Advances in Chemotherapy for Advanced Prostate Cancer Patients

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Dr. Beer:
I'm going to turn to Russ and ask him to comment a little bit on the developments with cabazitaxel (Jevtana). Cabazitaxel is a novel taxane which is currently approved as a second-line chemotherapeutic. There were some hopes that it might move up front. But the results of this meeting suggest that it's going to stay where it's currently used. Russ, do you want to comment on what we learned?

Dr. Szmulewitz:
Sure. Cabazitaxel was a designed therapy that was hoped to overcome certain resistance mechanisms with the initial drug docetaxel. The company that makes both of them conducted a randomized study comparing one to the other for patients with advanced prostate cancer in whom initial hormone therapy is no longer effective. It should be noted that cabazitaxel doesn't prove survival in patients who have already received docetaxel and had progression with docetaxel.

The question was if we move it forward, does that improvement persist up front? I was not entirely surprised by these data. The cabazitaxel was sort of designed to overcome resistance to docetaxel (Taxotere), and perhaps the men who receive docetaxel and then progress are the ones who are inherently going to drive the most benefit from cabazitaxel. So I would add that we aren't moving docetaxel even more forward into the hormone-sensitive setting, meaning that patients who

haven't yet had their hormone therapy fail them are receiving docetaxel up front. So we might, in fact, be still using cabazitaxel in the castrate-resistant setting first, and this study doesn't really answer that question.

Dr. Beer:
So in another study, two doses of cabazitaxel are compared to one another, and both showed by and large that we have the option of using a slightly lower dose of cabazitaxel with a similar result—a little bit less toxicity.

So with cabazitaxel is here to stay. It's likely to be a second-line drug after docetaxel. But as Russ alluded to, we're using docetaxel earlier. Emmanuel, maybe you could comment. The study that established docetaxel early first was the so-called charted study. In that study, men were treated for metastatic prostate cancer with standard hormonal therapy and six cycles of docetaxel right away. That study showed a significant survival advantage to moving chemotherapy up earlier. That's why we're doing that work. At this meeting, we heard about some of the quality-of-life results from that trial. Would you want to put that in context for us?

Dr. Antonarakis:
Two groups of men, the one had the hormone therapy alone up front, that is what we were doing for many years. The other group of men had the hormone therapy plus six cycles of the docetaxel given every three weeks.

So the quality-of-life study was basically showing the three-month quality-of-life data, and the subsequent long-term quality-of-life data after the chemotherapy actually had ended. And perhaps not surprisingly, at the three-month time point the patients that were receiving the chemotherapy and the hormone therapy had a slightly lower quality of life per their own report. However, the interesting thing and I think the take-home message is in the long term, several months after the chemotherapy had ended, the quality of life in those patients who had received the double therapy, the chemo and the hormones, was actually improved.

So, of course, our goal is the long-term horizon for these patients and not just the immediate toxicity of the therapy. Again, in experienced centers, I think the short-term toxicity can be well managed. So I think the lesson there is patients should try to get through it, with the help of their oncologist and their family members and their peers—try to stick with it.

And in the long term, that their quality of life will actually go up rather than go down, having had that chemo early.

Dr. Beer:
Joel, let me turn to you with a specific question. I must say when chemotherapy came along for this early use, I think some of us thought patients wouldn't want it. Chemotherapy has a bad name, if you will. But in our practice, our patients really have embraced it. When they hear about the survival advantage, they're in favor of being quite aggressive. Is that what you're hearing, or how do people feel about this?

Joel Nowak:
I don't have a statistic, but I will say I think a fair number of people, probably the majority of people, do feel the way you've just indicated, that you see in your practice. However, there's still this significant smaller number who think of chemotherapy and all the negative effects. It's not the chemotherapy that Aunt Edna had 25 years ago, and that's the reputation that chemotherapy still has.

And it takes a fair amount of work to get the men to understand that it's worth the risk, reminding them that you can start and if it's really something you can't tolerate, you can stop. There's no rule that says you can't stop. You need to discuss that with your doctor. And I think that this study is really going to give us a lot of conversation, an opportunity. Because I think if I remember correctly from the study, that a year after the chemotherapy, that the quality of life was actually reported as being better. And I think that that is really important and is something that I will continue to really stress with men who are having that "I don't know if I really want it."

Dr. Beer:
Emmanuel, I'm going to come back to you. You were involved in a trial called Taxinergy. It's going to be a real challenge to explain that trial to our audience, but we'll give you a crack at it. It's an interesting study.

Dr. Antonarakis:
It's an interesting study. The usual way that we prescribe chemotherapy is that we start the drug, either cabazitaxel or docetaxel, and we either continue that until the patient can't take the side effects anymore, or their cancer continues to grow despite the chemotherapy.

So we call that treat until progression, or toxicity. In this case, we tried to see whether switching the chemotherapy from one drug to another by some early indicator of response might be better than just sticking with the drug until the end. So what we did was we randomized patients, so they either started of with cabazitaxel or docetaxel. After four cycles of therapy, they had their PSA checked. And if the PSA had dropped by 30 percent or more, we said hey, listen, these guys are having a good response. They should remain on the same drug that they started with.

If their PSA had not dropped by 30 percent or more, or even if it had increased, in those patients we would switch them after the fourth dose, and then their fifth dose would be with the alternative drug. So, for example, a patient receiving docetaxel for four doses whose PSA doesn't go down adequately after the fourth dose, he will be switched to cabazitaxel rather than waiting for the docetaxel to stop working.

And what we found was in about half of patients who did not have that adequate PSA response with the first four doses, if you switched them to the alternative drug, you could salvage some of those patients. In other words, you could get them to respond to the second agent. And that was true in both directions. So in some patients, docetaxel was not as effective up front, but then the cabazitaxel can salvage them.

And the inverse was also true. Some men started with cabazitaxel, may not have had appropriate response but then would be salvaged by the older taxane, docetaxel. I'm not sure if that's ready for clinical practice, but it really does provide some interesting hypotheses that could be tested in other studies.

Dr. Beer:
So I think at this ASCO we're learning that chemotherapy continues to have an important role in the management of prostate cancer. Docetaxel is an important component of the initial treatment of metastatic disease, and we have some good data to suggest that the quality-of-life penalty that men pay in the first three months goes away, and in fact in the long term there are gains to doing that.

We've learned that cabazitaxel is going to stay as a second-line treatment, but we're learning how to refine it. There are studies of a lower dose. There are studies that Emmanuel pointed out where we may be able to switch into cabazitaxel therapy a little earlier in the appropriate patients. So the work continues to make the chemotherapy as tolerable and as effective as it can be for our patients.