PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

Overcoming Immune Evasion in Advanced Prostate Cancer

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H&O Why do some patients with prostate cancer respond to immune checkpoint inhibitors (ICIs), whereas others do not?

AA Several clinical trials with ICIs, either alone or in combination, have shown disappointing results in unselected patients affected by metastatic hormone-sensitive or castration-resistant prostate cancer. By contrast, durable objective responses have been reported in some patients with prostate cancer who have alterations in homologous recombination genes or who have mismatch repair deficiency (dMMR) or microsatellite instability–high (MSI-H) status. Pembrolizumab (Keytruda, Merck), an antibody targeting the programmed death 1 receptor, has been approved by the US Food and Drug Administration for the treatment of dMMR or MSI-H solid tumors, independent of the site of origin. However, only approximately half of prostate cancer patients with these alterations experienced a clinical benefit from immunotherapy. Further studies are needed to investigate mechanisms of resistance in this population.

H&O Are there any specific biomarkers that can let doctors know which patients might respond to immune checkpoint inhibition?

AA We could perform tests for dMMR and MSI-H status, but the optimal method for determining the presence of these remains unclear and the clinical implications of broader screening are not considered cost-effective. Indeed, the prevalence of MSI-H in prostate cancer patients is low but unclear, ranging in studies from 1% to 10%.

H&O What are some of the impediments to success in using ICIs in prostate cancer?

AA There are many possible reasons why patients with prostate cancer may not respond to ICIs. First, unlike melanoma and many other types of cancer, prostate cancer has a low mutational burden, meaning that it has relatively few genetic alterations associated with the presence of a dense stromal network. Second, studies in prostate cancer have demonstrated downregulation of programmed death ligand 1 in the primary tumor. Third, and most importantly, the prostate tumor microenvironment is considered cold rather than hot, meaning that it is usually less infiltrated by immune cells with anticancer activity (mainly CD8+ T cells) compared with other cancers that are known to respond well to immunotherapy. Why do the T cells fail to infiltrate prostate cancer? Our team has found, in both mouse models and humans with prostate cancer, that the main type of immune cell that infiltrates the prostate cancer microenvironment is myeloid-derived suppressor cells (MDSCs).[1] These MDSCs cells block the ability of T cells and natural killer cells to infiltrate and attack the tumor. In our 2018 study in *Nature*, we showed that we could restore sensitivity to androgen receptor signaling inhibition in mice by inactivating interleukin 23, thereby blocking the action of MDSCs.[2]

We are currently focused on identifying ways to change the tumor microenvironment in humans so that T cells and natural killer cells can be reactivated. One approach is to prevent the tumor from recruiting MDSCs by blocking CXCR2, which is a chemokine receptor expressed by MDSCs. In a clinical trial that we expect to publish soon, we were able to increase the activity of ICIs by interfering with the activity of CXCR2. We found that a CXCR2 antagonist was effective in some patients with metastatic hormone-sensitive prostate cancer, but not in all. We do not know why some patients responded and others did not.

The discovery that bacteria can convert precursor into testosterone is revolutionary because it means that the microbiota are behaving like an endocrine gland.

Another recent discovery of ours is that MDSCs can go through a process of cellular senescence that allows them to remain in the tumor microenvironment for an extended period. For many years, we believed that MDSCs have a very short half-life of just 48 to 72 hours. In prostate cancer, however, we have found that MDSCs age faster and enter a senescent state in which they do not die and instead accumulate in the tumor microenvironment. These older MDSCs are even more immunosuppressive and protumorigenic than the younger cells in the tumor microenvironment. So not only do we need to block MDSCs from entering the tumor, we need to eliminate the cells that are already present. We published a study earlier this year in which we identified agents that have the potential to eliminate this population of senescent MDSCs; we refer to this class of compounds as immunosenolytics.[3] We believe that the use of immunosenolytics could reactivate the T cells in patients who have already received therapy, potentially making their tumors once again sensitive to androgen receptor signaling inhibitors, chemotherapy, and immunotherapy.

H&O Could you discuss your work on the gut microbiota in prostate cancer?

AA I was lucky to have 2 postdoctoral fellows and a PhD student who were intrigued by the role of the gut microbiota in cancer; these organisms can drive tumor initiation, progression, and treatment response or resistance. Several studies have shown that the gut microbiota are important for the efficacy of ICIs in lung cancer.[4-6] We wanted to learn whether this was also the case in prostate cancer. We started by administering a cocktail of antibiotics to deplete the gut microbiota in a mouse model without depleting bacteria in the circulation, and found that this form of antibiotic therapy could delay the onset of castration-resistant prostate cancer in mice.[7] Also involved in this study were Dr Johann de Bono and his colleagues from the Royal Marsden NHS Foundation Trust. In addition, we were able to make hormone-sensitive mice resistant to treatment more quickly by administering a fecal sample from mice that were already resistant to therapy; the control group consisted of hormone-sensitive mice that received a fecal sample from mice that were not resistant to therapy. This finding raised the question of whether certain bacteria could be implicated in this phenotype, and indeed we observed in mice—and later in humans—that following castration, a selective expansion of *Ruminococcus* bacteria occurs in the gut. We found that *Ruminococcus* can convert the hormone pregnenolone into testosterone and docosahexaenoic acid. When this occurs, castration does not reduce testosterone to the optimal level of less than 50 ng/dL.

We are now further studying *Ruminococcus.* The discovery that bacteria can convert precursor into testosterone is revolutionary because it means that the microbiota are behaving like an endocrine gland. Although we have identified just 1 bacterium of interest so far, there are many more that we need to investigate. Studies in breast cancer have shown that *Ruminococcus* bacteria can pass from the gut into the tumor, and even into tumor metastases. We want to discover all the bacteria that play a role in testosterone production and learn whether these bacteria can migrate from the gut to the tumor in prostate cancer. This is currently a very active field of investigation in my laboratory and other laboratories.

H&O What are your next steps when it comes to research on the gut microbiota in prostate cancer?

AA Dr De Bono and I are going to be collaborating on a study called PROMISE that was recently approved. In this study, we will be testing, for the first time, a combination of antibiotics in patients affected by metastatic castration-resistant prostate cancer. We want to learn whether what we saw in the mouse model can apply to patients.

In addition, we have founded a startup company to

develop bacteria that can protect against the expansion of bad bacteria in the gut. I expect that it will be some time before this is available for clinical use.

Disclosures

Dr Alimonti has received consulting fees from Debiopharm, IBSA Institut Biochimique SA, and Relmada Therapeutics; has an ownership interest in Bottega Organica; has stocks/shares in Oncosence; has received royalties from patents number US11235017B2, US9668961B2, and EP2762131B1; is the inventor of patents US11168134B2 and US20200095314A1; and has received institutional research support from Astellas Pharma, AstraZeneca, Dompé farmaceutici, IBSA Institut Biochimique SA, and Sun Pharma.

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