Questions & Answers about Immunotherapy and Bladder Cancer

A Conversation with Dr. Jonathan Rosenberg

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Part I: Bladder Cancer & the Immune System

Stephanie Chisolm: Hello, and welcome to Questions and Answers about Immunotherapy and Bladder Cancer. This is a conversation with Dr. Jonathan Rosenberg.

Dr. Rosenberg: I’m going to talk today about some new breakthroughs in the treatment of bladder cancer through the development of immune checkpoint blockade in this disease. It really is, I think, the most significant thing that's happened in bladder cancer in over 25 years.

Just briefly, a little primer on bladder cancer, although I’m sure many of you are familiar with some of these. It is a relatively common cancer. About 80,000 patients are going to be diagnosed in 2017. Unfortunately, still about almost 17,000 people will pass away from bladder cancer. When patients have it within the bladder it's highly recurrent. It keeps coming back. There is a significant rate of metastasis with invasive disease. Only a small portion of
patients present with metastases, but that's still a very big clinical problem. There are many patients in the United States living with a history of or living with bladder cancer, over 600,000. Overall, it's the fifth most common cancer, the fourth most common in men and the eleventh most common in women.

Immunotherapy in bladder cancer has been with us for a very long time. The treatment of non-muscle invasive or superficial bladder cancer historically has been with BCG, which is a weakened bacteria related to tuberculosis administered in the bladder. That leads to inflammation in the bladder. After all these years, we've been using it for about 40 years, we really don't know exactly how it works, but the thought is that it works as an immunotherapy. Immunotherapy for advanced disease has not really made any inroads until the last several years.

The mainstay of treatment for advanced bladder cancer has been chemotherapy. The standard regimens use multiple drugs for muscle invasive and metastatic cancer. The backbone of these are the platinum drugs, cisplatin or carboplatin. For most patients, the treatment of choice is gemcitabine/cisplatin, gemcitabine/carboplatin, or an MVAC-based regimen, as listed here. Unfortunately, when we're thinking about metastatic bladder cancer, which is really what we're focusing on here, life expectancies have been short with our standard approaches, with the average being about a year and, unfortunately, many patients even with less time. This has been a huge unmet need, and we needed desperately to make advances in the treatment.

Unfortunately, when platinum chemotherapy either didn't work or stops working, patients do very poorly. There really are no good, or have not been any good treatments for patients where the cancer comes back after cisplatin or carboplatin-based therapy. We used a lot of different chemotherapy drugs. Occasionally they worked really, really well, but a lot of the time they didn't. Unfortunately, in this patient population the needs are even bigger, but there really was nothing available that helped people in a very meaningful way. This is the background of where we were even up to about a year ago, as far as what was available commercially or just that your doctor was able to prescribe you.

Fortunately, the implementation of immune checkpoint blockade has changed the management of metastatic bladder cancer for the better. It really has transformed the field. It reinvigorated research into bladder cancer in an unprecedented way, to the point where the doctors taking care of patients are worried there are more patients than there are clinical trials to test new treatments. I'd rather be in that position. There are more trials than patients. I'd rather be in that position than not having enough options for patients.
Just to talk a little bit about cancer and the immune system. Cancer is designed to invade the immune system. That's how it establishes. It uses multiple different strategies to hide from immune cells. The purpose of the immune system in the body is to detect things that are foreign and to get rid of them, and also not to attack normal cells. What happens with cancer is that they essentially deploy all the mechanisms that your normal cells deploy to prevent the immune system from recognizing it. We call this failure to recognize these cells a failure of immune surveillance. Cancer cells are able to activate multiple pathways that are designed to avoid the immune system attack. This is just a little cartoon. I wouldn't expect anyone to read it very carefully, but showing the balance between escape, where patients have tumor cells that really are not eliminated by the immune system versus the other way where the immune system was really able to attack the cancer cells. We want to shift that balance back towards elimination of cancer cells.

In order for the immune system to identify and attack a tumor, there really is a complex multi-step process that has to occur, and it occurs in multiple areas of the body. It starts with the fact that cancer cells release proteins called antigens. Any protein can be potentially an antigen. They are the things that the immune system recognizes. Those antigens have to be released. They have to be handed off to the immune cell's T cells. They then have to have those T cells turn on and get primed for action. That occurs usually in the lymph nodes. They then have to leave those lymph nodes, and they have to go through the bloodstream. They have to then land in the tumor and make their way inside the tumor. They have to recognize that the antigen that they're recognizing is the cancer cells that are in the tumor, and then they have to turn on all their mechanisms that they use to kill the cancer cells in order to lead to tumor cell death.

It's a complicated process, as you can see here. It starts in the tumor, leaves the tumor, goes through the peripheral immune system to the lymph nodes and the spleen and other places, then comes back to the tumor, hopefully in action to do something.

There are multiple different proteins on immune cells and on normal cells that either promote or interfere with this process. There are activating factors. You can see in step three these are things that when expressed turn the immune system on to recognize things are bad. There are inhibitory factors, like on the bottom, CTLA-4, PD-L1, and PD-1. All of those molecules serve to turn off the immune
The PD-1 and PD-L1 molecules also act within the tumor to turn the immune system off in the tumor cells. Many of these molecules can work in multiple different places throughout this cancer immunity cycle. We now have developed [inaudible 00:10:17] that primarily target PD-L1 and PD-1, and we’re going to talk about that, but the future may hold inhibition of CTLA-4 or using antibodies targeted to OX40 or GITR, all of which may turn the immune system on directly rather than getting rid of inhibition.

When we think about how the T cells in the immune system function, there's a balance between things that cause the T cells to turn on and things that cause the T cells to turn off. These are the activating receptors like I just mentioned that turn the T cells on. Things like CD28, OX40, etc. You’re not going to be tested on this, but these are the types of targets we're thinking about in the immune system, and none of these have any drugs that were ready for primetime, but they all have experimental drugs that are targeting them.

On the other side of the equation, the inhibitory receptors, if you can block the inhibitor ... If you turn off something that's turning off something, you may turn the T cell back on again. So a double negative gets you a positive. These blocking antibodies of CTLA-4 and PD-1, for example, are now in use in the clinic. The PD-1 antibodies in bladder cancer and CTLA-4 testing in bladder, they're experimental.

We're going to focus primarily on the PD-1 pathway. PD-1 stands for Program Death-1. PD-1 when it's turned on essentially turns the T cell off and kills the T cell, so PD-1 on immune cells binds to something called PDL-1, which is the ligand, which means the thing that binds PD-1. PDL-1 and PD-1 bind to each other. PDL-1 is present on normal cells, and it's part of how your body keeps the immune system from attack itself. It's basically a little flag saying, "Don't eat me, don't kill me, don't do anything to me," and it's present on normal cells.

When the T cell sees this PDL-1 molecule there, it turns off. It doesn't harass, it doesn't attack that cell, and leaves it alone. Tumor cells, though, of course, have turned this pathway on as well, and they use this as a way to escape the immune system. They display the same PDL-1 molecule on them, and they use that to turn off the immune system in many cases, not every case. Now we have ways to target both PD-1 and PDL-1. We have antibodies, monoclonal antibodies, that target these molecules that are all administered IV. What they do is they block the interaction of PD-1 with PDL-1, by either binding PD-1 or binding PDL-1. By blocking this interaction, the T cell doesn't turn off. If this pathway is pretty critical in
keeping the immune system at bay and the tumor, by doing this you actually elicit an anticancer immune response, which is how these drugs work.

It's important to remember when you're thinking about these medications, these drugs, these antibodies, these treatments that we're going to talk about don't directly kill cancer cells. They allow your immune system to do what we think it should do, which is eliminate the tumor.

The first study that was reported showed quite dramatic activity of an antibody targeting PDL-1. This drug was atezolizumab. It is an antibody binding PDL-1. I'm going to show you a bunch of these figures, so I want to explain what this figure shows. This is something called a waterfall plot. Each of these bars represents the amount of tumor measured lengthwise of an individual patient. If it goes up and it's high, it means there's a lot of cancer there. If it goes down, it means there's less. Every patient at the beginning of the study we gave a measurement, but we reset everyone at the same level, at zero. If the tumor grows, the line goes up. If the tumor shrinks, the line goes down.

In this clinical trial, patients who had had multiple different types of prior chemotherapies and other treatments for bladder cancer were enrolled. The expectation is that probably a treatment might work 5 to 10 percent of the time if you're lucky. Here we saw that a whole lot of patients had fairly significant shrinkage. There were even some patients where the amount of cancer went down to zero. This really sparked the excitement that we've now had over the last several years. This has been seen with other drugs targeting PDL-1. These two are investigational, experimental PDL-1 drugs, avelumab and durvalumab. Then we see again, if you look at these particular figures, they're not all that much different. They all seem to work quite well. In this figure they're sorting the samples differently, but this drug also has substantial anticancer activity.

About the same time, we found the same exact thing with PD-1 inhibitors. There was robust activity in a small phase 1 study of pembrolizumab, which is a PD-1 inhibitor, and in a later on study of nivolumab was reported showing the exact same type of findings. These results were very promising and sparked the frenzy of drug development for bladder cancer, which we are beginning to see bear fruit today.