Podcast Episode Title: Case-based discussion on which mCSPC patients benefit from early treatment intensification

Brought to you by:

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Transcript

Shilpa Gupta

Hello and welcome to this podcast covering treatment intensification for metastatic castrate-sensitive prostate cancer. Today we are going to discuss which metastatic castrate-sensitive prostate cancer patients are suitable for treatment intensification.

Tonke de Jong

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Shilpa Gupta

I'm Dr Shilpa Gupta, a genitourinary medical oncologist at the Cleveland Clinic in Cleveland, Ohio, USA and I treat all GU cancers with a special focus on prostate and bladder cancer. Today, I'm joined by my colleague and friend, Dr Fabio Schutz. Thank you for joining me Fabio, could you please introduce yourself?

Fabio Schutz

Sure Shilpa. I am Dr Fabio Schutz, a genitourinary medical oncologist focused in all areas of GU, like bladder cancer, prostate cancer, kidney cancer, testicular cancer. And I work at the BP hospital in São Paulo, Brazil.

Shilpa Gupta

Thank you. As you know, treatment intensification for metastatic CSPC patients is an area that has rapidly evolved over the last few years. We have seen treatment intensification with androgen deprivation with docetaxel from the CHARTED and the STAMPEDE trials and more recently, the use of ADT and novel hormonal androgen receptor inhibitors, including abiraterone from the LATITUDE and STAMPEDE, apalutamide from the TITAN trial and enzalutamide from the ARCHES and ENZAMET trial.

Over the past couple of years, we've gone a step further and seen this treatment intensification become a triplet therapy from the PEACE-1 and the ARASENS trial. The NCCN guidelines have been updated to include treatment intensification with triplet therapy following the ARASENS trial, and this also led to an indication for darolutamide in combination with docetaxel in metastatic CSPC patients both from the FDA and EMA.

So, with this in mind, we are going to do a dive into some of the subgroup data from these key trials and discuss how we can apply this in clinical practice. Fabio, do you want to start by giving us a summary of the PEACE-1 data?

Fabio Schutz

So very briefly, the PEACE-1 trial is a phase three trial that randomised patients with de novo metastatic castration-sensitive prostate cancer, meaning that patients with recurrent disease were not included in this trial, and they randomised the patients to standard of care. And the standard of care included ADT, androgen deprivation therapy, and docetaxel, and then they randomised the patients to receive abiraterone or abiraterone and radiotherapy or radiotherapy alone but it's not the matter of discussion here.

The results of the addition of abiraterone showed that we can improve survival of patients, both progression-free survival and overall survival of patients, meaning that it's not enough anymore to give ADT plus docetaxel alone. We learned by this trial, and also with the ARASENS trial that we're going to discuss later, that we have to add a new hormonal agent together with ADT and docetaxel.

The characteristics of this trial is that there wasn't a control arm with ADT plus new hormonal agents alone. So, we did not know the additional value of docetaxel to the backbone of ADT plus abiraterone, for example, in this trial. What we learned by this trial is that it is necessary to add the new hormone agent, in this case abiraterone, it's not enough to treat patients with ADT and docetaxel alone.

The subgroup analysis did not show any major difference including patients with low volume disease, high volume disease, or patients older than 70 years old or younger than 70-year-olds. So usually both patients or both subgroups benefit from the addition of abiraterone, and it also was safe. The adverse events profile of the trial did not show, I would say, much difference. We know the adverse events profile of adding abiraterone. We have more liver function abnormalities, we have more hypertension, but nevertheless we cannot say that it was a significant increase in the adverse events profile. So, I think this led to the understanding that we have to add abiraterone to the patients overall. And most important is that ADT plus docetaxel is not enough anymore because in the past people were discussing that some patients might do well with only ADT and docetaxel and with this trial and also with ARASENS trial, this is not true anymore.

Shilpa Gupta

Thank you for this excellent summary, Fabio, and this really has changed the way we are treating patients, especially those who are planned for chemotherapy. Right? This has answered the question that those who need docetaxel, docetaxel is not good enough, so we need to add abiraterone or, as we'll discuss in the next ARASENS trial, darolutamide, but it does not answer the question of whether docetaxel is needed or not.

And now moving on to the ARASENS trial in which darolutamide was used. This was a phase 3, double blind trial that compared the use of darolutamide and androgen deprivation therapy in combination with docetaxel to ADT and docetaxel alone in metastatic castrate-sensitive prostate cancer patients. Primary endpoint was overall survival. Secondary end points were the time to development of castrate resistant disease, time to pain progression, time to first skeletal event, time to initiation of subsequent therapy, safety and tolerability.

And in this study the darolutamide and ADT in combination with docetaxel significantly reduced the risk of death by 32.5% compared to ADT and docetaxel alone. Improvements were seen in the secondary end points besides this primary end point, and triplet therapy was well-tolerated and darolutamide did not appear to add to the toxicity. An overall survival benefit was observed in patients with synchronous or metachronous metastases. Greater benefit was seen in patients with bone metastases but was also seen in visceral metastases. And patients with non-regional lymph nodes appeared to have limited benefit. Patients irrespective of risk and volume, although patients with high volume had a greater degree of benefit, which is not unexpected. And serious adverse events were seen a little higher in the combination arm at 44.8% versus 42.3%. And many of these are known

toxicities of docetaxel, which was highest during docetaxel treatment period for both arms and progressively decreased thereafter.

Fabio, I'm interested in hearing your thoughts as to how you interpret all this data and do you believe that triplet therapy should be used for all metastatic castrate-sensitive prostate cancer patients?

Fabio Schutz

That's an excellent question, Shilpa and actually I think that the inclusion criteria of those trials, it was somewhat subjective because usually they included patients that were deemed to receive chemotherapy in the investigator's opinion. And for example, we had centers in São Paolo, for example, Brazil, that did not have access to the new hormonal agents from the public health care system that they would consider to chemotherapy just because they would be included in the trial so they could receive darolutamide, for example, or at least docetaxel.

So, this was very subjective and the same place in our clinical practice, or at least in my clinical practice. And because it's not enough to consider, for example, patients with high-risk disease or a high-volume disease because high risk disease patients with Gleason eight, nine or ten with three or four bone lesions, asymptomatic with a recurrent disease, it's not enough to consider patients for docetaxel.

But at the same time, I would consider that, to give docetaxel with new hormonal agents for those patients with perhaps very high volume, very high risk, fit enough to receive chemotherapy and are able to tolerate the chemotherapy regimen. And then we can consider those patients to receive chemotherapy. But like I said, I think that's very subjective. And if I look back in my past one year or two years of clinic, I may remember perhaps three, four or five patients I would have considered giving chemotherapy with new hormonal agents. Or I can say that I regret to not have considered chemotherapy for those patients. For example, I remember one patient I gave ADT plus abiraterone, and after six months, the patient was progressing, or meaning the patient became castration-resistant and also refractory to abiraterone in six months. It was a Gleason 10, 52-year-old. It's a very aggressive disease.

It's not enough to have only considered high volume or high-risk disease. I think that's going to be very subjective to an individual patient basis.

Shilpa Gupta

So, Fabio, I have a question for you. When you see a patient in your clinic, does the site of their metastases, whether it's in the bone or in visceral organs or in lymph nodes, also, depending on whether it's extra pelvic disease or not, does that drive you towards the use of triplet therapy?

Fabio Schutz

What I think is more important or that can suggest a more aggressive disease is patients that present with metastatic disease to the liver, for example. I would say that's more important or more aggressive disease, but I can say that's not very common, or I can say that's very rare usually because usually patients might present with metastatic disease to the lungs. I think that's more common than liver. But I don't make much difference between bone and lung usually. There is some data showing that patients with bone and lung disease metastases, usually they have a similar outcome. But patients with liver disease, they usually have a more aggressive disease and a lower survival. Nevertheless, in this regard, one important thing to mention is that, according to the STAMPEDE trial, even for those patients with the high-risk local disease and node positive disease, there is still benefit to adding new hormonal agents, in the case of STAMPEDE abiraterone has shown benefits in improving overall survival. So, like I said, even for patients with localised disease, high risk localised disease, if they don't have contraindication, I still consider giving abiraterone. But absolutely, for patients that present with high-volume and high-risk, and specifically with de novo metastatic disease and liver disease or lung disease, I think they are suitable to receive docetaxel in addition to abiraterone or darolutamide according to PEACE-1 or ARASENS trial.

But like I said previously, I think that's very subjective.

Shilpa Gupta

I totally agree. I think we now need to start focusing on which patients really benefit from triplet instead of doing this for everybody and I've also had some patients where I, in retrospect, would think triplet would have probably been better. But we are learning as we go and I think now we need to understand how will this triplet, compare to only ADT and novel hormonal therapy group and I believe some trials which are planned will address that.

So we are in agreement that not all patients require a triplet of chemotherapy, androgen deprivation therapy and novel hormonal therapy. And for many patients, just androgen deprivation and novel hormonal therapy or androgen deprivation and docetaxel might be enough. Is there any patient, Fabio, that you would not add a novel hormonal therapy to docetaxel?

Fabio Schutz

I cannot think of a patient population I would not give new hormonal agents because right now we have approved like four agents, we have abiraterone, we have enzalutamide, apalutamide and darolutamide for our patients. So, I think we have to consider the differences in adverse events profile, the cardiovascular adverse events, the neurological adverse events with enzalutamide, did dermatologic adverse events with apalutamide, the drug-drug interactions between the drugs, and that's very important because usually the elderly patient population, usually they take several medications for other health problems. So, we have to try to check the drug-drug interactions to see if one or the drug is more suitable for that patient.

Shilpa Gupta

I totally agree, you know, any time we are thinking patient may have more aggressive disease, it really makes sense to use that triplet. And my next question to you is, you know, now we've seen the data from PEACE-1, we've seen the data from ARASENS, how do you decide which regimen to go with? And I know you touched upon this based on their risk profile or, you know, comorbidities, if they have high risk cardiac condition, I usually tend to avoid abiraterone, but I would love to hear what you decide in your practice.

Fabio Schutz

I agree with you. I think I may have a personal bias here because I think regarding the different drugs, we have abiraterone being one class of drug and I can put, for example, apalutamide, darolutamide and enzalutamide in another class of drugs. We don't have much data to assume that, but I may think that abiraterone is a bit less effective than the other class agents like darolutamide, enzalutamide or apalutamide.

So usually in my practice right now, if I have the option to consider like darolutamide, enzalutamide or apalutamide I think it's better for patients. Darolutamide I think there is less drug-drug interactions. I may assume, based in the castration-resistant prostate cancer trials or non-metastatic therapy trials that perhaps darolutamide is a better tolerated drug compared to enzalutamide or apalutamide. But I cannot say that's a major difference. We have to consider that with caution because there are different trials with different times of accruals with different patient populations. So, we have to compare those trials carefully.

And what's your opinion? How do you choose between the drugs?

Shilpa Gupta

That's a great point. Many times, I'm also looking at their other comorbidities. For example, if a patient is morbidly obese or has poorly controlled diabetes, I tend to avoid abiraterone because we also have to give steroids with that. Even though I tend to reduce the prednisone to 5 milligrams. But I think it's more so, I have lately seen several patients developing some cardiac toxicities with abiraterone and I tend to just be more cautious with those with baseline toxicities. I totally agree with you that it would be good that besides our clinical discretion if we had some kind of biomarkers to guide us.

On the flip side, there are many patients, you know, very elderly patients who really don't need triplet and many times they do so much better with just ADT also. Right? You sometimes don't even need to do anything else for those patients if they have oligometastatic disease, really elderly, where, you know, prostate cancer is not going to be their biggest problem.

Fabio Schutz

Yeah, I think you are absolutely right there, and I have some patients like that. But like you said, I think usually they are elderly patients with oligometastatic disease, with recurrent disease. And that's a very important difference, for example, and I think it's important to make this clear. Usually, patients with de novo metastatic disease, meaning patients that present with metastatic disease, they usually have a much worse prognosis than patients with recurrent disease, meaning after the radical prostatectomy or after radiotherapy to the local disease in the prostate. So, I usually consider those patients with de novo metastatic disease as having a much more aggressive disease than patients with recurrent disease. But I have some patients that are frail that I may consider just as SBRT, for example, to try to delay the initiation of ADT for those patients. And I think we have the ORIOLE trial and the STOMP trial that's justified that we can delay the initiation of ADT for those patients.

What is your experience with the PET-CT-PSMA and how do you take that into consideration to classify patients in high volume compared to the older imaging techniques that we have?

Shilpa Gupta

That's a great question, Fabio, and I know you've been way ahead of the US in terms of availability of PSMA-PET. We just got it last year and many times here, you know, we are not able to get it for every patient. I think the areas where we are trying to prioritise use of PSMA-PET because of the supply chain demand issue, you know, is where the PSA is rising, and patients don't have any disease on conventional imaging and we think there must be some local disease. We still don't know. Right? All these studies that were done in the era of conventional imaging, how to extrapolate that with the PET. I think unless we see data from such ongoing studies like how did the PSMA-PET correlate with what was noted on the conventional imaging we won't know, but that's a long answer to your question that I still use conventional imaging for, you know, noting the disease burden.

But of course, if a PET scan is over staging the patient, then am more inclined to use triplet if we are able to get a PSMA PET, of course.

Fabio Schutz

That's interesting. Actually, I think the major benefit of the PET-CT-PSMA is for those patients with intermediate or high-risk local disease that we want to check if the patients have metastatic disease. And then we can avoid, for example, submitting the patient for a radical prostatectomy or for a radiotherapy to the local disease in the prostate. But usually overall, I would say that patients that present with high volume, high risk, younger, they are going to have like a best PSA, like more than 100 or 200 or even in the thousands. Usually for those patients PET-CT-PSMA is really not necessary.

Shilpa Gupta

Thank you, Fabio. That was really excellent and we could carry on talking about this topic all day, but we probably need to wrap up now. Thank you for a very interesting discussion and discussing the logistics, how care is for patients globally, right? I mean, everything is evolving so rapidly and it's also important to see which countries have access to these newer medications.

And in summary, I think what we've discussed that triplet therapy is certainly a way forward in metastatic CSPC patients and certainly indicated in patients with de novo metastatic disease who are symptomatic, whom we think need chemotherapy for sure. We still need to learn whether adding docetaxel is necessary for patients who are getting ADT and novel hormonal therapy. Hopefully some trials will address that question and other comorbidities of patients, their age and their risk of disease considerations for patient selection like we discussed between abiraterone and darolutamide. Is there anything you want to add to this Fabio for the summary?

Fabio Schutz

No, I think that's it Shilpa. Thank you very much for having me here. And I agree with you. I think this is a very interesting point that we have discussed. And like you said, we still don't know the additive effect of docetaxel for those patients. But the most important point is that patients, whenever possible, whenever available, must receive a new hormonal agent in the case they have metastatic disease.

Shilpa Gupta

I totally agree, Fabio. I think triplet is certainly a big step forward but as we have seen from real world data, there's a big percentage of patients, in fact, more than 50% who don't even get a doublet. So, I think drug approvals are important, but also access and availability. Thank you.

Tonke de Jong

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