PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

Biomarkers and Novel PET Imaging to Detect Neuroendocrine Prostate Cancer

Rahul Aggarwal, MD
Professor of Medicine
Division of Hematology/Oncology
University of California San Francisco
San Francisco, California

H&O What is neuroendocrine prostate cancer (NEPC), and how common is it?

RA NEPC is an aggressive histologic subtype of prostate cancer. The de novo form is present at the time of diagnosis, whereas the treatment-resistant form arises following the use of androgen deprivation therapy (ADT).

De novo NEPC is uncommon, accounting for less than 1% of all prostate cancers. Patients with this form of NEPC are likely to have metastatic disease at the time of diagnosis. The treatment-emergent form of NEPC occurs in up to 15% to 20% of metastatic castration-resistant prostate cancer (mCRPC) cases. Pathologists have become increasingly aware that prostate cancer that started out as an adenocarcinoma at the time of diagnosis may morph into treatment-emergent NEPC.

H&O What causes these 2 forms of NEPC?

RA We do not have a good handle on what causes de novo NEPC. We know that these tumors are likely to have deletion or inactivation of multiple tumor suppressor genes, especially *RB1* and *TP53*, but we do not understand what underlies these mutations.

Treatment-emergent NEPC occurs as an escape mechanism from longstanding ADT. One of the paths of resistance to ADT is lineage plasticity, in which the cells transition from one type of cancer to another. Lineage plasticity occurs through epigenetic modification that causes certain genes to turn on and others to turn off, leading to alterations in the expression of genes and proteins.

H&O Is lineage plasticity reversible?

RA If prostate cancer can go from adenocarcinoma to NEPC, the hope is that it can also go from NEPC to adenocarcinoma with the right therapeutic intervention. We do not yet know whether this is possible clinically, but it has been shown to be possible in preclinical models.

H&O How is NEPC detected?

RA The detection of de novo NEPC is based on biopsy of the prostate and is relatively straightforward. Under the microscope, it looks very much like small cell lung cancer, with small, round, dark cells and a high proliferation rate—very different than standard prostate adenocarcinoma. Morphologically, small cell NEPC appears as sheets of small tumor cells with minimal cytoplasm, nuclear molding, fine chromatin pattern, with extensive tumor necrosis/apoptosis, without appreciable glandular structure. In contrast, a typical prostate adenocarcinoma appears as large neoplastic cells with nuclear pleomorphism and hyperchromasia, and the tumor cells attempt to make glandular structures. Sometimes tumors are admixed, with a component of adenocarcinoma and another of small cell carcinoma within the same biopsy sample or in different samples from the same prostate.

The diagnosis of treatment-emergent NEPC is more difficult than that of de novo NEPC because it is based on biopsy of the metastatic site. The treatment-emergent NEPC cells have a high proliferation rate. Pathologists often deal with biopsies with a limited amount of tumor,

or with biopsies that contain a combination of adenocarcinoma and transformation into more neuroendocrine features, making diagnosis difficult. Adding to the difficulty, we do not have consensus criteria for what defines NEPC vs a high-grade, poorly differentiated adenocarcinoma.

H&O What is the role of biomarkers and novel positron emission tomography (PET) imaging in the detection of NEPC?

RA There is a high unmet clinical need for noninvasive markers of disease, such as liquid biopsy and PET imaging. We are currently dependent on metastatic biopsy, which has limitations, to detect the treatment-emergent form of NEPC. For example, it can be difficult to obtain useful tumor tissue from metastases that are confined to the bone.

Metabolic imaging can be helpful as part of a diagnostic work-up. For example, if a patient is fluorodeoxyglucose (FDG)-PET–positive and prostate-specific membrane antigen (PSMA)-PET–negative, that points to the need for further follow-up and biopsy.

More specific tracers for NEPC are currently being evaluated in clinical trials. For example, several trials are investigating agents that target delta-like ligand 3 (DLL3), which is a protein marker that is expressed in approximately 60% to 80% of NEPC cases (NCT04702737, NCT04471727).

A challenge in the treatment-emergent NEPC setting is the significant heterogeneity that can occur within the same patient, with different lesions having various levels of neuroendocrine differentiation. A potential advantage of PET imaging for diagnosis is that it can allow for visualization of heterogeneity, such as identifying areas that have a higher DLL3 uptake than other areas. This is a promising approach, and we hope to see more clinical data. Researchers are looking for other potential markers of neuroendocrine differentiation. Earlier research showed that PET imaging with lutetium 177 (^{177}Lu)-DOTATATE or ^{177}Lu-DOTATOC did not perform well in detecting NEPC, which is not as well-differentiated as neuroendocrine tumors of the gastrointestinal tract.

H&O What other research is ongoing?

RA We are working on a zirconium 89 PET imaging agent to target an epitope of the CD46 protein. This target is highly expressed in neuroendocrine-type prostate cancers, based on metastatic biopsies that have looked at CD46 expression in NEPCs. We do not have any clinical imaging data yet, but preclinical data are promising.[1]

We have also published preclinical data on the use of an antibody-drug conjugate (ADC) consisting of a tubulin inhibitor plus a macropinocytosing anti-CD46 antibody. This ADC was able to kill both adenocarcinoma and NEPC cell lines in vitro without killing normal cells.

Methylation profiling of circulating tumor DNA is another technique that is showing promise for the detection of NEPC.[2]

H&O How is NEPC treated?

RA De novo NEPC is not dependent on androgen signaling, so it is unresponsive to hormone therapy. As a result, we treat patients with de novo NEPC much like we treat other extrapulmonary small cell cancers and small cell lung cancer, with platinum-based chemotherapy and sometimes radiation therapy as well if it makes sense for patients clinically. Hormone therapy is not used.

There is not one standard accepted sequence of therapies for treatment-emergent NEPC. In general, we use platinum-based chemotherapy, although other therapies used for standard mCRPC may also have benefit, including taxane chemotherapy, radioligand therapies, and targeted therapies (including poly[ADP-ribose] polymerase inhibition) in the presence of sensitizing mutations.

I am excited about a number of promising investigational approaches for NEPC that are in clinical development, including new immunotherapeutics targeting DLL3 (eg, tarlatamab and HPN328), novel chemoimmunotherapy combinations (eg, nivolumab, ipilimumab, carboplatin, and cabazitaxel in the CHAMP trial; NCT04709276), and therapies targeting the epigenetic dysregulation that is a hallmark of NEPC transformation (eg, inhibitors of EZH2, BET bromodomain, and DNA methyltransferase).

Disclosures

Dr Aggarwal has served in a consulting or advisory role to Pfizer, Merck, Amgen, Jubilant Pharma, Alessa Therapeutics, Exelixis, Bayer, TeSera, OncLive, BioXcel Therapeutics, Janssen, Novartis, AstraZeneca, Boxer Capital, EcoR1 Capital, and PCCTC; has received research funding (to institution) from Zenith Epigenetics, Novartis, Xynomic Pharma, Janssen, Merck, Amgen, and AstraZeneca; has provided expert testimony to University of Utah Health; and has received travel, accommodations, or expenses from DAVA Oncology.

References

1. Wang S, Li J, Hua J, Su Y, et al. Molecular imaging of prostate cancer targeting CD46 using ImmunoPET. *Clin Cancer Res*. 2021;27(5):1305-1315.

2. Beltran H, Romanel A, Conteduca V, et al. Circulating tumor DNA profile recognizes transformation to castration-resistant neuroendocrine prostate cancer. *J Clin Invest*. 2020;130(4):1653-1668.