Immunotherapy in Urological Tumors

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The past decade has seen significant improvement in our understanding of tumor biological features, which has led to use of anti-programmed-death 1 (PD-1) and anti-PD-ligand-1 (PD-L1) agents and cytotoxic T lymphocytes antigen 4 (CTLA-4) inhibitors in a multitude of cancers. These immunotherapeutic agents have shown activity in melanoma, lung, head and neck, colorectal, urological, and other cancers. This article details the use of immunotherapy agents in urothelial, renal, prostate, and testicular tumors.

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KEY WORDS

Immunotherapy • Urological tumors • Immune checkpoint inhibitors • Recombinant BCG • Cell wall–derived therapies • Cytokines

The past decade has seen significant improvement in our understanding of tumor biological features, which has led to use of anti-programmed-death 1 (PD-1) and anti-PD-ligand-1 (PD-L1) agents and cytotoxic T lymphocytes antigen 4 (CTLA-4) inhibitors in a multitude of cancers. These immunotherapeutic agents have shown activity in melanoma, lung, head and neck, colorectal, urological, and other cancers. Immune checkpoint inhibitors reactivate an immune response against tumor cells, leading to cell death.

Urogenital tumors comprise renal, upper urinary tract, bladder, prostate, and germ-cell tumors. Bacillus Calmette-Guérin (BCG) is one of the most successful immunotherapies in cancer treatment and has widely been embraced by urologists globally as the standard of care for patients with high-risk non–muscle-invasive bladder cancer (NMIBC).[1] In its attenuated form, BCG was the first US Food and Drug Administration (FDA)-approved immunotherapy in patients with NMIBC and the first published use of immunotherapy in urological malignancy.[2]

The progress in immunotherapy for the treatment of cancer reflects attempts made to restore immune-mediated tumor elimination.[3] The versatility of immunotherapy in treating malignancies is a reflection of the different pathways that can be manipulated to redirect the immune system against cancer.[3] Immunotherapeutic agents can be broadly categorized into recombinant BCG and cell wall–derived therapies, cytokines, gene therapy, cancer vaccines, immune checkpoint inhibitors, oncolytic

viruses, adoptive immunotherapies, immune agonists, and immunomodulatory agents.[1]

Urothelial Carcinoma

The use of BCG for NMIBC is well documented to reduce the rates of disease recurrence and progression via stimulation of both cellular and humoral responses in non-muscle invasive disease (Table 1).[4,5]

Cisplatin-based chemotherapy regimens have been the standard of care in fit patients with urothelial malignancies both in the neoadjuvant setting before cystectomy and in those with metastatic disease. In patients with metastatic disease, these regimens help to improve survival to less than 15 months.[6] In patients who are cisplatin ineligible due to compromised renal function (glomerular filtration rate [GFR] <60 mL/min, PS-2), carboplatin has shown to have a response rate of 42% with a median overall survival (OS) of 9 months.[7]

Progression of immunotherapy from intravesical use for non–muscle-invasive disease to systemic delivery for advanced metastatic disease was enabled by the development of immune checkpoint blockers.[8] These immunotherapies have been shown to be efficacious and safe, resulting in a growing role in patients with early or metastatic urothelial carcinoma.[8]

BCG has demonstrated longevity in the treatment of high-risk NMIBC due to its impact on disease progression and favorable side-effect profile. Meta-analysis has shown BCG confers 27% relative risk reduction in disease progression.[9] It is taken up by cancer cells intravesically, and the subsequent effects are thought to be directly cytotoxic, as well as stimulation of mechanisms of innate and adaptive immunity.

Inhibition of the PD-1/PD-L1 pathway has been shown to have clinical activity in patients with advanced bladder cancer, which eventually led to FDA approval of atezolizumab in this setting.[1] This was the first new treatment approved for advanced urothelial carcinoma in 20 years.[1] The pivotal study using atezolizumab (an anti–PD-L1 monoclonal antibody) in cisplatin ineligible urothelial malignancy showed an overall response rate (ORR) of 23% with a complete response in 9% of patients; median OS was 15.9 months.[10] In the KEYNOTE-052 study, pembrolizumab, an anti–PD-1 inhibitor, showed good anti-tumor activity in cisplatin-ineligible patients.[11] In this trial, the ORR was 28.9% (95% CI, 24.3-33.8), and 8.1% and 20.8% of patients had complete response and partial response, respectively. In patients with PD-L1 expression combined positive score (CPS) of ≥10, ORR was 47.3% (95% CI, 37.7-57.0) and median OS was 19 months. Mullane and colleagues investigated the expression of PD-L1 on bladder tumor tissue and found a PD-L1 expression of 37% on mononuclear cells and 20% on tumor cells.[12] It was also shown that the PD-L1 expression on tumor-infiltrating mononuclear cells was associated with higher OS in those patients with urothelial malignancy and metastatic disease.[13]

Immunotherapy agents are now in clinical trials in muscle-invasive bladder cancer. In the phase II study examining the safety and efficacy of neoadjuvant atezolizumab in muscle-invasive bladder cancer (ABACUS), two cycles of atezolizumab were given prior to cystectomy. Pathological complete responses (pCR) occurred in 29% of patients, with 39% of patients down-staged to non–muscle invasive disease.[14] In another neoadjuvant study with pembrolizumab in muscle-invasive bladder cancer (PURE-01), 32% of patients had pT0 disease post-cystectomy.[15] The data from neoadjuvant clinical

TABLE 1

Immunotherapy Agents for Urothelial Carcinoma

Agent	Current Role	Mechanism	Outcomes
Intravesical BCG	Non–muscle-invasive bladder cancer	Stimulation of cellular and humoral responses	Reduces disease recurrence and progression
Atezolizumab	Systemic delivery in advanced disease	Anti–PD-L1 monoclonal antibody	23% overall response rate and 15.9-mo overall survival in cisplatin-ineligible group
Pembroluzimab	Systemic delivery in advanced disease	Monoclonal anti–PD-1 antibody	28.9% overall response in cisplatin-ineligible patients In neoadjuvant setting 32% pT0 disease post-cystectomy

trials will guide clinicians to develop further biomarker-driven studies to improve outcomes in muscle-invasive bladder cancer.

Renal Cell Carcinoma

In the mid-1990s, interleukin-2 (IL-2) and interferon alpha (IFNα) were developed for use in renal cell carcinoma.[16,17] These cytokines are thought to stimulate T-cell–mediated elimination of tumor cells. High-dose IL-2 has shown to have response rates of 20%, with long-term remission in a small subset of patients. Immunostimulatory cytokines Il-2 and IFNα have been used to treat renal cancer since 2007; however, they were associated with severe treatment-associated toxicities, and were largely superseded by the discovery of tyrosine kinase inhibitors in 2007.[18] These molecules act intracellularly to block downstream signaling from epidermal growth factor receptors, which are often overexpressed in tumors and act to promote cell division.

Over the past 10 years, rapid progress has been made with the development of checkpoint inhibitors. This class of drugs acts by reversing the tumor-derived inhibition of the immune system. One example, nivolumab, inhibits PD-1, a protein found on the surface of T cells that is highly expressed in certain cancers, and acts to down-regulate the immune response.[19] Nivolumab was the first immune checkpoint-inhibitor approved for pre-treated patients with metastatic renal cell carcinoma.[3] In the CHECKMATE 025 phase III trial in metastatic renal cell cancer (mRCC), nivolumab was compared with everolimus in mRCC in patients who had progressed on at least one angiogenesis inhibitor.[20] Median OS was 25.0 months with nivolumab and 19.6 months in patients treated with everolimus; ORR was 25% and 5%, respectively.

Immunotherapy for the treatment of renal has cancer has progressed to shift well-established paradigms in this disease (Table 2). The recently reported CHECKMATE 214 trial tested the combination of ipilimumab (CTLA-4 inhibitor) with nivolumab over sunitinib in previously untreated mRCC. At a median follow-up of 25.2 months, the immunotherapy combination showed an 18-month survival of 75% versus 60% in the sunitinib arm in intermediate- to poor-risk patients. The median survival was not reached in the combination arm versus 26 months in sunitinib-treated patients (hazard ratio for death, 0.63; $P < 0.001$). ORR was 42% versus 27% ($P < 0.001$) and complete response rate was 9% versus 1%.[21]

The efficacy of checkpoint inhibitors in RCC have further been evaluated in combination with VEGF inhibitor. In the IMmotion150 study, atezolizumab, atezolizumab plus bevacizumab (VEGF inhibitor), and sunitinib were studied in patients with mRCC. In this trial, patients who progressed in the atezolizumab or sunitinib arms could be treated with atezolizumab plus bevacizumab as second-line therapy. The preliminary data showed improved efficacy of atezolizumab plus bevacizumab

TABLE 2

Immunotherapy Agents for Renal Cancer

Agent	Current Role	Mechanism	Outcomes
Interleukin-2	Systemic delivery in advanced disease	Cytokine stimulation of T-cell–mediated elimination of tumor cells	20% response, remission in a small subset
Interferon alpha	Systemic delivery in advanced disease	Cytokine stimulation of T-cell–mediated elimination of tumor cells	
Nivolumab	Metastatic renal cell cancer	Checkpoint inhibitor	Median overall survival 25 mo with 25% overall response rate
Ipilimumab	Metastatic renal cell carcinoma	CTLA-4 checkpoint inhibitor	In combination with nivolumab as a first-line treatment showed superiority to sunitinib; 75% 18-mo survival, 42% overall response rate
Atezolizumab + bevacizumab	Metastatic renal cell carcinoma	Anti-PD-L1 monoclonal antibody + VEGF inhibitor	Patients who progressed on atezolizumab or sunitinib alone, atezolizumab had improved efficacy with bevacizumab

combination in mRCC.[22] Currently, trials with checkpoint inhibitors in combination with VEGF inhibitors are underway in mRCC to understand the clinical activity of this dual targeted therapy to improve outcomes and achieve long-term durable responses.

Prostate Cancer

Prostate cancer is the second most common cancer in men, with a 5-year survival in patients with metastatic disease of 29.3%.[23]

There is a wide range of treatment strategies available, with immunotherapy emerging with a role in specific groups (Table 3). Sipuleucel-T is a therapeutic cancer -vaccine for men with metastatic castrate-resistant prostate cancer (mCRPC) and the first of its kind approved by the FDA.[24] In the phase III IMPACT trial, sipuleucel-T demonstrated a survival improvement of 4.1 months and reduction in risk of death in a subset of vaccinated, hormone-refractory patients.[24]

Using immune checkpoint inhibitors to modulate the tumor microenvironment to enhance the immune response against cancer cells has also shown encouraging results in mCRPC.[3] Ipilimumab has been evaluated in several clinical trials in conjunction with other growth factors, hormonal therapy, cytotoxic therapy, and radiotherapy.[3] Pembroluzimab, a monoclonal anti-PD-1 antibody, was the first-in-class agent shown to have activity in metastatic prostate cancer.[25] In the phase 1b KEYNOTE-028 trial, pembroluzimab showed an ORR of 17.4% (95% CI, 5.0%-38.8%); 34.8% had stable disease. Median duration of response was 13.5 months, and median progression-free survival (PFS) and OS were 3.5 and 7.9 months, respectively. In the subsequent phase 2 KEYNOTE 199 trial, the disease control rate (DCR) was 11%, with anti-tumor activity seen in patients regardless of PD-L1 status.[26] Further use of immunotherapy in prostate cancer remains an experimental but rapidly developing field.

Testicular Cancer

The small proportion of patients with germ-cell tumors who fail to achieve complete cure rates following chemotherapy may potentially benefit from immunotherapy (Table 4).[3] Brentuximab vedotin is an antibody-drug conjugate that has shown early signs of clinical activity and immunomodulatory effects in highly pretreated patients with testicular germ-cell tumors.[27] Immune checkpoint inhibitors have also emerged as an option in patients with seminoma and non–seminomatous germ-cell tumors, as PD-L1 expression has been documented in up to 73% of samples in a retrospective study.[28]

Toxicity

The key toxicity of immune checkpoint inhibitors is immune-related adverse events (irAEs) and infusion reactions. The most frequently occurring irAEs affect the skin (rash/pruritis), colon (diarrhea/colitis), endocrinopathy, liver, and lung. Other side-effects are rare but can be seriously life threatening and include inflammation of organs resulting in hepatitis, pancreatitis, myocarditis, and neurological system.[8,29,30] The authors have reported a case of fatal myocarditis in a patient with mRCC treated with a checkpoint inhibitor.[29] The most frequent adverse event seen with these drugs is fatigue (12%-37% of patients).[31] Patients suffering from mild adverse events can continue their immunotherapy.[8] However, in more severe cases, prompt initiation of corticosteroids helps to

TABLE 3

Immunotherapy Agents for Prostate Cancer

Agent	Current Role	Mechanism	Outcomes
Sipuleucel-T	Therapeutic cancer vaccine for metastatic castrate-resistant prostate cancer		4.1-mo survival improvement
Ipilimumab	Metastatic castrate resistant prostate cancer in conjunction with other agents	CTLA-4 checkpoint inhibitor	Encouraging results with growth factors, hormonal therapy, cytotoxic therapy, and radiotherapy
Pembroluzimab	Metastatic prostate cancer	Monoclonal anti-PD-1 antibody	Overall response rate of 17.4%, overall survival 7.9 mo

TABLE 4

Immunotherapy Agents for Testicular Cancer

Testicular	Current Role	Mechanism	Outcomes
Brentuximab vedotin	Highly pre-treated patients with germ-cell tumors	Antibody-drug conjugate	Early signs of clinical activity and immunomodulatory effects
Immune checkpoint inhibitors	Seminoma and non-seminomatous germ-cell tumors	Checkpoint inhibitors	An option, 73% expression PD-L1

MAIN POINTS

- The past decade has seen significant improvement in our understanding of tumor biological features, which has led to use of anti-programmed-death 1 (PD-1) and anti-PD-ligand-1 (PD-L1) agents and cytotoxic T lymphocytes antigen 4 (CTLA-4) inhibitors in a multitude of cancers. These immunotherapeutic agents have shown activity in melanoma, lung, head and neck, colorectal, urological, and other cancers.
- The use of Bacillus Calmette-Guérin for non–muscle-invasive bladder cancer is well documented to reduce the rates of disease recurrence and progression via stimulation of both cellular and humoral responses in non-muscle invasive disease. Progression of immunotherapy from intravesical use for non–muscle-invasive disease to systemic delivery for advanced metastatic disease was enabled by the development of immune checkpoint blockers. These immunotherapies have been shown to be efficacious as well as safe, resulting in a growing role in patients with both early and metastatic urothelial carcinoma.
- In the mid-1990s, interleukin-2 and interferon alpha were developed for use in renal cell carcinoma. These cytokines are thought to stimulate T-cell–mediated elimination of tumor cells. Currently, trials with checkpoint inhibitors in combination with VEGF inhibitors are underway in metastatic renal cell carcinoma to understand the clinical activity of this dual targeted therapy to improve outcomes and achieve long-term durable responses.
- Sipuleucel-T is a therapeutic cancer vaccine for men with metastatic castrate-resistant prostate cancer and the first of its kind approved by the FDA. Ipilimumab has been evaluated in several clinical trials in conjunction with other growth factors, hormonal therapy, cytotoxic therapy, and radiotherapy. Pembroluzimab, a monoclonal anti-PD-1 antibody, was the first-in-class agent shown to have activity in metastatic prostate cancer.
- Brentuximab vedotin is an antibody-drug conjugate that has shown early signs of clinical activity and immunomodulatory effects in highly pretreated patients with testicular germ-cell tumors. Immune checkpoint inhibitors have also emerged as an option in patients with seminoma and non–seminomatous germ-cell tumors, as PD-L1 expression has been documented in up to 73% of samples in a retrospective study.
- Patients suffering from mild adverse events can continue their immunotherapy. However, in more severe cases, prompt initiation of corticosteroids helps to prevent life-threatening consequences, subsequently followed by discontinuing immunotherapy.
- Biomarkers may help identify patients who would benefit most from immunotherapy, or to help tailor the most effective combination of agents. Those currently described as being available for testing are PD-L1 expression, the neoantigen and mutational burden, molecular subtypes, and interferon gamma signature. The results seen thus far with immunotherapeutic agents are encouraging, and further research is required to preselect patients for different checkpoint inhibitors and to minimize toxicity.

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Diagnostic Tools

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Conclusions

For all the successful trials mentioned herein, some questions remain. Immunologic signatures like tumor mutational burden, tumor proportion scores, and combined positive scores require prospective validation. Because most patients with all tumor types are non-responders, proper biomarker-driven selection is essential to improve response rates and clinical outcomes. The next important question is whether these agents provide enough value to justify cost-effectiveness especially in a resource-constrained healthcare system. These novel agents are sometimes associated with life-threatening adverse events, which if not diagnosed and treated at an early stage can prove fatal. ■

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