantly, that was consistent across all trials. And importantly, as I said before, quality of life was maintained for the majority of patients. There were definitely some side effects that we need to think about. Apalutamide tested in SPARTAN, was associated with the development of rash at a bit of a higher rate than we would expect with the other agents and certainly higher than placebo, which is what was compared in that trial.

Additionally, hypothyroidism occurred associated, we believe with the apalutamide. Enzalutamide is importantly known to cross the blood brain barrier and has some risk of seizure activity for patients who have a history of seizure. So, it's those patients, patients with a history of seizure were not included in the PROSPER trial in which enzalutamide was studied. So, we did see hypertension as we have seen with enzalutamide before, and some patients developing fatigue and some cognitive type

effects in that study as well. ARAMIS was unique in these studies that included patients who could have had a seizure history. And the reason is that darolutamide does not cross the blood brain barrier. That's the androgen receptor antagonist tested in the ARAMIS trial. Importantly, there was pretty minimal risk of side effects that were really strongly elevated over those seen with placebo and ADT in this trial. There was some mild risk of fatigue, but generally it seemed that this drug was very well tolerated. I think that when we think about all of these drugs, I just want to emphasise that most patients tolerate them, but they do have these slightly different side effect profiles. And if you do have a patient with a seizure history, darolutamide is probably the drug that you're going to want to use, though of course, having a history of seizure is rare.

Brenda Martone
That's all great information. You know, in my clinical practice, when patients, like you've said, are thinking about things and then they get the printout of the side effects or they've seen commercials on TV and all these things are listed. They often become overwhelmed and they can kind of lose focus in terms of what is most common. And so we as providers, and especially the time we take with patients, we say, yes, you know, this is the list of side effects, etc, but the most common side effects that we often see in clinical practice would be sort of X, Y and Z and that really does help patients in their decision making. And they become a little less overwhelmed and a little bit more open to listening to treatment, discussion and treatment choices.

So, you mentioned some particular side effects in regards to certain agents. I wanted to take a little bit of time here to talk about the more common side effects and the things that maybe we should be considering as nurses when we're seeing our patients so we can help our patients manage them early on before they become extreme. Or before, you know, maybe there's an impact in quality of life, that is something that we, we always want to maintain their quality of life. So early identification, good patient education and good patient management strategies.

Some of the most common side effects that we can see with these second-generation AR Inhibitors quite often include fatigue. So encouraging our patients to maintain regular exercise, a healthy diet, making sure they're well hydrated and incorporate rest periods as needed. I also tell my patients that the fatigue shouldn't be so severe that they can't get dressed, can't go to the table, can't do normal things in their life. That fatigue is not expected, and they should be letting us know if they are feeling that tired. Bone health is important for these patients, making sure that my patients are on vitamin D and calcium supplements and monitoring for bone health in terms of thinning of the bone, such as osteopaenia or osteoporosis. A DEXA scan is very helpful in measuring this. And if a patient does have osteopaenia, making sure that we calculate the FRAX score to see if they're at increased risk of a fracture and bisphosphonate or denosumab therapies, these additional bone strengthening therapies may be warranted. For that FRAX score for osteopaenia, anything that is a ten-year fracture risk for any overall fracture that's greater than 20% or greater than 3% for the hip, would qualify these patients for bisphosphonates or denosumab.

Rash, as mentioned, can happen with that apalutamide. Encouraging patients to make sure they're well moisturised with good topical emollients if they do develop a rash. Oral antihistamines might be helpful, especially if it's pruritic. You can use topical corticosteroids. If the rash does become quite bothersome, you can use oral corticosteroids. I would recommend a dose interruption if oral corticosteroids are needed. Sometimes just giving that patient a little break will allow their rash to resolve and you can restart the medication.

There could be metabolic changes of course, with all of these treatments. So again, not only for fatigue is exercise helpful, but exercise and diet modifications to have a heart healthy diet, good proteins, fruits, vegetables and complex carbohydrates. Monitoring for changes in fasting glucose or LFTs is important while on treatment. Making sure patients have good cardiovascular baseline health. So, if they do have hypertension or cardiovascular disease, making sure that their blood pressure is well controlled, monitoring that blood pressure throughout treatment and also encouraging that heart healthy diet as well as exercise and good oral hydration.

There can be hot flashes, treatments to manage these can be something as simple as soy products. There are some devices on the internet where it's like a wristband, sort of like those anti-nausea wristbands, and it can send a little tap that can help with reducing the incidence and the severity of hot flashes. I've had several gentlemen say it's helpful and then I've had several say they really didn't notice anything, so it may not be beneficial for everyone. There are medications that we can use if there are hot flashes that are bothersome and of course just different strategies to make sure that they're wearing lighter clothing, maybe sleeping with a fan and just trying to help them keep them manageable.

Sexual health is another component or a potential side effect or impact just on the fact that there's no testosterone or we've greatly suppressed the testosterone. So, talking to patients and letting them know that with the testosterone suppression from androgen deprivation therapy as well as therapy intensification from one of these second-generation AR inhibitors, they will develop erectile dysfunction. They will have a loss of libido, and they may also have actual changes to the size of their genitalia. So, putting that on the side effect reviews such as, you know, when we're managing talking about fatigue, there can be some cognitive changes and just including the sexual health kind of opens that door to let the patient know that they have permission to talk about that with us. At my institution, we have a sexual health clinic. They do cognitive therapies and as well as medications. And there can be different mechanical devices and strategies to help maintain or be able to allow them to perform sexually with their partner.

And also, I always loop in their either medical, primary medical provider, their PCP, cardiologist, who else may be taking care of them before they actually get started on a medication, as Alicia mentioned, making sure about drug:drug interactions, because there can be drug:drug interactions where certain medicines are already on, maybe go up or down in strength, as well as those medications can influence the second generation AR inhibitor. Reaching out to those providers to let them know these are the potential side effects. And if we're ever concerned that there is a serious adverse event, definitely holding the medication and working that up completely.

Dr Alicia Morgans
That's a great review. My gosh, what a lot of things that you you deal with, with the team of nurses and certainly with the doctors that you work with, it's so helpful to hear you talk through all of those things. From a doctor's perspective, I am absolutely thinking about the same things and grateful to team members who are really focussing on them so intensely like you just described. There are also things in terms of medical management that you alluded to that I am also thinking about. I think that addressing reversible risk factors for cardiovascular disease, that's really important when patients are on androgen deprivation therapy generally, but also so important when we start patients on one of these additional drugs, because we know that there is some evidence that targeting the androgen receptor more intensely, at least with some of these agents, can have some increase in cardiovascular risk.

So, ensuring that we have good blood pressure control, cholesterol management, that healthy lifestyle in terms of activity and exercise as much as someone can have, as well as dietary interventions that reduce saturated fats and increase healthy green vegetables and other vegetable consumption and fibre is always really good, too.

And one of the other things that I'm constantly thinking about and really relying on my pharmacy colleagues to deal with is drug:drug interactions as I mentioned before. There are multiple medications, including things like antiplatelet agents or statins, blood pressure medications and others where we really do have to think and make sure that the medicines that we're using for prostate cancer are not going to interact with these medicines that we're using to maintain optimal health in these other domains and with their comorbid illnesses. So really running those medicines through the pharmacy and ensuring that patients have a complete list of medications as we're doing

that, to make sure we identify drug:drug interactions and then select the best treatment based on the lowest degree of drug:drug interactions, I think is really, really helpful.

I have had patients who have pre-existing thyroid issues or sensitive skin or other reasons to potentially push them from one drug to another drug or, as I mentioned before, seizure history that we want to avoid on enzalutamide and potentially don't have to consider as strongly when we have patients being treated with darolutamide because it doesn't cross the blood brain barrier. But in general, I just want to emphasise that intensification is the right thing to do. In general, patients feel better, or at least just as well as they do on the ADT that they're already on. And it's nice to know that we have options if we absolutely have to, we can always start one and then switch to an alternative if we find that things are not going to work with that particular agent. So as a nurse practitioner, Brenda, you're certainly making these treatment decisions to starting and stopping therapy. How do you approach these questions about co-morbidities?

Brenda Martone
So, your disclosure earlier that we work together, so you're not going to be surprised that I have a very similar approach as you do, just looking at all those things that you talked about, trying to find the right treatment for the right patient. And it is very exciting that we have three different agents. So, we do have an opportunity to find the right drug for the right patient based on their co-morbidities and their current medications and the side effect profile. So, I am totally in agreement and practise, very similar to what you do.

I want to thank you, Alicia. This was a great discussion. We discussed a lot of information which needs to be considered when making treatment decisions and to maintain a patient's quality of life. I think it's important that nurses ensure this information is provided in a way that is easy to understand for the patient and signpost them to additional support where appropriate. It's also important to encourage the patients to ask questions and to answer their questions as honestly as possible. Always listen to that patient, take some time just to be present with them so they can answer these questions. So perhaps we could finish off by you summarising. What you consider to be the key points for our listeners?

Dr Alicia Morgans
Great. Thank you so much, Brenda. So first and foremost, ADT alone and continuing to watch a rising PSA in the setting of non-metastatic castration resistant prostate cancer is no longer acceptable. That is not the standard of care. This is the setting where we intensify therapy if we have no radiographic evidence of metastatic disease on conventional scans. Intensify. Even if you have radiographic evidence of disease on a PSMA or other form of PET scan, that patient still qualifies as non-metastatic CRPC, intensify. It's important to do that because we can prolong metastasis free and overall survival. And it's also so important because one of the other key messages is that patients maintain or improve their quality of life as compared to ADT alone and two additional years without the development of metastases on conventional radiographic imaging is hugely powerful and important to our patients.

So we have to take these steps and intensify, make sure we support the patient through bone health assessments, as you mentioned, through monitoring their side effects and symptoms, encouraging them to have the best lives that they can have, quality of life as well as lives in terms of energy, exercise, reversible cardiovascular risk factors, doing the best things for themselves and their bodies each day, and making sure that we engage with our patients and share these decisions so that they can feel confident and empowered in their treatment choices along every step of the way.

Brenda Martone
Thanks again and I want to say thanks to our listeners. We hope you found this discussion useful.