The promise of immunotherapy in genitourinary malignancies

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Abstract

A broad understanding of the tumor immune landscape has led to a revolution of immune checkpoint inhibitors in the treatment of multiple cancer types. In genitourinary malignancies, immune checkpoint inhibitors have improved outcomes for patients with metastatic renal cell carcinoma and metastatic urothelial carcinoma; however, these treatments have not yet proven broadly beneficial for patients with metastatic prostate cancer. Numerous prospective trials are ongoing to further improve outcomes with immunotherapy combinations and for biomarker development to predict benefit from immune checkpoint inhibition. This perspective article highlights our current immunotherapy approaches in each of the genitourinary malignancies and the ongoing clinical trials that may inform our future treatments in renal, urothelial, and prostate cancers.

Key words: immune checkpoint inhibition; urothelial carcinoma; renal cell carcinoma; prostate cancer

Introduction

Over the past decade, we have come to understand much more about the complicated interactions between tumors and the adaptive immune system. The checkpoint receptors on T-cells (the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor and programmed cell death 1 (PD-1) receptor) have been exploited with a class of immunotherapy checkpoint inhibitors (ICIs). These ICIs have improved survival for patients with metastatic renal cell carcinoma and metastatic urothelial carcinoma; however, these treatments have not yet proven broadly beneficial for patients with metastatic prostate cancer. Numerous prospective trials are ongoing to further improve outcomes with immunotherapy combinations and for biomarker development to predict benefit from immune checkpoint inhibition. This perspective article highlights our current immunotherapy approaches in each of the genitourinary malignancies and the ongoing clinical trials that may inform our future treatments in renal, urothelial, and prostate cancers.

Immune checkpoint inhibition in metastatic renal cell carcinoma

High dose interleukin 2 (IL-2) induces durable complete responses (CRs) for about 5–8% of patients with metastatic renal cell carcinoma (mRCC). Other drugs for mRCC include inhibitors of angiogenesis and tyrosine kinase inhibitors (TKIs) targeted to vascular endothelial growth factor receptors (VEGFRs). Nivolumab (a PD-1 inhibitor) showed efficacy for mRCC including VEGF-refractory mRCC. The combination of ipilimumab (targeting CTLA-4) and nivolumab improved median overall survival (mOS) when compared to sunitinib for mRCC. The CR rates are highest in the most aggressive cases, such as those with sarcomatoid components, where PD-L1 expression is highest, suggesting that aggressive tumors utilize immune checkpoints to evade the immune system during the metastatic process, and that ICIs may overcome this selective advantage.

The ipilimumab/nivolumab combination immunotherapy has changed standard of care for first-line...
treatment of intermediate-poor risk mRCC. However, the majority of patients do not have CR, and more work is needed to answer questions around optimization of immunotherapies, when to integrate VEGF therapies with immunotherapies, and how best to sequence currently approved therapies.

The first combination study reported for mRCC was the combination of atezolizumab and bevacizumab compared to sunitinib for first-line mRCC. The first co-primary endpoint of progression free survival (PFS) for PD-L1 positive tumors was improved with atezolizumab/bevacizumab upon the initial interim analysis, but the OS data was still immature at the time. At the time of this article, atezolizumab/bevacizumab has not been approved for treatment and is awaiting overall survival data. More recently, the phase 3 trial of avelumab-axitinib compared to sunitinib was reported and showed improvement in PFS. OS data were immature at the time. Additional data are emerging around the combination of pembrolizumab and axitinib in the front line setting. These VEGF and ICI combination strategies are promising to improve survival outcomes; however, optimal patient selection for combination approaches is still unclear. In particular, it is unclear which patients may benefit from combination therapy versus sequencing monotherapies.

A number of adaptive trials are ongoing to inform on patients who can benefit from treatment breaks with the potential to for less ICI therapy and reduce toxicities. There is also an ALLIANCE cooperative group trial, PDIGREE, which will help inform on patients for whom immunotherapy is sufficient versus patients who need early integration of VEGF targeting therapies.

Other ongoing clinical trials are circumnavigating possible resistance mechanisms of ICIs, including targeting other inherent activation receptors on effector T-cells, suppressing inhibitory cytokines, increasing infiltrating effector T-cells, and decreasing regulatory T-cells and myeloid derived suppressor cells. The therapies aim to suppressing the adenosine pathway and CD39, activating receptors such as CD27, and inhibiting receptors such as LAG3. Cellular therapeutics of engineered T-cells are also in the pipeline.

Finally, ICIs have the promise to change systemic therapy options in the localized setting. The perioperative PROSPER study is investigating nivolumab given in the neoadjuvant vs adjuvant settings (NCT03055013), and adjuvant studies IMmotion 010 (NCT03024996) and Keynote 564 (NCT03142334) are respectively testing the addition of atezolizumab and pembrolizumab as treatment after nephrectomy.

Immune checkpoint inhibition in metastatic urothelial carcinoma

Urothelial carcinoma has been known to be immunogenic since the Bacille Calmette-Guerin (BCG) vaccine showed efficacy for generating local inflammation and reducing recurrence rates in non-muscle invasive urothelial carcinoma. For metastatic urothelial cancer (mUC), cisplatin-based chemotherapy is commonly used for first-line treatment. However, for patients who are cisplatin-ineligible or have cisplatin-refractory disease, there is an unmet need for effective therapies. The dose expansion cohort of urothelial cancer in the phase 1 trial of atezolizumab (a PD-L1 inhibitor) was the first to show efficacy in mUC. Phase 2 single arm studies of atezolizumab, durvalumab, avelumab, nivolumab and pembrolizumab all showed promising results in mUC.

The phase 3 Keynote 045 trial randomized patients to either pembrolizumab or investigator choice second-line chemotherapy (usually either docetaxel or vinflunine). Pembrolizumab improved mOS, providing level 1 evidence to support current NCCN guideline recommendations. Pembrolizumab also had better ORR of 21% compared to 11% for chemotherapy. Based on Keynote 045 as well as the IMvigor 211 trial (randomizing patients to atezolizumab versus chemotherapy), ICIs have been established as effective second-line therapies in mUC.

Patient selection for ICI therapy remains challenging. Early studies of ICIs used PD-L1 as a biomarker with good dichotomy of response rates based on PD-L1 positivity, which remains controversial. Multiple companion diagnostic assays have been developed, each with a different ICI therapeutic agent. These tests use several different antibodies directed against PD-L1 (including Dako 22C3 with pembrolizumab, Dako 28-8 with nivolumab, Ventana SP263 with durvalumab, and Ventana SP142 with atezolizumab). The different assays have defined positivity differently in the different tumor types. In addition, PD-L1 tumor or immune cell expression is heterogeneous in tumors within patients and over time with exposures to different therapies. Therefore, although the FDA-approved indications for atezolizumab and pembrolizumab recently changed to include PD-L1 status for cisplatin-ineligible patients, further biomarker studies of PD-L1 positive diseases across assays are needed to determine whether the different antibodies are selecting for the same population of patients across interventional trials.

The promise of ICIs in mUC has established an effective second-line treatment for cisplatin-refractory mUC patients. The mUC field continues to await further data to determine if single agent ICIs will improve outcomes for cisplatin ineligible patients. Other ongoing trials are exploiting combination immunotherapies for mUC, including importantly the DANUBE trial with durvalumab and tremelimumab (NCT02516241) and early phase trials combining PD-1 therapies with vaccination strategies (NCT02897765), other receptors such as CD122 (NCT02983045) and GITR (NCT03126110), and chemotherapy via novel delivery systems (NCT03518320).

In localized UC, ICIs are under clinical investigation as adjuvant treatment after cystectomy. There are also clinical trials evaluating ICIs for treatment of recurrent non-muscle invasive urothelial cancer (NCT02844816). The completion of these important studies will establish the utility of adding ICIs as adjuvant treatment to improve cure rates of localized UC.
Immune checkpoint inhibition in metastatic castration resistant prostate cancer

The immunogenicity of metastatic castration resistant prostate cancer (mCRPC) has been controversial, with many studies showing the absence of infiltrating T-cells in the prostate cancer microenvironment, thus leading to common references of mCRPC as an immune desert. However, the first cell-based immunotherapy for solid tumors, sipuleucel-T, improved mOS compared to placebo, and has been approved for treatment of mCRPC.

ICI monotherapies in unselected patients with mCRPC have not been as successful as in other genitourinary malignancies. Ipilimumab (targeting CTLA-4) trial in mCRPC was overall negative. However, there was a potential improvement in survival over time in some patients, particularly those with a lower burden of disease, which was counterbalanced by an increase in the early risk of death. Ipilimumab did not improve mOS as a single agent, but is being tested in combination strategies with nivolumab (CHECKMATE 650, NCT02985957). Interestingly, ipilimumab/nivolumab may have a greater benefit in patients with homologous repair deficient mCRPC, based on a small prospective study demonstrating an objective response rate of 40% and PSA response rate of 33%, many of which were durable, as compared to a 0% response rate in men with mCRPC without homologous repair deficiencies. Thus, men with mCRPC and greater mutation burdens and neoantigens may have a greater response to ICI.

Selected patients with mCRPC may benefit from ICI therapy based on their germline or somatic tumor mutation profile. In select populations including patients with microsatellite instability (MSI-high) somatic alterations, PD-1 inhibitors are indicated and have been associated with durable responses, and pembrolizumab is currently recommended in NCCN guidelines based on a large basket study of patients with microsatellite instability-high (MSI-H) tumors across a range of histologic subtypes, including prostate cancer. However, there were very few patients in this study with MSI-high mCRPC, and thus, more studies are needed to understand the relative benefits and durability of responses to PD-1 inhibition in mismatch repair deficient and/or MSI-high prostate cancer. A second subset of men with mCRPC who may respond to ICI therapy are those who have somatic biallelic loss of CDK12, an enzyme important to DNA repair. CDK12 loss is present in about 5% of men with mCRPC and is associated with a tandem duplication genotype and a high prevalence of fusion neoantigens, leading to immunogenicity and a higher response to ICIs targeting PD-1.

PD-1 ICI monotherapy in men with mCRPC is associated with a low but significant probability of response. In a pilot study of ten such men who were progressing on enzalutamide and who continued enzalutamide and were treated with pembrolizumab, a response rate of 30% was observed, including dramatic and durable responses. In the Keynote 199 study, pembrolizumab monotherapy was associated with a lower response rate of around 5%, suggesting the combination approaches with PD-1 inhibition may be more successful. Ongoing trials are adding ICIs to more promising and active therapies in mCRPC including combining nivolumab with rucaparib, docetaxel, or enzalutamide, and combining pembrolizumab with olaparib, docetaxel, or enzalutamide.

There is now further characterization of both genomic alterations and the immune landscape in prostate cancer, with the emergence of targets in the prostate cancer tumor microenvironment, such as VISTA and PD-L2. These targets warrant further investigation for combination strategies of immunotherapeutics in mCRPC. Moreover, treatment-related neuroendocrine prostate cancer (trNEPC) has emerged as a distinct complication of hormonal therapies in prostate cancer, with shortened clinical courses, and DNA repair pathway alterations seem to drive these more aggressive disease courses. ICI therapy with PD-L1 inhibition for men with mCRPC, particularly those with trNEPC, is under prospective study alone and in combination with additional immunotherapies in phase 2 trials. For mCRPC, the promise of ICIs may lie in providing synergistic effects of known treatment options that stimulate the immune microenvironment and engage T cells to the tumor interface, such as CAR-T cells or bispecific antibodies, or with approaches that increase DNA damage or impair DNA repair. Such therapies may have efficacy alone in mCRPC subsets with high mutational burden and neoantigens, including these trNEPC-like aggressive clinical phenotypes and is the subject of intense investigation.

Conclusion

Across genitourinary malignancies, immunotherapies have expanded the treatment landscape for metastatic disease. There are many ongoing trials in combination therapies to exploit T-cell biology as well as suppressive cell subsets in the tumor microenvironment. Once completed, the promise of these trials will improve combinations of immunotherapies with known treatment options in each disease, bring immunotherapies into the localized disease setting, and potentially improve outcomes in more aggressive disease settings.

Competing interests

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