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April 12, 2013
Expert Q&A

Study Could Extend Survival Benefit of Provenge: Interview with Samir Khleif, MD

As the only FDA-approved therapeutic cancer vaccine, Provenge (sipuleucel-T) is a breatkthrough treatment option for men with asymptomatic or minimally symptomatic metastatic, hormone-resistant prostate cancer.

However, the therapy comes at a steep price: The three-dose schedule costs $93,000, in exchange for extending life for a median 4.1 months. But Provenge may soon prove to be an even more valuable—and more cost-effective—component of prostate cancer treatment now that Samir N. Khleif, MD, director of the Georgia Regents University Cancer Center in Augusta, Ga., and colleagues are exploring whether the vaccine's survival benefit can be increased by the addition of cyclophosphamide and/or the antibody CT-011.

Dr. Khleif explained the motivation behind the pilot study to Renal & Urology News.

Samir N. Khleif, MD

Why is your research focused on Provenge?

Dr.Khleif: It's not the Provenge itself. We found in the lab that if we combined therapeutic cancer vaccines with agents that enhance the immune system by inhibiting the inhibitory mechanism of the tumor, such as cyclophosphamide and the anti-PD-1 antibody CT-011, we can improve the effects of these vaccines.

Since Provenge is the only therapeutic cancer vaccine that's approved for use by the FDA, because of its proven efficacy in prostate cancer patients, this was the most obvious choice. In this case we're combining standard therapy with the agents in the clinical trial.

Why are you using cyclophosphamide/CT-011 in combination with Provenge?

Dr. Khleif: Because of what we found in preclinical experiments. Provenge is a vaccine that enhances the immune system specifically against prostate cancer. However, cancers have developed very effective mechanisms to inhibit the immune system. What we do in our lab is to understand these mechanisms and develop strategies to break the mechanisms by which tumors inhibit the immune system, so we can make the specific immune response that is created by the vaccine work better.

The tumor expresses a molecule called PDL-1, which binds to receptors on T-cells and prevents T-cells from attacking tumor cells, which is one of these mechanisms by which tumors inhibit the immune system. Anti-PD-1 (CT-011) prevents the tumor's PDL-1 from binding to the T-cell PD-1 receptor. It is already in use in clinical trials as a single agent or in combination with other therapies.

The cyclophosphamide works on another mechanism by which tumors inhibit the immune system: It decreases suppressor T-cells, which inhibit the immune system from acting against the tumor.

So in the lab we combined therapeutic vaccines plus these two agents, and we found that they highly enhance the effect of the cancer vaccine. Based on that, we combined Provenge as the cancer vaccine, since it is approved by the FDA and works on prostate cancer, with CT-011 and cyclophosphamide, to test if we could enhance Provenge's efficacy in patients with prostate cancer. We hope that the combination will increase the positive effect of Provenge by increasing its positive survival effect.

How many arms will the study have?

Dr. Khleif: There will be three arms: One will be Provenge alone, one will be Provenge plus the CT-011, and one will be the combination Provenge, CT-011 and cyclophosphamide. We'll follow patients for a couple of years.

You plan on enrolling 63 men. What are the eligibility criteria?

Dr. Khleif: We follow the same criteria that the FDA approved Provenge for: prostate cancer patients who have progressive, hormone-resistant disease that is minimally symptomatic. Of course, there are other criteria, but this is the main one. As long as men are eligible to use Provenge, they can contact us about the trial.

Will you look at whether Provenge should possibly start being used earlier in the course of disease?

Dr. Khleif: That is not part of the trial.

If your trial does show an extended survival benefit beyond the already established median of 4.1 months, do you think the universe of men who use Provenge, a costly therapy, will expand?

Dr. Khleif: This is a phase 2 clinical trial. The intention is to determine feasibility and immunologic responses. Survival is a secondary endpoint; accordingly, it will not answer the question definitively but will provide data to build on for a phase 3 study to address the survival question.

If your trial proves successful, your findings may make the decision easier.

Dr. Khleif: What we're hoping to do with this clinical trial is to enhance the currently available standard therapy, which is the only therapeutic cancer vaccine available for patients. And our goal is actually to see how we can enhance an available therapy for patients who otherwise don't have many therapeutic options. This hopefully will provide prostate cancer patients with more and better options to choose from.

Would the addition of CT-011 and cyclophosphamide substantially drive up the costs of Provenge?

Dr. Khleif: I am not qualified to answer this question. Having said that, cyclophosphamide is a very inexpensive drug. It costs less than few dollars. But in general, the cost of drugs usually decreases with time because of enhancement in technology and because more people will be using it. Our goal as scientists is to improve therapies based on our new discoveries. So it's very difficult to predict what might happen to the costs.

Will we start seeing more therapeutic vaccines as a result of your research?

Dr. Khleif: There are lots of therapeutic vaccines coming closer and closer to market. Our study will show that a therapeutic vaccine plus this combination [of CT-011 and cyclophosphamide] might be better than giving the vaccine as a single agent.

What role will Provenge manufacturer Dendreon have in your study?

Dr. Khleif: Dendreon is not sponsoring the drugs, but the company is providing a grant to conduct immunologic testing and to cover some of the costs of patient care.

For study enrollment information, call 888-658-0422, or visit http://www.georgiahealth.edu/cancer/trials (Genitourinary/11-C-0231).