PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Targeted Therapy in Prostate Cancer: Beyond PSMA

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H&O What are the limitations of prostate-specific membrane antigen (PSMA)–targeted therapy in prostate cancer?

MM PSMA is a very good target in prostate cancer, but not every tumor expresses copious amounts of PSMA. Prostate cancer is a highly heterogeneous disease biologically, which includes heterogeneity in the degree of PSMA expression. Even within the same patient, some lesions are more PSMA-avid than others. This heterogeneity is an important reason why only about half of patients with metastatic castration-resistant prostate cancer (mCRPC) respond to PSMA-directed radioligand therapy. Another reason for this less-than-ideal response rate is that PSMA-targeted therapy is used at a very advanced stage of the disease, when resistance mechanisms have had an opportunity to develop fully. Of course, increases in disease heterogeneity and resistance mechanisms are inherent to advanced disease.

Another limitation of PSMA-directed therapy is that PSMA-directed small molecules tend to be taken up by the salivary glands. The resulting xerostomia is a significant dose-limiting toxicity, especially with some of our newer agents, which have an alpha rather than a beta radiation payload. In contrast, new targets, such as human kallikrein 2 (hK2), may be associated with less xerostomia because there is less uptake by the salivary glands. Another benefit of alternative targets to PSMA is that they may be expressed in prostate tumors that do not express PSMA, so that patients with these tumors can benefit from radioligand therapy.

H&O What other radioligand treatments are being examined for use in prostate cancer?

MM Some promising radioligand targets in prostate cancer beyond PSMA are hK2, which I just mentioned, and delta-like ligand 3 (DLL3). The human kallikrein family is widely expressed in prostate cancer; indeed, prostate-specific antigen (PSA) is actually hK3. We are looking at targets all along the spectrum of diversity of prostate cancer, which ranges from poorly differentiated neuroendocrine prostate cancers to well-differentiated adenocarcinomas.

hK2 is an especially good target for radioligand therapies in patients who have adenocarcinomas and androgen receptor (AR)–driven disease. An important difference between hK2 and PSA is that PSA is expressed primarily as a soluble molecule (hence its ease of use, being measured with a simple blood draw), whereas hK2 is expressed as both a soluble molecule and a membrane-bound molecule. Having a target on the cell membrane of prostate cancer means that when a radioligand attaches to the target, the drug is internalized and the cell is exposed to the radioligand therapy. In fact, our current hK2-directed therapy preferentially binds to the membrane-bound form of hK2 rather than the soluble form of hK2. This is valuable because it means that most of the drug ends up

in the cancer rather than circulating in the blood.

DLL3 is an especially good target for radioligand therapies in patients who have treatment-emergent neuroendocrine prostate cancer, which affects approximately 15% of patients who have mCRPC. These patients have disease that has progressed through an AR pathway inhibitor (ARPI), and their target expression may be more similar to that of patients with small cell lung cancer than of typical patients with prostate cancer. Some of these patients have disease with both AR and neuroendocrine features, and some have disease with just neuroendocrine features. We do not have a durable, effective therapy for patients with this condition, which makes the DLL3-based approach so promising for those patients who have a significant component of DLL3-positive disease.

H&O Could you describe your group's research on hK2-targeted therapy in prostate cancer?

MM Our research on hK2 here at Memorial Sloan Kettering Cancer Center (MSKCC) goes way back. The research group of Dr Hans Lilja, who was originally based in Sweden and is now at MSKCC, was an initial and crucial discoverer of hK2. The 4Kscore Test, which has been available as a laboratory-developed test since 2014 and received US Food and Drug Administration approval in 2021, is a risk assessor for people with newly diagnosed disease or suspected prostate cancer. The use of hK2 as a target became feasible thanks to the work of the laboratory of Dr Steven Larson here at MSKCC and Dr H. David Ulmert, formerly of MSKCC. They were the researchers who developed the original humanized antibody for this target, now known as h11B6. The antibody was first tested here preclinically as a carrier with a radioactive payload; it then underwent a phase 0 study to show that we could target hK2 in humans and that hK2 could be imaged with a tracer.[1] This study showed that unlike PSMA, hK2 has almost no salivary gland uptake.

That finding led to a phase 1 study of hK2 radioconjugated to actinium 225 as a therapy in mCRPC. We presented early results of this study, which was sponsored by Johnson & Johnson, at the most recent American Society of Clinical Oncology (ASCO) Annual Meeting.[2] This study is looking at use of the alpha emitter ^{225}Ac conjugated to an hK2 antibody in patients with mCRPC who have received at least one ARPI, such as enzalutamide (Xtandi, Astellas) or abiraterone. Patients did not undergo selection with imaging, so these were essentially all comers. Patient eligibility also was agnostic to prior exposure to chemotherapy, although patients were not allowed to have received prior radioligand therapy with lutetium Lu 177 PSMA 617 (Pluvicto, Novartis).

The dosing schedule was iteratively developed. We started out with a very traditional phase 1 dose escalation by cohort schedule. This more traditional approach turned out to be disadvantageous. The primary reason is that at a certain threshold of exposure, approximately 500 to 600 μCi of cumulative exposure, pulmonary toxicity and thrombocytopenia tend to develop. What we ultimately arrived at was an adaptive dosing schedule, in which we gave a single dose of 250 μCi and re-dosed only as needed, remaining below a cumulative dose of 500 to 600 μCi. Some people experienced a response lasting for many months with only one dose of this agent. With this approach, we have seen no pulmonary toxicity and have significantly mitigated thrombocytopenia.

I think that hK2 targeting has great potential to move forward.

H&O Could you discuss the research with DLL3-targeting radioligand therapy?

MM Our group recently published the first paper on DLL3 imaging in neuroendocrine prostate cancer, showing that neuroendocrine prostate cancer can be imaged and therapeutically targeted with DLL3-directed radioligand therapy.[3]

This 18-person study showed that we can detect DLL3 positivity in patients who have neuroendocrine cancers with the use of positron emission tomography/computed tomography (PET/CT). The study showed that many patients have a blend of DLL3-positive and PSMA-positive disease, and such heterogeneity really became appreciated only after this imaging trial. For example, a patient who is on AR-directed therapy could have stable bony metastases that express PSMA in combination with emerging liver metastases that express DLL3. The suite of imaging modalities allows us to see not only the diversity biologically of prostate cancer but also what is driving the worst disease—which is what we want to target.

We already have an FDA-approved DLL3-directed therapy for small cell lung cancer, the bispecific antibody tarlatamab (Imdelltra, Amgen). A small phase 1b study that was presented at the 2024 ASCO Annual Meeting showed that tarlatamab is also effective in patients with high-grade neuroendocrine prostate tumors.[4] Patient selection is much more important with neuroendocrine

prostate tumors because not all of these tumors express high levels of DLL3, whereas virtually all neuroendocrine small cell lung tumors express DLL3.

We are developing a protocol for the first study of DLL3-targeting theranostics for prostate cancer, which is being funded by the National Cancer Institute and will be led by Dr Lisa Bodei at MSKCC. MSKCC is developing an additional DLL3 theranostic pair in a study that is being funded by the Prostate Cancer Foundation.

H&O What do you see happening next with hK2- and DLL3-targeting radioligand therapy in prostate cancer?

MM I think that hK2 targeting has great potential to move forward. I would like to see widespread use of imaging to detect hK2 positivity and determine the best candidates for treatment. Even PSMA-directed therapy is enhanced by imaging to determine the best candidates for treatment. I would like to see hK2 imaging eventually done with PET, which is more quantitative than imaging done with single-photon emission CT.

The world is wide open in terms of future research with DLL3. We are just at the nascency of understanding DLL3 expression, and we are only beginning to develop theranostic drugs for DLL3. I think that there is a huge future not just in theranostics but also in the development of multiple drug families.

Furthermore, each time we identify a new target in prostate cancer, we have the potential to target it not only with radioligand therapy but also with antibody-drug conjugates, bispecific antibodies, and chimeric antigen receptor T-cell therapies. This opens the door to the development of multiple families of agents.

This is a very exciting time in prostate cancer drug development. We are getting much better at making these tools efficiently, and rapid advances offer a lot of hope to our patients.

Disclosures

Dr Morris is a paid consultant for Lantheus, AstraZeneca, Daiichi, Convergent Therapeutics, Pfizer, ITM Isotope Technologies, Clarity Pharmaceuticals, Blue Earth Diagnostics, POINT Biopharma, Telix Pharmaceuticals, Progenics Pharmaceuticals, Z-Alpha Therapeutics, Ambrx, Flare Therapeutics, Fusion Pharmaceuticals, Curium, TransThera Biosciences, Bristol Myers Squibb/Celgene, Arvinas, and Exelixis. He receives institutional research funding from Corcept Therapeutics, Janssen, Celgene, Novartis, and Astellas. His institution receives royalties from Telix Pharmaceuticals.

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