

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Antibody-Drug Conjugates in Prostate Cancer



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H&O What makes antibody-drug conjugates a good choice in treating cancer overall?

DD Antibody-drug conjugates (ADCs) are designed to deliver potent cytotoxic agents directly to tumors by aiming at overexpressed epitopes. This approach improves the therapeutic window by reducing the exposure of normal tissue, which makes ADCs well tolerated and increases clinical benefit for patients whose tumors express the therapeutic target.

H&O Where have we seen the greatest successes with ADC approaches?

DD Gemtuzumab ozogamicin (Mylotarg, Pfizer) and inotuzumab ozogamicin (Besponsa, Pfizer) have been approved by the US Food and Drug Administration (FDA) in leukemia, and brentuximab vedotin (Adcetris, Seattle Genetics) has been approved in lymphoma. The prototype for the use of ADCs in solid tumors is breast cancer, for which trastuzumab emtansine (T-DM1; Kadcyla, Genentech) and trastuzumab deruxtecan (Enhertu, Daiichi-Sankyo/AstraZeneca) have been approved on the basis of their strong clinical benefit. In bladder cancer, enfortumab vedotin (Padcev, Astellas/Seattle Genetics) has received approval for use following 2 lines of prior therapy. These are all great examples of efficient ADCs.

H&O Would you say that prostate cancer is a good target for these ADC approaches?

DD The treatment options for men with metastatic castration-resistant prostate cancer (mCRPC) have expanded significantly with the addition of abiraterone,

enzalutamide (Xtandi, Astellas), apalutamide (Erleada, Janssen), darolutamide (Nubeqa, Bayer), radium-223 (Xofigo, Bayer), and cabazitaxel (Jevtana, Sanofi-Aventis). More recently, the poly(ADP-ribose) polymerase (PARP) inhibitors olaparib (Lynparza, AstraZeneca) and rucaparib (Rubraca, Clovis Oncology) and the programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck) have received FDA approval for patients who have disease with a specific genetic profile—that is, deleterious homologous recombination repair gene-mutated mCRPC—or metastatic disease with a high mutational burden, respectively. Unfortunately, the long-term benefit of these agents remains limited, and novel approaches are needed. We are seeing that prostate cancers are amenable to ADC treatment because of the abundant expression of highly specific epitopes/antigens on these tumors.

H&O What are the specific antigens that could make good targets for ADCs in prostate cancer?

DD The antigens that have been the subject of the most research so far are six-transmembrane epithelial antigen of the prostate 1 (STEAP1), prostate-specific membrane antigen (PSMA), and tumor-associated calcium signal transducer 2 (TROP2).

STEAP1 is a multi-transmembrane protein thought to act as an ion channel or transporter protein. As a cell-surface protein frequently expressed in prostate cancer, with limited expression in non-prostate tissues, STEAP1 is an ideal candidate for antibody-derived therapies in patients with mCRPC.

PSMA, also known as folate hydrolase 1 (FOLH1) or glutamate carboxypeptidase II (GCPII), is highly expressed on the prostate cancer cell surface as well as

in the neovasculature of multiple tumors, normal renal tubules, the salivary glands, the duodenum, and the brain. In addition, a biological effect of targeting PSMA occurs through phosphoinositide 3-kinase (PI3K) and serine/threonine kinase (AKT) signaling that goes beyond epitope expression.

TROP2 is a transmembrane glycoprotein that is upregulated in tumor compared with matched normal tissue. In prostate cancer, TROP2 may be a driver of neuroendocrine features, a phenotype in major need of more effective specific therapeutic agents.

Cell-surface expression of the relevant antigen is essential for an ADC to bind to the tumor cell, become internalized, and deliver the payload. STEAP1 makes a good target because it is highly expressed in prostate cancer and even more highly expressed in metastatic prostate cancer, whereas expression is very low in other tissues. The same is true for PSMA, which is also found in papillary renal cell carcinoma. The targeting of TROP2 is more novel. TROP2 is being studied primarily in non-small cell lung cancer, but also in neuroendocrine tumors and certain categories of prostate cancer.

H&O What are the potential limitations of ADCs in prostate cancer?

DD The general limitations relate to cross-linking of the antibodies to nonspecific sites. For example, the fact that PSMA is also found in the salivary glands, gastrointestinal tract, and kidneys may result in side effects such as xerostomia, gastrointestinal toxicity, and renal toxicity. Another limitation is the difficulty of regulating the target of the ADC epitope. For example, STEAP1 and PSMA can both be regulated by anti-androgens, which can make them less likely to be effective in patients who have received these agents. The toxicity of ADCs can also be a limiting factor in prostate cancer. Monomethyl auristatin E (MMAE), a potent microtubule inhibitor, is the payload of most ADCs; MMAE is also a potent antimetabolic agent with possible side effects of neuropathy, so its use may be limited in men whose prostate cancer has previously been treated with taxanes.

H&O How toxic are ADCs?

DD They are relatively well tolerated; the overall toxicity profile largely depends on the presence of the target in normal tissues and on the toxicity of the payload bound and delivered by the ADC. With taxanes, neurologic and hematologic toxicities are the most significant. Currently, we are studying different methodologies to deliver the payload to tumor cells while avoiding the penetration of normal tissue to improve the tolerability of ADCs.

A phase 1 study of ASG-5ME, an SLC44A4-targeting, MMAE-carrying ADC being developed by Agensys, demonstrated a narrow therapeutic index in mCRPC. As a result, the development of this compound in prostate cancer was halted. Toxicities occurred that were possibly related to on-target effects in normal tissue expressing the SLC44A4 protein; free MMAE was less likely the cause, according to a 2019 study by McHugh and colleagues.

H&O What are the anticipated mechanisms of resistance to ADCs in cancer?

DD It is important to highlight the possible resistance of tumor cells to the ADC payload; for example, cross-resistance to MMAE may occur in patients who have prostate cancer previously treated with taxanes. Most likely, the resistance is not caused by specific tumor mutations or multidrug resistance mechanisms but rather by the specificity of the ADC delivery to the cells, with narrow therapeutic windows resulting from distribution in normal tissues. Other possible mechanisms of resistance that are of unclear clinical significance include a theoretical buildup of autoantibodies to the ADCs and blockage of the target by similar antibodies used in imaging techniques before targeted therapy. More importantly, disease in prostate cancer is heterogeneous. Multiple metastases develop genetic profiles that are diverse, resulting in possible different expression of the epitopes targeted by ADC, and therefore varied killing efficacy by the ADC. In the evolution of metastases and under the pressure of treatment, prostate cancer cells may downregulate the pathway targeted by the ADC, resulting in tumor plasticity that allows disease progression during treatment.

H&O What are the most important trials that are looking at ADCs in prostate cancer?

DD The trial that we published in the *Journal of Clinical Oncology* in late 2019 looked at the use of DSTP3086S, a humanized immunoglobulin G1 anti-STEAP1 monoclonal antibody that is linked to the antimetabolic agent MMAE. This trial enrolled patients whose tumors had a very high expression of STEAP1 on immunohistochemistry because we thought that high expression would increase ADC targeting and clinical efficacy. The trial found that the recommended phase 2 dose of 2.4 mg of DSTP3086S every 3 weeks showed anti-tumor activity in patients with mCRPC who had been heavily pretreated with agents that included taxanes. We saw prolonged treatment responses and the conversion of circulating tumor cell-based biomarkers from unfavorable to favorable numbers. Changes in prostate-specific antigen (PSA) were also

noted; however, this particular ADC will require further enhancements to optimize future clinical trials. STEAP1 is an interesting target for the development of novel ADCs, chimeric antigen receptor T cells, and immune cell–recruiting bispecific antibodies against STEAP1.

Another ADC strategy in men with mCRPC utilizes a fully humanized monoclonal antibody targeting PSMA and linked to MMAE. The PSMA ADC being developed by Progenics Pharmaceuticals has demonstrated antitumor activity with doses up to and including 2.5 mg/kg with acceptable toxicity, according to a 2019 study by Petrylak and colleagues. Additionally, PSMA-targeting approaches have been studied in conjugates with radiopharmaceuticals. For example, lutetium 177 has recently been shown to improve PSA levels and radiologic response, consistent with potential clinical benefit.

As ADCs mature, they may replace nonspecific systemic therapies because of their superior efficacy and reduced toxicity.

Additionally, targeting of STEAP1 and PSMA has been accompanied by the development of positron emission tomography tracers to study the expression of such targets in mCRPC. These tracers could potentially guide patient selection and trial enrichment by predicting treatment benefit, according to a 2019 study by Carrasquillo and colleagues.

A potential new target that is enriched in prostate cancer is TROP2. TROP2 is targeted by sacituzumab govitecan (Trodelvy, Immunomedics), an irinotecan metabolite payload/SN-38–based ADC that was recently granted accelerated approval by the FDA for the treatment of patients with metastatic triple-negative breast cancer who have received at least 2 prior therapies. This ADC is currently being evaluated for safety and efficacy in a phase 1/2 trial in men with mCRPC that is progressing on androgen-directed therapy (NCT03725761).

H&O Where do you see the future of ADCs in prostate cancer?

DD I am hopeful about the future of ADCs in prostate cancer. I think they are a viable next class of targeted

therapeutics in mCRPC. Additionally, we have the promise of the biomarker-based selection of patients most likely to benefit from such “surgical strikes” on tumor cells.

As ADCs mature, they may replace nonspecific systemic therapies because of their superior efficacy and reduced toxicity. Although we may begin to see ADCs studied in earlier clinical states in patients with prostate cancer, their natural development space is in patients with disease progressing after hormonal ablation therapies, before systemic chemotherapy.

ADCs hold the advantage of delivering highly toxic payloads specifically to prostate cancers, with improvement in therapeutic windows resulting from a reduction in the exposure of normal tissue. ADCs are an ideal, well-tolerated targeted therapy, benefitting patients with tumors expressing a specific target.

Disclosures

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Suggested Readings

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