BCAN Patient WEBINAR SERIES

Questions & Answers about Immunotherapy and Bladder Cancer

A Conversation with Dr. Jonathan Rosenberg

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Part IV: Question & Answer Session

Presented by

Dr. Jonathan Rosenberg *is an Associate Member and Section Head for Non-Prostate Genitourinary Cancers of the Genitourinary Oncology Service at Memorial Sloan Kettering. He's also an Associate Attending Physician at Memorial Hospital at Memorial Sloan Kettering, and he holds the Enno W. Ercklentz, Jr., Endowed Chair. After earning his medical degree from Harvard in Boston, he did his internship and residency in internal medicine at New York Presbyterian Hospital, Cornell, in New York. His research focuses on testing novel therapeutic approaches and correlating novel genetic biomarkers with clinical outcomes in bladder cancer.*

Question 1: Do anti-inflammatory drugs, like prednisone or NSAIDs, being taken for rheumatoid arthritis decrease the oncologic effectiveness of the PDL?

Dr. Rosenberg: PDL-1 or PD-1. Yeah. That's a great question. Most of the clinical trials allowed people who are on low doses of daily prednisone to go on. Not a lot of subset analyses has been done on those patients. There have been some other reports of successful treatment of patients who are on steroids or other immunosuppressants. The data on nonsteroidals has not been looked at in bladder cancer. There maybe is a hint that perhaps they may not be great in terms of anticancer activity in other cancers, as far as immunotherapy, but I think that's far from clear. It's probably better not to be on corticosteroids if you can get off of them, but depending on the disease it may be reasonable to try immunotherapy if you need it, because you have to balance the risks between a life threatening cancer versus an auto-immune disease that might be very serious if it exacerbates, but might not be also.

Question 2: "With my cancer spreading into the liver and lungs, how successful is Opdivo. I've had one treatment with three more to go. What's the percentage of survival rate? I had chemo and radiation last year, and went through that with flying colors with no side effects. All my blood work says I should not have cancer."

Dr. Rosenberg: We're still trying to tease out places in the body and does it matter. It does seem to be that for some of the medicines that if it's in the liver, in fact for all of them probably, if it's in the liver it may be less likely to work than if it's, let's say, just in lymph nodes or just in the lungs. I also have to say I have a lot of patients where they do have liver metastases and the liver metastases shrink, so it doesn't mean that it's not going to work, but it probably means it's a little less likely to work. It sounds like the fact that the organs are all functioning well, that stands the patient in good stead and hopefully would be a sign that the body can rally and fight here. Cancer in the liver is a difficult problem. These immune drugs, while they can work, it may not be quite as often as if it wasn't in the liver.

Question 3: Do you have any recommendations for folks who would like to use probiotics to improve their weight gain and things that would be nutritionally sound for them when they're on immunotherapy? Would you have any recommendations for that?

Dr. Rosenberg: It's a very interesting question and it's a hot topic right now understanding how the interaction between the bacteria that live in your intestine and your immune system. There is some data, although it's far from conclusive, that sort of a healthier microbiome, they call it, microbes living in your intestine, that certain bacteria are better for you than others. The jury is still out to some degree on what we should do for patients. My own practice is if people want to use probiotics, I have no objection. It might be a very good thing, but I can't guarantee it. There's probably differences between different probiotics. I don't have a particular opinion about one versus another at the moment, but we know that there are probably different bacteria that are better to have in your intestines. We just are not sure exactly what the probiotics always contain, and that's the concern. I think over the next several years we're going to get a lot more information about this. That's a great question.

Question 4: I know we'd all be in a different place if we had a crystal ball, but if you were able to see in the future, do you see this therapy moving down the line so that it might replace BCG or some of the other therapies down the road?

Dr. Rosenberg: That's a great question, and there's reason to be optimistic about it, and there's some reasons for concern. We're learning a lot about particular types of bladder cancer, subtypes I would say, that have expression of different proteins or mutations of different proteins, and there seems that there's a shift in the type of cancer cell from the superficial bladder cancer to the invasive and metastatic cancers. There's some reason to think that the superficial bladder cancers may not be as sensitive to PD-1 inhibition or PDL-1 inhibition, but that's not been tested yet. There are trials going on now doing that. If I had to guess, Stage 1 tumors and carcinoma in situ, I would bet that they're going to work well, that PDL-1 and PD-1 inhibitors will work well in those patients. But for the very superficial low-grade bladder cancers for whom BCG probably wouldn't be given anyway, they probably won't work, because those tumors don't seem to be recognized by the immune system so much. The jury is

out. I think it's going to be a complicated answer to that question as time goes on, but I think there's going to be a role for at least some of those patients.

Question 5: Can epigenetic therapies improve results for patients who fail immunotherapy. Alternatively, can studies that have found oxaliplatin and cyclophosphamide for lung cancer patients improve response to checkpoint inhibitors?

Dr. Rosenberg: Those are good questions. Epigenetic therapies, epigenetic-targeted treatments are being tested in several clinical trials in bladder cancer right now. They're starting to be tested, I should say. Bladder cancer is relatively unique in the high frequency of mutations and genes that are involved in epigenetics. Epigenetics, for people who don't know what it is, is a sort of layer of regulation of genes on top of the DNA that help to control when certain genes turn on and turn off. So if your epigenetics are altered, you turn on inappropriate genes, and that can help maintain the malignant phenotype. It also probably is happening in immune cells in similar ways. The answer is in theory it's great, and we have to test it and test it rigorously, and that's happening or starting to happen, and trials are being planned and are launching.

Cyclophosphamide and oxaliplatin, I think combinations of chemotherapy and PD-1 and PDL-1 drugs are warranted, and we're doing some ourselves here at Memorial Sloan Kettering, and others are underway elsewhere. The idea behind it is that you induce immune cell death. The cells then when they die are able to be recognized by the immune system and the PD-1 or PDL-1 inhibition helps to clean up the cancer and start an immune reaction that can perpetuate itself. The caveat is that those drugs can also kill lymphocytes. So are they actually going to, at the same time they're turning on the immune response, kill the cells that are responding. That's the open question.

In lung cancer there's good and provocative data with extraordinarily high response rates in these very tough to treat lung cancers when you combine certain chemotherapies with immunotherapy, and so we're hoping we're going to see that with bladder cancer.

Question 6: Please describe the use of immunotherapies in plasmacytoid variance of bladder cancer for plasmacytoid bladder cancer. Does it tend to recur even after chemotherapy surgery, and is immunotherapy indicated?

Dr. Rosenberg: It's a great question. Plasmacytoid bladder cancer is a rare subtype that's being recognized more over the last several years as we understand it better. It has a unique appearance under the microscope to the pathologist, and it has a unique pattern of spread where it tends to migrate along single cells rather than sort of a discrete tumor mass. They tend to be sensitive to chemotherapy and they do have a tendency, unfortunately, often to come back after chemotherapy, but not always. I have had some patients with plasmacytoid bladder cancers go on to receive immunotherapy, and I've had some do extraordinarily well, and I've had some that haven't.

Because it's a very rare subtype, probably about 1 percent of bladder cancers, we don't really have a sense overall of how well immunotherapy works. I think in the next couple of years we'll be able to tell. My own feeling is that it's no different in terms of its responsiveness to immunotherapy as regular old

bladder cancer is, but that's my gut feeling and that's based on anecdotal data at the moment, but I have certainly seen some very good responses with plasmacytoid bladder cancer, both to chemotherapy as well as to immunotherapy. It's often hard to measure is the problem for us with plasmacytoid cancer, because it doesn't form discrete tumor balls, so to speak, the way you see on a CAT scan, nodules or masses. It often looks very wispy on the films and is very hard to put a ruler across and see if its working. Sometimes it's very hard to tell what's actually going on with the cancer, but when it works ... In that situation, even if it's just not changing and the patient feels well and they're living their life and they're just getting their treatments, then it's probably being successful.