PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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New Approaches to Immunotherapy for Metastatic Castration-Resistant Prostate Cancer

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H&O What are the benefits and limitations of sipuleucel-T in metastatic castration-resistant prostate cancer?

SKS Sipuleucel-T (Provenge, Dendreon), which was the first therapeutic cancer vaccine to receive approval from the US Food and Drug Administration (FDA), works to kill cancer cells by driving T cells into them. This vaccine has several benefits. First, studies have shown that it improves overall survival. Second, treatment lasts for just 1 month—patients receive a series of 3 biweekly doses over a 4-week period (weeks 0, 2, and 4), and then they are done. In addition, the side effect profile of sipuleucel-T is pretty limited, mostly consisting of flu-like symptoms that occur while patients are receiving the infusion. Occasionally these symptoms continue for a couple of days after the infusion, but most of the time they occur while patients are being monitored by the nursing staff and have little effect on their quality of life.

Sipuleucel-T remains an important option in metastatic castration-resistant prostate cancer (mCRPC), as few treatments are available. Although multiple agents have been approved for use in mCRPC, most of them add little benefit because they tend to target the same pathway, the androgen receptor pathway

One limitation of sipuleucel-T is that prostate-specific antigen (PSA) levels often continue to rise during and after treatment, and scans can show that the cancer is progressing. These findings are confusing and concerning to patients, who often ask how a drug can improve survival without leading to improvements in PSA and scans. I tell my patients that their cancer probably would be progressing much faster if they were not receiving the vaccine.

H&O What other therapeutic cancer vaccines are being studied for use in mCRPC?

SKS A vaccine that combined rilimogene galvacirepvec and rilimogene glafolivec (PROSTVAC) was in development. A phase 2 randomized trial showed a benefit in overall survival, but data from the phase 3 PROSPECT trial (A Randomized, Double-Blind, Phase 3 Efficacy Trial of PROSTVAC-V/F +/- GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic Castrate-Resistant Prostate Cancer), which Dr James Gulley presented at the 2018 annual meeting of the American Society of Clinical Oncology, did not confirm this benefit.[1,2] Several factors may explain the lack of benefit in the phase 3 trial. First, the vaccine simply may have been overcome by mechanisms of immune evasion. Second, patients in this study may have been different than those in the phase 2 study—people with mCRPC are a heterogeneous population. Finally, the availability of life-prolonging agents may have changed the equation. For example, prior to the opening of the phase 3 study, the only FDA-approved mCRPC agent available was docetaxel, but after its opening, sipuleucel-T, radium-223, cabazitaxel (Jevtana, Sanofi-Aventis), abiraterone acetate, and enzalutamide (Xtandi, Astellas) were approved.

H&O Which patients seem to benefit the most from sipuleucel-T?

SKS The patients who tend to benefit are the ones with the lowest PSA levels when they begin treatment. These are mostly patients with the lowest tumor burden and the ones with the fewest symptoms. I generally use sipuleucel-T as frontline treatment in patients with mCRPC that is asymptomatic or minimally symptomatic. I define minimally symptomatic patients as those who do not require anything stronger than non-narcotic agents such as ibuprofen for their pain. Retrospective data from Schellhammer and colleagues support the use of a PSA level of 22.1 ng/mL as a cut-off for those benefitting the most from sipuleucel-T.[3]

> Our group is turning our attention to vaccines that target tumor neoantigens.

H&O Do you think that studies of sipuleucel-T or PROSTVAC plus immune checkpoint inhibition are warranted and will be successful?

SKS We recently conducted a phase 2 trial with Dr Padmanee Sharma here at MD Anderson and Dr Lawrence Fong of UCSF Medical Center in which we compared 2 combinations of sipuleucel-T and ipilimumab (Yervoy, Bristol-Myers Squibb).[4] We are just beginning to analyze the data, which we hope to publish later this year. I think that the trial would have been more successful if we had chosen a programmed death 1 (PD-1) inhibitor instead of a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor. In 2014, after we began our trial, Dr Fong published an article in the *Journal of the National Cancer Institute* in which he reported that T cells in the prostate tumor microenvironment expressed PD-1 after treatment with sipuleucel-T.[5] Based on that finding, a different immune checkpoint inhibitor that targets PD-1 may work better in combination with sipuleucel-T.

H&O Are you planning to conduct another study with a different checkpoint inhibitor?

SKS Other groups are likely to do those studies. Our group is turning our attention to vaccines that target tumor neoantigens, whereas sipuleucel-T and PROSTVAC target conventional tumor antigens.

H&O Which immune checkpoint inhibitors are being studied for use in mCRPC?

SKS Just about every FDA-approved immune checkpoint inhibitor has been studied or is being studied in the mCRPC setting. Pembrolizumab (Keytruda, Merck) has been approved for all solid tumors that are microsatellite instability–high or have mismatch repair deficiency, which represents up to 12% of mCRPC.[6-9]

Other promising combinations that are being studied are hormonal therapy with enzalutamide plus pembrolizumab[10] or nivolumab (Opdivo, Bristol-Myers Squibb),[11] poly(ADP-ribose) polymerase (PARP) inhibition with olaparib plus durvalumab (Imfinzi, AstraZeneca),[12] and rucaparib plus nivolumab.[13] PARP inhibition is an especially exciting area of research because these agents tend to work well on their own in patients with DNA damage response (DDR) or homogenous recombination deficiency (HRD) within the tumor or in the germ line. When combined with immunotherapy, these agents have produced responses in unselected patients who do not necessarily have these defects. This suggests that the PARP inhibitors somehow enhance the effects of immune checkpoint inhibitors.

H&O Why is the response to single-agent therapy with PD-1/programmed death ligand 1 blockade so poor?

SKS Looking across numerous solid tumors, including melanoma, kidney cancer, and bladder cancer, the response rate to single-agent PD-1 or programmed death ligand 1 (PD-L1) blockade is between 15% and 30%. Patients who have a good T-cell infiltrate around the tumor microenvironment tend to respond well, and those who have a poor T-cell infiltrate tend to respond poorly. Overall, prostate cancer is considered an immunologically "cold" tumor, characterized by poor T-cell infiltration.

H&O What other factors may account for reduced response rates in prostate cancer?

SKS In addition to the lack of T cells in the tumor microenvironment, prostate cancer tends to have a low tumor mutational burden and a lot of myeloid cells that are thought to be immunosuppressive.

H&O What is the significance of the VISTA inhibitory immune checkpoint, and how can it be targeted therapeutically?

SKS VISTA is a novel immune checkpoint. Some cancers, such as acute myeloid leukemia and pancreatic cancer,

naturally express high levels of VISTA in their microenvironment.[14] But in prostate cancer, immune checkpoint inhibitors such as ipilimumab induce VISTA expression within the tumor microenvironment, which suggests that the combination of ipilimumab plus a drug targeting VISTA would improve clinical outcomes. Pharmaceutical companies have developed drugs to target VISTA, which we hope will be evaluated in the clinic sometime this year.

H&O Can you discuss the data on combination checkpoint inhibition with ipilimumab and nivolumab in men with mCRPC that were presented at the 2019 Genitourinary Cancers Symposium?

SKS Our group at MD Anderson, including Drs Padmanee Sharma, James Allison, and Ana Aparicio, began studying the use of CTLA-4 inhibition in prostate cancer several years ago. We have seen amazing responses in small subsets of patients, and we wanted to understand why this approach was not working in all our patients. We examined tumor tissues from patients who had received ipilimumab and found that the samples taken before treatment had very few T cells and those taken after treatment had a lot of T cells. We were excited initially because we had succeeded in turning a "cold" tumor "hot" by increasing infiltration of activated T cells with cytolytic activity. However, this clearly was not enough, because the tumors were not dying. The T cells were behaving like a loaded gun with its firing pin in the locked position. That locked firing pin was upregulation of the immune checkpoints PD-1, PD-L1, and VISTA.

At the time we did not have a good VISTA clinical antibody, so we used a combination of the CTLA-4 inhibitor ipilimumab and the PD-1 inhibitor nivolumab. This combination produced dramatic responses in our mouse models of prostate cancer. When we showed these data to Bristol-Myers Squibb, they sponsored a phase 2 multicenter international trial with 90 patients called CheckMate 650 (A Study to Evaluate Preliminary Safety and Efficacy of Nivolumab Plus Ipilimumab in Men With Metastatic Castration-Resistant Prostate Cancer).[15] We treated 30 of the patients here at MD Anderson, and saw some remarkable responses in heavily pretreated patients. Dr Sharma recently presented early results from this trial at the Genitourinary Cancers Symposium.[16] At a median follow-up of approximately 1 year, 8 patients continued to experience ongoing responses, 5 of which lasted more than a year. So it looks like combination treatment with nivolumab plus ipilimumab can be a game changer. Another interesting early finding is that on biomarker analysis, the patients with a higher tumor mutational burden seemed to be benefiting the most from this approach.

Although these data are really exciting, the toxicities of combination immunotherapy are pretty high and a lot of patients were not able to receive the full treatment. A total of 51% of patients in cohort 1 and 44% of patients in cohort 2 had severe adverse events, which included diarrhea, fatigue, skin rash, nausea, and hypothyroidism. Four patients died of treatment-related adverse events. As a result, we are designing a larger phase 2 trial with altered dosing (decreasing the dose of ipilimumab to 1 mg/kg while increasing nivolumab to 3 mg/kg, as much of the toxicity is attributed to ipilimumab) and scheduling (the combination is given every 6 weeks instead of every 3 weeks) in an effort to minimize toxicity with the hopes of further improving efficacy. This trial will be an expansion of CheckMate 650.

H&O What are we learning about novel immunogenic subsets of prostate cancer, such as mismatch repair deficiency, CDK12 loss, and high tumor mutational burden?

SKS Patients who fall into one of these subgroups have tumors that tend to be more infiltrated with T cells, and therefore are more likely to respond to immune checkpoint therapies. That does not mean, however, that 100% of these patients respond. Aberrations in CDK12 are present in up to 7% of patients with mCRPC. CDK12 regulates the cell cycle and DNA replication; however, biallelic loss of CDK12 extensive tandem duplications within the genome leads to gene fusions. These gene fusions can serve as neoantigens, which in turn promotes intratumoral T cell infiltration. We and others have found that prostate tumors that are highly infiltrated with T cells are more likely to respond to immune checkpoint therapies. Our group has treated 3 patients with CDK12 loss (up to 7% of patients with mCRPC), and none of them responded to immune checkpoint therapies. The general response rate to immune checkpoint inhibition in mCRPC is approximately 6% to 10% among unselected patients, whereas it may be 50% or greater among patients with mismatch repair deficiency, CDK12 loss, and/or high tumor mutational burden. In a study by Le and colleagues that appeared in the *New England Journal of Medicine* in 2015, the response rate to pembrolizumab among patients with mismatch repair deficiency was 40% for colorectal cancer and 71% for non-colorectal cancer.[17]

H&O How common are these subsets, and what are the clinical implications for therapy?

SKS These subsets are not very common. In a study by Abida that was published in *JAMA Oncology* in 2018, only 3.1% of 1033 patients with prostate cancer fell into

the category of high microsatellite instability or mismatch repair deficiency.[18] It is important for us to identify patients with prostate cancer who fall into these subsets, however, because too many patients with prostate cancer are treated with a one-size-fits-all approach. We should emulate the model of lung cancer, in which the 5% to 6% of patients with non–small cell lung cancer who have an *ALK* rearrangement are eligible for treatment with an ALK inhibitor.

H&O What is the role of myeloid-derived suppressed cells in CRPC?

SKS Myeloid-derived suppressed cells (MDSCs) are very well defined in mice, but not in patients—this is one of many times when mouse does not equal human. In fact, we just call them immunosuppressive myeloid cells in patients. Our group has found that prostate cancer contains far more of these myeloid cells than many other tumors.

Studies have shown that depleting these cells in mice, through the use of cabozantinib (Cabometyx, Exelixis) can enhance the effects of immune checkpoint therapies and improve survival.[19] As a result, our group and others are looking at combining agents targeting myeloid cells with checkpoint inhibitors. These are exciting times, and we are giving our patients a lot more hope than we could even a few years ago.

Disclosures

Dr Subudhi has served as a consultant or advisor for Apricity Health, Bayer, Compugen, Dendreon, Janssen, and Polaris. He owns stock in Apricity Health.

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