PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

PSMA-Targeted Therapy in Prostate Cancer

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H&O What is prostate-specific membrane antigen (PSMA), and what makes it a good target for the treatment of prostate cancer?

ST PSMA is a cell surface antigen that is expressed to a limited degree on certain normal cells in the body but generally is highly overexpressed in the setting of prostate cancer. Normal cells that express PSMA are located in the prostate, salivary, and lacrimal glands; the proximal part of the small intestine; the proximal renal tubules; and some ganglia. In the setting of prostate cancer, PSMA expression generally increases along with the cancer grade, and it also increases following hormonal therapy. In addition, PSMA expression tends to be higher in metastatic sites than in primary tumors. Some heterogeneity exists, however, so that PSMA may not be present on 100% of prostate tumors or on 100% of the cells within a prostate tumor. Biopsy and autopsy studies of PSMA imaging reveal positivity in approximately 90% of prostate cancer sites.

PSMA levels are tightly linked to the androgen receptor pathway, and they increase as resistance to hormonal therapy develops. However, tumors that are not driven by the androgen receptor—that is, neuroendocrine, small cell, and aggressive-variant prostate cancers—are more commonly PSMA-negative.

The fact that most men with prostate cancer have elevated PSMA levels, and that expression is limited outside the main site, makes PSMA an excellent target in the treatment of prostate cancer. Some agents that target PSMA may damage a tumor and cause just a bit of damage to other sites if the agents are not completely ablative, resulting in low-grade toxicity. Alternatively, an agent such as a monoclonal antibody might be able to target a tumor without binding to other PSMA-positive sites owing to its large size and physical inability to reach luminal sites of expression that are separated from the vasculature by tight junctions.

H&O How is PSMA positivity established?

ST Imaging and biopsy are the main ways to establish PSMA positivity. Multiple imaging modalities are available worldwide. The agent indium In 111 capromab pendetide (ProstaScint) has been approved for years in the United States, and the US Food and Drug Administration (FDA) approved the use of gallium Ga 68 PSMA-11 at 2 institutions in California (similar to the prior limited approval for ^{11}C-choline) in December of 2020. Other sites now have the opportunity to apply for their own approval, with potential future approval of a kit for the preparation of ^{68}Ga-PSMA-11 (TLX519-CDx, Telix Pharmaceuticals) to facilitate availability. Additional agents, such as ^{18}F-DCFPyL (PyL, Lantheus Holdings), also appear to be close to FDA approval. Imaging makes it possible to look at individual tumor sites and see whether all are positive, or just some. For biopsy, we stain a needle biopsy or surgical specimen with the relevant protein. A third method, which has been used in research studies, is to examine levels of PSMA in circulating tumor cells.

An argument can be made that establishing PSMA positivity is not necessary, however, depending on the clinical setting and goals. First, PSMA positivity will be found in nearly all patients with prostate cancer, and second, all of the testing methods produce some false-negative results.

H&O What types of PSMA-targeted therapies are being developed for use in prostate cancer?

ST The 3 main categories of PSMA-targeted therapies are cytotoxic, immune-targeted, and radionuclide-directed.

The initial approach to cytotoxic therapy started nearly 15 years ago, with an older type of antibody-drug conjugate (ADC). The problem was that the antibody and the cytotoxic agent were weakly conjugated and fell apart, which defeated the purpose of the agent. A more recent approach to cytotoxic therapy, which is in early-phase trials, employs the use of ADCs or small molecule–ligand toxin conjugates. Some of these trials have produced somewhat positive results, but toxicity still occurs, especially if the toxin is highly potent. One interesting agent that is being studied is a PSMA-targeted nanoparticle that contains docetaxel, although it is unclear how much better this formulation is than standard docetaxel.

The 2 types of immune-targeted approaches use chimeric antigen receptor (CAR) T cells and bispecific antibodies. Researchers at the University of Pennsylvania have shown some efficacy in the treatment of prostate cancer with PSMA-directed genetically modified autologous T-cell immunotherapy; that trial was temporarily halted after a death but is being restarted (NCT03089203). Progress is slow in CAR T-cell research because the technique is risky, with a high chance of causing toxicity. On the other hand, it has the potential—at least in theory—to provide a cure. One difference between targeting CD19 and targeting PSMA is that patients can be okay after all their CD19 has been wiped out, even if they need intravenous immunoglobulin. By contrast, we have some concern that renal failure, for example, might develop if the PSMA-targeting agents target certain normal tissues, such as the proximal renal tubules, too well.

Several companies are investigating the use of bispecific antibodies in prostate cancer, so this research is moving more quickly than the research on CAR T cells. The most recent bispecific antibodies do not require continuous infusion because the molecules are large enough to have a long circulating half-life. Another advantage of these larger molecules is that the agents are not able to reach certain PSMA-positive areas, such as the kidneys. The 2020 ASCO (American Society of Clinical Oncology) Virtual Scientific Program included phase 1 results on HPN424 from Harpoon Therapeutics, the ESMO (European Society for Clinical Oncology) Virtual Congress 2020 included phase 1 results on AMG 160 from Amgen, and the 2019 ASCO Annual Meeting included phase 1 results on AMG 212 from Amgen. Researchers are currently determining the best way to dose bispecific agents and how to combat cytokine release syndrome.

The oldest of these approaches is PSMA-targeted radionuclide therapy, which was first developed more than 20 years ago. The initial approach, which used the capromab antibody that binds an intracellular domain of PSMA, was not effective because viable PSMA-positive cells could not be targeted. Since then, additional antibody and small-molecule agents labeled with beta emitters have been developed in phase 1 and 2 trials, such as lutetium 177, iodine 131, and yttrium 90.

The agent that is the farthest along in regulatory pathways is ^{177}Lu-PSMA-617. Lutetium 177 is a beta emitter with a fairly short range and low potency compared with other therapeutic radionuclides. Clinicians have also become somewhat familiar with this radionuclide since the FDA approval in 2018 of a somatostatin-targeted agent labeled with ^{177}Lu, called lutetium Lu 177 dotatate (Lutathera, Novartis), for use in neuroendocrine tumors.

The first prospective trial of a radioactively labeled PSMA-targeted small molecule to be published in this area was the LuPSMA trial, which studied the use of ^{177}Lu-PSMA-617 in 30 men. The results were first published by Hofman and colleagues in *Lancet Oncology* in 2018. This study was eventually expanded from 30 patients to 50 patients, with longer follow-up on the initial 30 patients published by Violet and colleagues in the *Journal of Nuclear Medicine* in 2020.

^{177}Lu-PSMA-617 is currently being tested in the ongoing TheraP trial, which Hofman presented at the 2020 ASCO Virtual Scientific Program. TheraP is a randomized phase 2 trial of men with metastatic castration-resistant prostate cancer (mCRPC) who received prior docetaxel; most patients also received abiraterone or enzalutamide (Xtandi, Astellas). Patients needed to be strongly positive for PSMA by ^{68}Ga-PSMA-11 and any PSMA-negative areas also negative by ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography (PET/CT) to be eligible. A total of 200 men were randomly assigned to ^{177}Lu-PSMA-617 or to cabazitaxel (Jevtana, Sanofi-Aventis). The researchers found a higher response rate, defined as a reduction in the prostate-specific antigen (PSA) level of at least 50%, with ^{177}Lu-PSMA-617 than with cabazitaxel. Grade 3 or 4 adverse events occurred in 32% of the men treated with ^{177}Lu-PSMA-617 vs 49% of those treated with cabazitaxel. This was an open-label study, and more men dropped out before treatment in the group assigned to cabazitaxel, but sensitivity analysis maintained the superiority of the PSA response to ^{177}Lu-PSMA-617. Adverse events were different in the 2 groups; thrombocytopenia and xerostomia were more common with ^{177}Lu-PSMA-617, and neutropenia was more common with cabazitaxel. Discontinuations for toxicity occurred in 1% of the ^{177}Lu-PSMA-617 group vs 4% of the cabazitaxel group, and no treatment-related deaths occurred.

A trial called VISION, which completed enrollment in late 2019, should produce initial results in early 2021. In this phase 3 trial, patients with PSMA-positive mCRPC by ^{68}Ga-PSMA-11 PET/CT who had previously received androgen receptor–targeted therapy and chemotherapy were randomly assigned in a 2:1 ratio to receive standard-of-care treatment with or without ^{177}Lu-PSMA-617. The dual primary endpoints are radiographic progression-free survival (rPFS) and overall survival. Patients have been undergoing fewer scans right now because of the novel coronavirus pandemic, which has likely delayed the results, but we expect to see rPFS results in several months and overall survival results shortly thereafter. VISION is a registration study, so we can expect to see FDA approval if the results are positive—which would be the first FDA approval for one of these therapeutic agents in prostate cancer.

When we are dealing with late-stage, heavily pretreated cancer, the risk-to-benefit ratio will generally favor the administration of ^{177}Lu-PSMA-617.

Another important study, which is taking place in Australia, is the randomized, phase 2 UpFrontPSMA study (NCT04343885). This trial is enrolling men with metastatic hormone-naive prostate cancer and randomly assigning them to either ^{177}Lu-PSMA-617 followed by docetaxel or docetaxel alone. An additional phase 1 study, called LuPARP, is looking at olaparib (Lynparza, AstraZeneca) in combination with ^{177}Lu-PSMA-617 in men with mCRPC (NCT03874884). A planned study from the Prostate Cancer Clinical Trials Consortium (PCCTC) will be randomly assigning men who have chemotherapy-naive mCRPC to pembrolizumab (Keytruda, Merck) with or without PSMA-targeted radionuclide therapy with 225Ac-J591. Could targeted radiation allow the immune checkpoint inhibitor to work better? That would be useful to know.

Several more prospective, randomized phase 3 trials will be launched in early 2021 that will look at various agents and/or combinations in various disease settings. Some trials will be in hormone-sensitive metastatic prostate cancer, and others in mCRPC. These newer trials will look at earlier lines of treatment than those used in VISION.

H&O What are the disadvantages of using PSMA-targeted radionuclide therapy?

ST Common side effects include dry mouth, blood cell count abnormalities, nausea, and pain flares; these are usually mild and resolve after several weeks. Longer-term toxicities are more concerning. One of the biggest concerns with radiation therapy, whether it be internal or external, is the risk for secondary cancers down the line. In the case of systemically infused radionuclides that flow through the bone marrow, these include leukemia. Another concern with PSMA-targeted small molecules is the possibility of renal failure because of specific targeting of the kidney with PSMA.

When we are dealing with late-stage, heavily pretreated cancer, the risk-to-benefit ratio will generally favor the administration of ^{177}Lu-PSMA-617. If radiation is used earlier in treatment, however, secondary cancers are likely to become more of a concern. This is a good problem to have, but the risks for secondary cancers and for renal failure are certainly on our radar as we move these trials to earlier disease states.

H&O What questions remain to be answered regarding PSMA-targeted therapy?

ST Two of the biggest questions related to the use of PSMA-targeted therapy—in earlier disease states and in new combinations—are now being addressed on a large scale. Another question relates to the best way to select patients for PSMA-targeted therapy. Do we need imaging or biopsy to establish PSMA positivity before treatment? That is a question few people are asking. One reason might be that doctors are willing to try a treatment in someone with metastatic prostate cancer even if it is unlikely to work, as long as the treatment is relatively safe and the patient has no other options. We take that approach all the time in treating patients with late-stage prostate cancer, such as giving enzalutamide after abiraterone in a patient who has already received chemotherapy and radium Ra 223 dichloride (Xofigo, Bayer). It usually does not work, but sometimes it does, and that makes it worth trying. However, as we move to treating earlier-stage disease for which many more treatment options are available, the question of PSMA positivity will increase in importance and will lead to further questions. What type of imaging is best? What should the cutoff level be for positivity? And how does the timing of imaging affect the results, especially if hormonal treatment alters those results? I

encourage physicians to recommend clinical trials for their patients whenever appropriate.

Disclosure

Dr Tagawa reports institutional research support from Sanofi, Medivation, Astellas, Janssen, Amgen, Progenics Pharmaceuticals, Dendreon, Lilly, Genentech, NewLink Genetics, Bristol-Myers Squibb, Inovio Pharmaceuticals, AstraZeneca, Immunomedics, Aveo Oncology, Rexahn Pharmaceuticals, Atlab Pharma, Boehringer Ingelheim, Millennium Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Merck, AbbVie, Karyopharm Therapeutics, Endocyte, Clovis Oncology, Seagen, and AAA/Novartis; honoraria from Sanofi, Medivation/Astellas, Dendreon, Janssen, Genentech, Bayer, Endocyte, Eisai, Immunomedics, Karyopharm Therapeutics, AbbVie, Tolmar, Seagen, Amgen, Clovis, QED Therapeutics, Pfizer, AAA/Novartis, Genomic Health, POINT Biopharma, and Blue Earth Diagnostics.

Suggested Readings

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