ASCO 2015: Prostate Cancer Updates from a Roundtable of Experts

Recorded on June 1, 2015

Robert Bruce Montgomery, MD
Clinical Director of Genitourinary Oncology, Professor of Medicine
The University of Washington and Seattle Cancer Care Alliance

Emmanuel Antonarakis, MD
Assistant Professor, Oncology
Johns Hopkins School of Medicine

Tomasz Beer, MD, FACP
Deputy Director, OHSU Knight Cancer Institute
Oregon Health & Science University

Thomas N. Kirk
President & CEO
Us-TOO International Prostate Cancer Education and Support Network

Dr. Montgomery:
My name is Dr. Bruce Montgomery. I'm clinical director of genitourinary oncology at the University of Washington and the Hutchinson Center in Seattle. We're coming to you from the American Society of Clinical Oncology meeting in Chicago in 2015.

We're going to have a conversation today with a panel of experts. Cannot imagine a better group of folks to interpret the newest and greatest data coming out of prostate cancer research for us at this meeting. So we're lucky to have Dr. Emmanuel Antonarakis, Assistant Professor of Oncology at the Johns Hopkins Institute and University in Baltimore; Dr. Tomasz Beer, Deputy Director of the Knight Cancer Institute at the Oregon Health and Sciences; and Tom Kirk, who is President and CEO of Us TOO International which is, for any of you who don't already know, the preeminent advocacy, education and support group for men dealing with prostate cancer in the United States. So welcome to all of you.

I'm going to start with Dr. Antonarakis. So you are a member of this committee called the Prostate Cancer Working Group 3, which is—we heard about this week. It's a guideline mostly to clinical cancer research but also to providers to help us to decide how to begin and to stop therapies at the right time. If you could give us sort of your highlights about that document and what it means to patients and to providers and sort of give us really your interpretation of how we should be using this day-to-day.

Dr. Antonarakis:
Thank you. So the Prostate Cancer Working Group 3 actually is a—is a redo of the Working Group 2. Our criteria, which came out about seven years ago—actually Dr. Beer is also a panelist on the committee. As you said, this meanly guides clinicians designing trials for castration-resistant prostate cancer, but I think there's some clinical messages that we can give to patients and to physicians out there.

The first is that the field is moving away from using PSA alone as the main indicator or sole indicator to stop therapy. So if a patient appears to be benefitting from the therapy and their PSA may be rising slowly, that patient is encouraged to remain on treatment until or unless he develops radiographic progression of disease on his scans or a clinical worsening of his disease. So that's the first message, which was mentioned in Working Group 2 and now reinforced again in Working Group 3.

There [are] a few other things as well. One of the questions is how do we interpret bone scans? And we all know that when a bone scan might look worse it could actually represent a flare reaction. In other words, it could get worse before it gets better. And one of the recommendations of the Working Group 2 which has been carried over and reinforced in Working Group 3 is the so-called two-plus-two rule. Essentially this means that we need to see two new lesions which are confirmed in a subsequent scan by two additional lesions.

And what this does is it prevents people from stopping a therapy which could potentially be effective by just seeing two lesions without the confirmation. So again for the community oncologist and for patients, I think the message there is on your first scan after you start a new therapy if there are one or two new lesions, don't stop that therapy. Remain on the clinical trial and then wait for the confirmation scan, which is about eight to 12 weeks later. If that second scan shows additional new lesions, then it's probably fair game to stop the therapy.

Dr. Montgomery:
That's great. So I think those are two messages that I think everybody really should hear very loud and clear. That is, PSA is not the be-all and end-all in terms of starting and ending therapy, and bone scans are difficult to interpret. And you really need somebody who is doing this day-to-day to decide whether an abnormal bone scan, something that's getting worse may actually be a sign that things are getting much, much better.

We, I think everybody here, has had patients who have been on particularly the second-line hormonal therapies and bone scans look dramatically worse even though patients are really benefitting from the therapy. So I think those are two really high-level messages to get across.

So, Dr. Beer, to you. So you've done a lot of work with docetaxel-based (Taxotere®) chemotherapy in patients at all different stages of the disease. There were two actually presentations that came out of this meeting, which I think built on what we heard last year. I think everybody may remember that last year we got some information from a very large randomized study that said that giving chemotherapy early in men who had a lot of disease at the time of their diagnosis may really benefit them.

And so now there have been two additional studies, one called the STAMPEDE Study and one through the Radiation Oncology Group that was presented here, and I was hoping perhaps you could give us some information about those and how to interpret them.

Dr. Beer:
That's right, Bruce. I think our audience probably knows that chemotherapy, particularly docetaxel has been available to men with prostate cancer for a little over a decade, and up until really last year we were only using it for men with metastatic disease that had progressed on hormonal therapy. And in that setting, treatment can be helpful. It can reduce the burden of disease, improve pain and extend life, but the life extension benefits are modest and on average are in the two- to three-month range.

So it was a real surprise last year to learn that the same regimen of chemotherapy actually delivered for a shorter period of time, six doses of chemotherapy instead of the traditional 10, when deployed in the initial management of metastatic prostate cancer. So this is a setting where men have metastatic disease and traditionally begin hormonal therapy. And in

the CHAARTED trial six cycles of chemotherapy were added to that, and the benefit was far larger than when chemotherapy is used for more advanced disease, about a year-and-a-half gain so a really tremendous benefit.

I think many of us embrace that approach to treat patients, but we're a little nervous that STAMPEDE, a very large British trial, might not confirm those results. And we're very pleased to see that at this ASCO the data coming out of the UK clearly speak to the fact that early chemotherapy in metastatic prostate cancer extends survival substantially. So I think we all came out of this meeting with a firm conviction that men who present to a physician with metastatic prostate cancer for the first time and are about to begin hormonal therapy really should also consider a six cycles of chemotherapy course in addition.

There was a Radiation Therapy Oncology Group study as well that looked at the addition of chemotherapy to radiation and hormonal therapy for high-risk localized cancer. It also showed favorable results. In my view, we need a little longer follow-up for those results to really establish a new standard of care, but the results were quite consistent. And I'm optimistic and hopeful that we can also help men with newly diagnosed localized disease with the addition of chemotherapy in the future.

Dr. Montgomery:
That's great. Do you mind commenting a little bit about tolerance of chemotherapy? I think there's a perception on the part of many patients that, you know, it's something that really is reserved to til the end, because it's not well tolerated and they're going to feel horrible. Could you comment a little bit about how you feel about the side effect profile…

Dr. Beer:
Sure.

Dr. Montgomery:
…of docetaxel?

Dr. Beer:
There's no question that chemotherapy is a more intensive therapy than hormonal shots, which we're all very used to. Having said that, you know, it's worth remembering that women with breast cancer receive actually more intensive chemotherapy quite routinely following surgery and radiation to reduce their risk of relapse, and I think in prostate cancer we've been a little slower to embrace that.

The vast majority of men in my experience get through the treatment successfully. We occasionally have to make an adjustment in the dose or take a short break, and certainly we're well aware of potential side effects, but for the most part it's well-tolerated therapy. And frankly, when you're thinking about four months of chemotherapy yielding a year or year-and-a-half of benefit that's a much better equation than six months of therapy yielding three months of benefit in advanced disease. So I think the case is very, very compelling.

Dr. Montgomery:
Dr. Antonarakis, you're an expert in resistance and sensitivity to hormone therapy in prostate cancer, so I think you're particularly well-qualified to comment on the new studies that have been done at this ASCO.

So there were two studies presented that I think are really going to be important to a lot of men out there that are dealing with prostate cancer and the therapy that goes along with it. So one of them was the use of hormonal therapy along with radiation and how that does or doesn't help with regards to outcomes for men. The second one was related to this really far-too-common problem that when men receive surgery or radiation therapy and yet it isn't curative as indicated by a rising PSA, you know, most of our therapies really consist of hormonal therapy, and trying to decide when to do that has been a very gray area about when to start.

So if you could comment on those two studies and bring some of your expertise to the table in trying to decide whether these are things that should be informing therapy for these folks today, that would be spectacular.

Dr. Antonarakis:
So let's start with the first presentation. So here the question was in a man who has had a recurrence after radical prostatectomy who would otherwise be a good candidate for salvage radiation therapy should you add hormone therapy along with the radiation to improve the outcomes?

There has been a precedent here. Several years ago, there was a study showing that 150 milligrams of bicalutamide or Casodex®, which is arguably a high dose, given for two years' time along with salvage radiation therapy might potentially improve outcomes in that setting. That study has not yet been published, but it's been presented at national meetings.

So the question is what about standard androgen-deprivation therapy, which is given as an injection. Well, the trial that you mentioned was a randomized study where all patients had failed radical prostatectomy. Their PSA was rising. They had no evidence of metastatic disease. Half of the patients were randomized to standard conventional seven-week course of external beam radiotherapy as a salvage, and the other half received the same radiotherapy together with six months of standard androgen-deprivation therapy injections.

And the bottom line for me was although recurrence rates were slightly diminished and metastasis rates were improved as well, the overall survival data is still immature to guide our decisions. So for me until those overall survival data are available showing that the hormone therapy together with radiation therapy improves life span of these patients, I myself may not change my practice.

Now, the truth is that we do all have our own beliefs about hormone therapy in that setting, and there are many radiation oncologists in this country and even medical oncologists that might reasonably recommend that in a high-risk patient, for example. I don't think we have the gold standard evidence yet to make that decision, but I also don't think it's an incorrect decision for a patient that might have a very high risk of recurrence, let's say Gleason score eight through 10 or very rapidly rising PSA.

The second issue is a little bit more complicated, which is in patients that have missed their chance for a cure, so to speak, so these are men that either had a radical prostatectomy and they recurred or they have had radiation therapy and they've recurred. Or in some cases they've had both radical prostatectomy followed by radiation therapy, and yet their PSA continues to rise or it drops and then rises in the future. So these are men that currently do not have any curative paradigms, so the question is how should you manage those patients?

And there's been a longstanding controversy in the field, and even key opinion leaders have opposing views on this. So the one view is that these patients should receive standard hormonal therapy, androgen deprivation, early or immediately. And then the contrary view is that these patients should wait, that the hormone therapy should be deferred or delayed until either they have a symptom or they have a radiographic metastasis.

And the study that was presented at this ASCO meeting was a trial asking the question is early hormone therapy better than late hormone therapy. So this was a trial where patients were randomized to receive hormone therapy immediately if their PSA was rising after initial failure, and the other half of the patients did not start hormone therapy immediately, and the hormone therapy was deferred until a later time point.

It was unclear to me based on the presentation what were those trigger points that would cause the hormone therapy to be initiated? And I think that really needs to be clarified a little bit more in the manuscript, but the bottom line is although there did potentially seem to be a survival advantage maybe in those patients that got the hormone therapy early I myself am not completely convinced yet.

And one of the reasons for that is this is not the only trial to test this question, and it's about the eighth or ninth trial. And when looking at the totality of the evidence, in other words all the data that we have to date, I personally don't feel that there's convincing evidence that giving the hormone therapy immediately after a rising PSA recurrence is the right thing to do.

Now, you know, we all have to make decisions in real life when we're sitting in front of our patients. And we all know that there are men out there who have very high Gleason scores who recur very quickly or immediately after their radical prostatectomy who have a very rapid PSA doubling time—in other words, the PSA might be doubling every two months, every three months--and we all feel very nervous about those patients.

And often even in the absence of data we have to make our best guess as physicians and as advocates for our patients. And, you know, I can't say that I never use hormone therapy in those patients. I do sometimes, but I think that decision is tailored to the individual patient. So the bottom line is, you know, there isn't like a blanket solution for this. I think it has to be an individual decision, and also the patient's own wishes and expectations need to be considered in there.

And one of the things that we need to discuss is the toxicities, in other words the side effects of hormone therapy. So 10, 15 years ago, you know, we gave it almost to everyone because it made the PSA go down and made patients feel better, made us feel better as physicians. But now as we're learning more and more about the negative consequences of hormone therapy, you know, to the metabolism, to the weight gain, to the blood vessels, to the heart, to the brain, you know those things can add up with time. So I think the field is a bit more cautious with the indiscriminate use of hormone therapy, although it could be appropriate for some patients.

Dr. Montgomery:
Sure. That was a spectacular summary of that, and I would reinforce a couple of aspects of it. This study which was done was again done with the best of intentions. I think there was—there were so many variables that were part of it. Patients could be on intermittent or continuous therapy. Part of the study actually included men who hadn't failed therapy initially, and some of the results were actually entirely in conflict with previous large randomized studies that showed that intermittent versus continuous therapy in this setting was essentially equivalent. And the results of this study were somewhat in conflict with that, so it's a little hard to reconcile this study with others.

And as a result, I think the jury is still out about whether the conclusions of that study necessarily should inform therapy today. But thank you for such a nice summary of all that.

Any comments that you wanted to make, Tom, based on a patient's perspective from any of the things that we were discussing earlier?

Tom Kirk:
Well, I think in a short time you've covered a great deal of territory here, and it's all been very hopeful. And we recognize the seriousness of the decisions that physicians and their patients and family members have to make as they battle this disease. It covers a great deal of turf and serious discussions, and it involves a solid relationship. It's wonderful to see the physicians around the room who are this poised and articulate about the understanding of the evolving knowledge that we have about prostate cancer.

It's also very hopeful for us to know that this kind of work is going on, and now the challenge before us is to inform people and give clear messages about it that will help them make the right decisions for themselves.

Dr. Montgomery:
Right. It's worthwhile emphasizing that Us TOO does a great job of doing that. They distribute flyers about ongoing research trying to provide just the sort of information that comes from Patient Power, which is what this is all about, and so Us TOO should be recognized for providing a great service to men dealing with prostate cancer.

Tom Kirk:
Well, I appreciate it. It's about patients and families and physicians working together to support a better understanding of this disease and then translating that information out to patients who are living with this disease, and together we can form a strong union and battle this disease.

Dr. Montgomery:
Dr. Beer, as I think you and a number of other people who are in the field have been participating in a very large study that's been ongoing trying to decide what the underlying molecular changes are in advanced prostate cancer, it's this, called Stand Up to Cancer effort. It's supported by Stand Up to Cancer, the Prostate Cancer Foundation and AACR. They've supported two very large efforts, one of them is yours, trying to figure out how prostate cancer changes over the course of therapy and how we can as a result of the findings treat cancer differently and better.

There was some data presented at this meeting about the effort from your team. There was also a publication very recently from the other team working on this. I was hoping perhaps you could give us some insights about what's been found from those two efforts and how that's important to men out there in the field.

Dr. Beer:
Sure. So I suspect many people will be surprised to know that we actually don't know a lot about the kind of prostate cancer that kills men. So men die from metastatic disease that is resistant to treatment, and we historically have very rarely obtained biopsy samples for study in the laboratory in that situation. So we know a lot about localized prostate cancer that is treated with surgery, but we don't actually know a lot about what happens in very advanced prostate cancer.

And these two teams have focused on obtaining samples of cancer from bones, liver, lymph nodes and other distant sites and analyzing them in the laboratory to see what the enemy really looks like. And we're beginning to see some really remarkable results.

So what was reported at this meeting is a new subtype of prostate cancer called intermediate atypical carcinoma, which is responsible for about a quarter of patients with advanced prostate cancer and hadn't really previously been appreciated. This variety of cancer is biologically distinct and has a poor prognosis and a very aggressive course of action, so we're going to be working very hard to understand the biology of that disease and design treatments specifically for that subtype of prostate cancer.

A recent publication that came out about a week-and-a-half ago from the other team was really equally if not more surprising, and in that publication we learned that nearly a quarter of advanced prostate cancers have defects in DNA repair genes. The most well-known of those are the BRCA genes. Our audience may have heard of those as the breast cancer genes, and we weren't expecting to find them in a quarter of prostate cancers.

It's important to note that these are not for the most part inherited defects, so men who have prostate cancer with a BRCA gene don't necessarily have to worry that his daughters are at high risk of breast cancer. These are defects that the cancer manages to acquire on its own, but they open a whole new avenue for prostate cancer therapy that we haven't really been thinking about a lot.

I expect that these two team efforts are really going to continue to deliver revolutionary information about what advanced prostate cancer is really like, what makes it tick and how we can target it best.

Dr. Montgomery:
Yeah, I think the results of both of those studies are I think a huge step forward from my perspective. And, as you said, I think this is going to continue to produce new and really informative results that we hopefully will be able to use to change therapy for the next five to 10 years at a minimum, so.

Dr. Beer:
I think we're finally getting to know the enemy.

Dr. Montgomery:
Exactly. So I also wanted to finish by asking each of you if there was anything that we haven't discussed that was particularly important to you or exciting or really gave you hope for the future that you thought was going to be something that in the very near future men out there will be able to benefit from, or simply just a new biology that you think is revolutionary. So, Dr. Antonarakis, could you give me any insights that you have from this meeting?

Dr. Antonarakis:
Well, there was an abstract presented in a different disease, colorectal cancer, actually from Johns Hopkins investigators, showing that a particular type of DNA defect repair called mismatch repair, also called microsatellite instability, patients that had that instability actually responded better to a type of immunotherapy called checkpoint blockade. The drug specifically was pembrolizumab (KEYTRUDA®), which blocks the PD-1 antibody.

So the question is now we have all the sequencing data from these dream teams, one of which Dr. Beer is part of, is it possible that those patients, those 20 percent of patients or maybe a smaller fraction, that do have these defects in DNA repair, in other words their cells are unable to fix DNA damage, might those cells be more susceptible, might those patients be more responsive to immunotherapies such as these checkpoint blockades? And I think that's been a big theme at this meeting but not necessarily in prostate cancer.

So the question is if we are sitting at this room two years from now, could we have some breakthroughs, you know, based on that discovery? And I think we might.

Dr. Montgomery:
That's very exciting. Dr. Beer, anything that you wanted to highlight?

Dr. Beer:
You know, it's funny that Emmanuel brought that up, because I want—wanted to highlight immunotherapy from yet another tumor type. There was a plenary presentation in melanoma where the combination of two checkpoint inhibitors

was shown to really have a remarkable level of activity against this extremely difficult-to-treat cancer. We haven't seen results of that magnitude in prostate cancer yet. But given what we're seeing with immunotherapy and in particular checkpoint inhibition in other tumor types, I think we're going to be working very hard in understanding how to exploit that for prostate cancer patients. So we're seeing advances in molecular understanding of prostate cancer. We're seeing advances with chemotherapy, and I'm looking forward to advances with immunotherapy.

Dr. Montgomery:
Yeah, that's great. And it's worthwhile reminding people that prostate cancer was the first tumor for which really an FDA-approved vaccine and immunotherapy was available, which again raises hope that we will be able to leverage that in the future for benefit.

So, Tom, do you want to comment at all about the things that you've seen and heard that might bring you hope that we're making some progress here?

Tom Kirk:
I will be really happy because isn't this stunning, isn't this amazing? And watching year to year the kind of progression in the depth of understanding that we have of prostate cancer across its course is exciting to patients and to people, family members who are there seeking solutions to their own individual case. It's a very hopeful situation, and it's one of appreciation to all of you who are researchers that together we may even in our lifetime see this continued progress in the disease and hopefully the cure of prostate cancer.

Dr. Montgomery:

Well, I want to thank all of you for all your insights into this research. And that's it for us from ASCO 2015. Thanks to all of you.