Understanding New Drug Protocols: Managing Hormone Sensitive, Non-Metastatic Relapse/Castrate-Resistant Metastatic Prostate Cancer

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I. Immunotherapy Advances

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Many people recently have said that we have had a revelation in the world of prostate cancer by finally validating using immunotherapy for the treatment of recurrent prostate cancer. There is a significant paradigm change in our thinking, but it may not be a standalone type of approach. The rationale for using vaccines in prostate cancer is, while we have known biomarkers, we have, on the surface of a variety of different prostate cancer cell lines, as well as the prostate cancer cells themselves from the patients, a wide variety of carbohydrates or sugar molecules as well as protein molecules. These glycoproteins and carbohydrate antigens are well characterized; as normal cells from various organs change, these molecules become overexpressed or underglycosylated, losing some sugars which coat them, and therefore allow the immune system to recognize them as completely different foreign molecules to the immune system.

We are fortunate in not only having PSA as a validated biomarker to help determine whether we are impacting on the disease, but also being able to use immune therapy through all clinical states, from a man with a rising PSA postsurgery, to patients who have failed hormones, to patients who have had failed hormones and have metastatic disease, to even patients who have failed chemotherapy. Immunotherapy as single agents may be insufficient, and therefore, combinatorial approach with certain available molecules, such as cytokines and checkpoint inhibits, are now coming into play.

Vaccination against cancer was reported in The Globe from Toronto in 1925, reporting on British medical experts and experiments, and stating that cancerous growths had a common virus. Immunotherapy impacts either the humoral immune system component, which are the cells that make antibodies, or the cellular immune system component, which are specialized white cells called lymphocytes. Approaches to immunotherapy are via recombinant technology, by passive immunization or technologically-made monoclonal antibodies; via vaccine, which means you make the immune response and antibody yourself via active immunization; and via T cell immunotherapy.

This slide shows a brief history of vaccines. We have improved from mixing whole cells or shed antigen via a crude blender approach to purified proteins to peptides to the amino acids and to actually the DNA that comprised the antigens. Looking at cell membrane glucoconjugates, mucins project through the cell membrane; with malignant change, some sugars on the surface of the mucin molecule are lost, thus exposing areas of the protein backbone which become subject to immune attack.

Prostate specific membrane antigen, or PSMA, is a molecule that is seen on some normal tissues in brain, gall bladder, and liver, but is also present on neovasculature. Certain monoclonal antibodies can bind for radioactive labeling and tracing prostate cancer.

In clinical trials using immune therapy, one of four scenarios occurs: the tumor responds (gets smaller) and the target is hit, resulting in a biologic effect; the tumor responds but the target is missed; the target is hit but the tumor does not respond; or the target is missed and the tumor does not respond. Each of these scenarios says something about the biology of the tumor and how we should direct therapy.

For patients who have failed hormonal therapy or chemotherapy, immunotherapy approaches include: tumor antigen vaccines; antigen presenting cells or autologous dendritic cells, which are scavenger cells in the circulation associated with MHC; cytokines and DC stimulation; and CTLA4 blockade.

Ipilimumab is a human monoclonal antibody that will block interaction of T cell with dendritic cells and other cells in the body; dramatic antitumor effects have been observed with this agent in multiple tumors, and its use in prostate cancer is now beginning. Immune-related adverse events include development of an autoimmune breakthrough event in which the body attacks itself. CTLA4 blockade enhances tumor specific immune responses: normally, CTLA4 attenuates or terminates proliferation; CTLA4 blockade stops CTLA4 from inhibiting proliferation to allow the T cell to do what you want it to do and not what Mother Nature wants to do.

This monoclonal antibody has been used in concert with vaccine. A vaccine was developed, which was genetically altered prostate cancer cell lines; these prostate cancer cell lines were genetically altered with a gene that allowed them to produce a cytokine called GMCSF. The idea was to recruit other cells into the area where the immunization occurred. In sum, the drug impacted the PSA but there were problematic side effects. Radiation is accompanied by release of the tumor antigens into the circulation; immune cells can take up these antigens. Following radiation, CTLA4 will abort withholding of immune reactivity, leading to antitumor effect. There is safety is using ipilimumab, but any immune therapies can be fraught with events that can be extremely serious and may or may not impact on the patient's quality of life.

Moving from the passive approach with an monoclonal antibody, we will look at an active approach. There are concerns now that we have achieved for the first time the introduction of immune therapy into an approved setting; this is a paradigm shift. Provenge is a cellular product vaccine, which means that the white cells in the body are removed physically via leukapheresis, which are then sent to a secondary center where they are cultured with a fusion protein. Acid phosphatase has been genetically altered to bind with a cytokine GMCSF. After 48 hours, cells are returned to the patient intravenously, and we hope to see beneficial results.

The goals of an initial vaccine trial using Sipuleucel published in Journal of Clinical Oncology were to delay time to disease progression and improve overall survival using Sipuleucel, a cellular product vaccine. There was some benefit, yet minor, in terms of disease progression, while overall survival showed a median benefit of 4.5 months. The subsequent IMPACT trial was a randomized phase 3 trial with overall survival as the primary endpoint. Results showed a median survival benefit of 4.1 months in favor of the Sipuleucel arm. The drug was approved for hormone resistant disease, metastatic to bone irrespective of prior therapy. A concern is that the agent costs $93,000 for three injections, but the patient lives an additional four months without any antitumor effect. We know we can break immune tolerance, we can rev up the immune system, but this has not completely translated to impacting on the disease; there are survival benefits but the question is, is it sufficient? Questions arise such as do vaccines need immune modulators to exert more relevant responses, and is autoimmunity good in the short run but bad in the long run? Are we affecting other populations of cells that will be problematic?

Male Participant

Was there enough study time to whether the improvements seen while using ipilimumab were durable?

Dr. Slovin

The longest data we have out in prostate cancer is about two years; we have nothing further. You cannot compare cancers because they are completely different diseases. The toxicity which I have seen with ipilimumab in prostate cancer, such as diarrhea and fatigue, supersedes what has been seen with melanoma. We need to look at the benefit-risk ratio. Also, the dosing may not be correct.

Male Participant

Could you add prednisone? Would that negatively affect outcome?

Dr. Slovin

Prednisone will knock out some of our suppressor cells that we really want to keep. The standard dose of 10 mg/kg with ipilimumab was extrapolated from melanoma.

Female Participant

What possible effects exist for people with preexisting autoimmune conditions who use these drugs?

Dr. Slovin

Those people would be excluded from trials, including those with rheumatoid arthritis and autoimmune colitis. These would even remotely put the patient at risk; we are very cautious about that.

Male Participant

I am a trial participant. Can you briefly describe the trial? What is the problem is with getting a booster vaccination? What is behind the general inability to obtain funding for more clinical trials? What can we as consumers and patients do to help the medical profession get additional funding?

Dr. Slovin

That is an excellent question, a multipart question. The participant was involved in a trial looking at a carbohydrate vaccine; this involved one of those molecules that is present on the surface of the cancer cell. The vaccine was hooked up to a protein to make it look bigger to the immune system, then given with a drug that revved up the immune system. This was a phase 1 trial looking at safety and dosage. One problem with phase 1 is that they are very small trials; unless an immediate impact on PSA is seen, and it takes weeks to months to see antitumor activity of immune therapy drugs manifest as change in PSA, no one seems to care about proof of concept. From a scientific standpoint, we have great questions and we have the right patients, but senior leadership wants to see zero PSA and you are done. In terms of seeking funding, I have talked, I have pled, I have put in for grants, a lot of funding decision-making is bias, or this is not sexy enough, why go there? When I sit on grant study sections, I look for something that is contributing, not something that is being rehashed.

Mr. Simons

The DOD's Prostate Cancer Research Program administers $80 million to prostate cancer research, which is about one-third of what goes to breast cancer. We get more money by all us going to our Congresspeople and saying we want more money for research. We want men going up to The Hill, being aggressive, angry, distressed, and vehement about wanting to have this changed.

Dr. Slovin

Keep in mind that the number of clinical trials on which men enroll is far inferior to breast. If it weren't for the spouses and partners, none of the men would go in clinical trials.

Male Participant

I cannot understand why more money does not go into prostate cancer since most of Congress is male.

Mr. Simons

And many of them are prostate cancer survivors, and they will still not move.

Male Participant

I have met with members of Congress, unfortunately with myself or one other person, and when I say let's take our gloves off, why aren't you really listening to me, the answer

is because you are sitting there by yourself, and when other groups come in, they come in in numbers. Numbers are important.

Dr. Slovin

I think it is a political agenda: prostate just does not seem to have the bulk. Michael Milken has made a tremendous difference, as has the Department of Defense, but compared with women, women are out there, they are doing the march, yet nobody is involved with the Father's Day run. I have lost my brother, my father, and my father-in-law to prostate cancer, I live this miserable disease 24/7, yet I cannot explain to you why men are the way they are. Why don't more men go on clinical trials? What is it, a control issue? I do not know: I do not know whether it is fear or ignorance. And these are not stupid people coming into clinic; these are well educated Northeasterners.

Male Participant

Regarding clinical trials using immune therapy for people with autoimmune diseases, could you explain why those people are excluded? Does that mean that those approved therapies would not be viable treatment for somebody with an autoimmune illness? What about use in people with multiple cancers?

Dr. Slovin

With ipilimumab, the exclusion is autoimmune problems such as rheumatoid arthritis or colitis. In sum, anti-CTLA4 is what stands between you and reacting to your body; if you release the brake on that molecule, then an autoimmune event occurs. That is what the monoclonal antibody does: it blocks the interaction and the cells go crazy. For patients with preexisting colitis or arthritis, adding this drug could be tantamount to killing them. Also, regarding multiple malignancies, it is always inherently written into clinical trials that a patient may only have one malignancy, but it must be five years since your other malignancy and you must be cured from those other malignancies. We do not want other malignancy to start to grow, in which case we would have to take you off the clinical trial.

Male Participant

Does having had prostate cancer, which I see as immune system failure, put me at risk for developing other cancers at other sites, nonmetastatic prostate cancer but perhaps new malignancies such as colon?

Dr. Slovin

In general, the answer is no, you are not at risk for developing other cancers because you have had prostate cancer. I would clarify that by saying to you that patients with prostate cancer are living longer and longer; they are not to the extent of being immunosuppressive and more likely to get cancer. Patients with cancer are immunologically competent: you can get through a viral illness, pneumonia, secondary and tertiary malignancies; there is nothing inherently wrong with you. But we say there is something amiss with the immune system, yet we do not know what it is. We do not know how cancer began: it may be the immune system being suppressed due to

environmental toxins, due to diet, or due to genetics; we just do not know. I wish we did, but we do not know. Would I worry? No.

Male Participant

I had a prostatectomy three years ago, and within three months, the PSA was back. I underwent radiation, yet the PSA continued to rise. I started hormone treatments a year ago, Lupron; the PSA initially went down, then started rising again. Since I began a clinical trial in April, the PSA has gone, approaching undetectable levels. Is there a risk in stopping the hormone and monitoring PSA?

Dr. Slovin

You bring up a very good question about the use of hormonal therapy intermittently. On a clinical trial, it is very hard to stop treatment when you want to stop; inherent trial endpoints must be addressed. What you had was a biochemical relapse; I do not really know all the details. I personally believe that intermittent hormonal therapy is okay when PSA is down to zero and metastatic disease is not present. Many of us use hormonal therapy intermittently to avoid resistance over time.