Bladder Cancer 6 (2020) 425–433
DOI 10.3233/BLC-200362
IOS Press

Review

Diagnosis and Management of Checkpoint Inhibitor Side Effects in Patients with Bladder Cancer: the Urologist's Perspective

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Received 30 July 2020
Accepted 13 October 2020
Pre-press 21 November 2020
Published 14 December 2020

Abstract. From 2016 through the present day, we have witnessed extraordinarily rapid advances and regulatory approvals of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway, which has significantly improved survival among patients with advanced and metastatic urothelial carcinoma (mUC). Although these agents usually are well tolerated, their unique mechanism of action may enhance cytotoxic T-cell mediated immunity, evoking unique side effects that differ from conventional chemotherapy or molecularly targeted agents. The most common immune-related adverse events (irAEs) are dermatitis, colitis, pneumonitis, thyroid dysfunction, and transaminitis, but any organ system permeated by the lymphatic vasculature can be affected; also, neuropathies and arthralgias may occur. Immune-mediated events of any grade require prompt recognition and appropriate management to mitigate the risk of irAE exacerbation. Most patients with mild (grade 1) irAEs may continue checkpoint inhibitor treatment with careful monitoring. For grade 2 irAEs, it is appropriate to suspend treatment, initiate corticosteroid therapy, and only resume treatment if the irAE resolves to < grade 1. Events classified as > grade 3 may require permanent treatment cessation and high-dose corticosteroid therapy. In clinical trials of PD-1/PD-L1 inhibitors across multiple cancer types, approximately 15% of patients with mUC developed irAEs requiring corticosteroid therapy. Training physicians and nurse providers and counseling patients regarding the early recognition of irAEs are mandatory to ensure timely irAE detection and optimized patient management. Hence, operationalizing an advanced bladder cancer clinic requires collaboration and coordination amongst urologists, medical and radiation oncologists, and other medical specialists who participate in the increasingly multimodal and multidisciplinary care of patients with bladder cancer.

Keywords: Urinary bladder neoplasms, bladder cancer, bladder tumors, immunological antineoplastic agents, drug-related side effects and adverse reactions, drug toxicity, adverse drug event, side effects of drugs

INTRODUCTION

In 2015, patients with cisplatin-ineligible or refractory advanced or metastatic urothelial carcinoma (mUC) had few therapeutic options beyond palliative care [1, 2]. This heretofore dismal option has been greatly expanded by the advent of immune checkpoint inhibitors, humanized monoclonal antibodies that increase immunity against various tumor types by counteracting the ability of some tumor cells to evade immune surveillance [3]. In registrational trials, approximately 25% to 30% of patients with post-platinum mUC experienced significantly improved

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ISSN 2352-3727/20/$35.00

survival compared to the existing standard of care when they received checkpoint inhibitor monotherapy targeting either programmed cell death protein 1 (PD-1) on the T cell surface, or its tumor cell ligand, PD-L1 [4–9]. In recent years, five PD-1/PD-L1 inhibitors—pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo), durvalumab (Imfinzi), and avelumab (Bavencio) — have been approved in the United States for the second-line treatment of mUC, and atezolizumab and pembrolizumab also have been approved in the first line for patients with platinum-ineligible mUC and for specifically cisplatin-ineligible patients whose UC tumor cells express PD-L1 (Table 1) [10–12].

A subset of patients receiving first-line mUC PD-1/PD-L1 inhibitors have shown durable complete responses and prolonged survival times [13], which is especially noteworthy considering the elderly age and comorbidity burden of this afflicted population. Consequently, there has been keen interest in exploring checkpoint inhibitor use more proximally within the bladder cancer disease continuum [14–16]. In January 2020, pembrolizumab was approved by the U.S. Food and Drug Administration (FDA) for the treatment of high-risk, Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* (CIS) with or without papillary tumors in patients who are unwilling to receive or are ineligible for cystectomy [14]. Currently, there are a plethora of clinical trials evaluating PD-1/PD-L1 inhibitors for the treatment of high-risk patients with BCG-naïve non-muscle invasive bladder cancer, the neoadjuvant treatment of muscle-invasive bladder cancer prior to radical cystectomy, and as a component of multi-modal bladder-sparing strategies [16]. Positive outcomes from these trials will assuredly expand the use of immuno-oncologic agents by urologists within the framework of advanced bladder cancer clinics.

Checkpoint inhibitors, particularly anti-PD/PD-L1 monotherapy, have favorable toxicity profiles and are generally better tolerated than traditional chemotherapeutic agents [2, 17]. Nonetheless, a minority of patients enrolled in clinical trials have developed immune-related adverse events (irAEs) requiring treatment interruption or immediate cessation with implementation of high-dose corticosteroid therapy. For these patients, prompt irAE detection and appropriate management are crucial to prevent exacerbations and potentially irreversible pathophysiologic consequences. In this article, I review these unique side effects and discuss best practices for their recognition, detection, and management by urologists and other physicians practicing with the advanced bladder cancer clinic.

ETIOLOGY AND SCOPE OF IRAES

The mechanism of action of checkpoint inhibitors explains both their broad antitumor activity and their unique toxicity profile. In brief, some tumor cells evade immune surveillance by expressing receptors or ligands that enhance immune regulatory pathways, which suppresses T-cell activity and proliferation [18]. Immune checkpoint inhibitors block these interactions, "unleashing" cytotoxic T cells against tumor cells [18, 19]. However, immune checkpoint pathways also function within immune homeostasis: the PD-1/PD-L1 pathway helps maintain peripheral tolerance, and both murine and human studies indicate that its disruption can lead to autoimmune disease [3, 20, 21].

For these reasons, irAEs differ from the toxicities of molecularly targeted or cytotoxic agents [22]. Immune-mediated toxicities of checkpoint inhibitor therapy can potentially affect any organ system, and neuropathies and arthralgias also may occur. Although the presentation of irAEs usually begin within the first 3 months after treatment initiation, they can occur at any time during treatment and have been documented as long as one year after treatment cessation [23]. Also, unlike conventional chemotherapy, the timing of irAEs also does not generally coincide with treatment cycles [22].

The incidence of irAEs has varied considerably among registrational trials, in part because of a lack of uniform definitions or reporting protocols [24]. In meta-analyses of clinical trials of PD-1/PD-L1 inhibitors for mUC, approximately 15% of patients developed irAEs requiring treatment with topical or systemic corticosteroid therapy [24, 25].

Immune-mediated adverse events of PD-1/L-1 inhibitors most frequently involve the skin (maculopapular rash, pruritus), endocrine organs (thyroiditis), lungs (pneumonitis), liver (elevated liver enzymes), and gastrointestinal tract (diarrhea, colitis) [24, 26]. Dermatologic toxicities often are the first to appear, typically as a reticular, maculopapular, erythematous rash on the trunk or extremities [27]. Patients may also report oral mucositis and dry mouth. Immune-mediated adverse events of the eye (episcleritis, conjunctivitis, or uveitis) and kidneys (nephritis, granulomatous lesions and thrombotic

Table 1
Checkpoint inhibitors approved for use in urothelial carcinoma

Drug	Mechanism of action	Initial Approval Date	Current indications in urothelial cancer
Atezolizumab	Anti-PD-L1	May 2016	Locally advanced or mUC in: • patients who are ineligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells cover ≥ 5% of tumor area) as determined by an FDA-approved test • patients who are ineligible for any platinum-containing chemotherapy regardless of PD-L1 status • patients whose disease has progressed during or after any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy
Nivolumab	Anti-PD-1	February 2017	Locally advanced or mUC that has progressed during or after platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy
Avelumab	Anti-PD-L1	May 2017	Locally advanced or mUC that has progressed during or after platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy
Durvalumab	Anti-PD-L1	May 2017	Locally advanced or mUC that has progressed during or after platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy
Pembrolizumab	Anti-PD-1	May 2017	Locally advanced or mUC in: • patients who are ineligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [CPS ≥ 10] as determined by an FDA-approved test • patients who are ineligible for any platinum-containing chemotherapy regardless of PD-L1 status • patients whose disease has progressed during or after platinum-containing chemotherapy, or within 12 months of receiving neoadjuvant or adjuvant platinum-containing chemotherapy • BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors in patients who are ineligible for or elect not to undergo cystectomy

BCG, Bacillus Calmette-Guérin; CIS, carcinoma *in situ*; CPS, Combined Positive Score: number of PD-L1 staining cells divided by total number of viable tumor cells, multiplied by 100; mUC, metastatic urothelial carcinoma; NMIBC, non-muscle invasive bladder cancer; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

Table 2
Immune-related adverse events and recommended management [38]

Organ System	irAEs	Recommended Management			
		Grade 1	Grade 2	Grade 3	Grade 4
Skin	Rash Blisters Severe cutaneous adverse reactions (SCARS)	Rash: Continue CPI with close monitoring. Blisters: if < 10% BSA, asymptomatic, noninflammatory: continue CPI with close monitoring. SCARS: All grades require thorough evaluation. For suspected Stevens Johnson syndrome or any mucous membrane lesions, stop CPI and have low threshold for ICU, burn unit admission.	Rash, blisters: Pause CPI. Initiate prednisone 0.5–1 mg/kg/d or equivalent, tapered over > 4 wks. Do not resume CPI without concomitant steroids unless irAE resolves to < gr1. By definition, symptomatic blisters or erosions of skin or mucosa are > gr 2. Initiate high-dose topical corticosteroids, reassess patient every 3d. Consult dermatology if needed.	Rash, blisters: Stop CPI. Initiate high-dose corticosteroids, e.g. IV prednisolone (or equivalent), 1-2 mg/kg, tapered over > 4 wks.Consult dermatology.	
Gastrointestinal	Colitis Enteritis Gastritis	Continue CPI with close monitoring.	Pause CPI until symptoms resolve to < gr 1. Consider < 10 mg prednisone or equivalent, tapered over 4–6 wks. Consult gastroenterology.	Stop CPI. Initiate high-dose corticosteroids, tapered over > 4 wks. Consult gastroenterology.	
Lungs	Pneumonitis Pleuritis Sarcoid-like granulomatosis	For pneumonitis, pause CPI if imaging shows progression. Repeat CT in 3-4 wks—may resume CPI if evidence of improvement. Pleuritis and sarcoid-like granulomatosis can be asymptomatic or have nonspecific chest symptoms. Biopsy helps differentiate from bladder cancer progression.	Pneumonitis that does not resolve after pausing CPI is > gr 2. Initiate prednisone 1-2 mg/kg/d, taper over 4-6 wks. Perform frequent pulse oximetries, consider bronchoscopy with bronchoalveolar lavage, empirical antibiotics. Do not resume CPI unless resolution to < gr 1.	Pneumonitis: Permanently discontinue CPI. Initiate empirical antibiotics and prednisolone IV 1-2 mg/kg/d. If no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g BID or IVIG for 5 d or cyclophosphamide. Taper corticosteroids over 4–6 wks. Consult pulmonary and infectious disease if needed.	Permanently discontinue CPI. Initiate high-dose corticosteroids, e.g. IV prednisolone 1-2 mg/kg or equivalent, tapered over > 4 wks. Refractory gr 4 irAEs may require additional immunosuppressive therapy, hospitalization, multidisciplinary specialist support.
Liver	Hepatitis	Continue CPI with close monitoring.	Pause CPI. Initiate prednisone or equivalent < 10 mg/d. If improvement to < gr 1, resume CPI followed by corticosteroid taper over > 4 wks.	Permanently discontinue CPI. Initiate 1-2 mg/kg methylprednisolone or equivalent. Monitor LFTs every 1-2 d. Consult hepatology if steroid refractory or receiving a combination regimen.	
Musculoskeletal	Arthritis Myositis Polymyalgia	Continue CPI, initiate analgesia (NSAIDs, acetaminophen). For patients with elevated CK and muscle weakness (myositis), treat as gr 2.	Pause CPI until symptom control. Initiate prednisone < 10 mg/d, increase to 10–20 mg/d if needed. Escalate analgesia as needed. For myositis, consider prednisone 0.5–1 mg/kg, refer to rheumatology.	Pause CPI, initiate prednisone, refer to rheumatology. For prednisone-refractory arthritis, consider DMARDs. For myositis with any sign of myocardial involvement, permanently discontinue CPI.	
Eye	Uveitis Sjögren syndrome Blepharitis Episcleritis	Continue CPI, refer to ophthalmology within 1 wk, offer supportive treatment (e.g. artificial tears).	Pause CPI pending urgent ophthalmology consult. Consider cycloplegic agents, topical and systemic corticosteroids. Do not resume CPI until patient is off systemic corticosteroids.	Permanently discontinue CPI. Urgent ophthalmology consult. Initiate topical/periocular/intravitreal and systemic corticosteroids.	
Endocrine system	Thyroiditis Adrenalitis Hypophysitis	For thyroiditis, continue CPI with close monitoring. For any grade primary adrenal insufficiency and hypophysitis, pause CPI until patients are stabilized on replacement hormone therapy. Consult endocrinology.	Pause CPI until symptom resolution. Prescribe TH supplementation for symptomatic patients with any TSH elevation and asymptomatic patients with persistent TSH levels >10mIU/L. For hyperthyroidism, offer beta-blockers, hydration, supportive care. Refer Graves disease patients to endocrinology.	Pause CPI until symptoms resolve with appropriate therapy. Consult endocrinology.	Manage as for gr 3. Consider IV therapy for patients with myxedema or concern for thyroid storm.
Hematologic	Lymphopenia Thrombocytopenia AIHA ATTP	Lymphopenia, AIHA, thrombocytopenia: Continue CPI with close monitoring. Acquired TTP: Pause CP and consider cessation; consult hematology.	Lymphopenia: manage as for gr 1. All others: hold CPI. Initiate prednisone 0.5–2 mg/kg/d or equivalent. Consult hematology. For gr 2 thrombocytopenia (platelets < 75/ μ1), initiate prednisone 0.5–2 mg/kg/d for 2-4 weeks and then taper. Consider IVIG. May resume CPI after resolution to < gr1.	Lymphopenia: Consider pausing CPI if < 250 PB count. Consider prophylaxis for *Mycobacterium avium* complex and *Pneumocystis jirovecii*; screen for CMV, HIV, hepatitis. Thrombocytopenia: Manage as for gr 2, pending hematology consult. AIHA: Permanently discontinue CPI. Consider admitting patient. Initiate prednisone 1-2 mg/kg/d or equivalent. aTTP may require PEX. aTPP: Consult hematology. Consider PEX, methylprednisone IV, rituximab.	
Nervous system	Neuropathies (peripheral, autonomic) Meningitis Encephalitis Transverse myelitis	For neuropathies, maintain low threshold to hold CPI and monitor for 1 week. If continue CPI, monitor closely. For any grade meningitis, encephalitis, or transverse myelitis symptoms, stop CPI, consult neurology.	Pause CPI. Observe or initiate prednisone 0.5–1 mg/kg. Resume CPI only after improvement to < gr 1. Offer gabapentin, pregabalin, or duloxetine.	Permanently discontinue CPI, consult neurology. Initiate IV methylprednisolone 2–4 mg/kg. Monitor pulmonary function. Consider inpatient admission for intensive monitoring.	

Table 2
Continued

Organ System	irAEs	Recommended Management			
		Grade 1	Grade 2	Grade 3	Grade 4
Pancreas	Diabetes	Continue CPI with close monitoring.	Consult endocrinology. Pause CPI until glycemic control.	Seek urgent endocrinology consult. Pause CPI until glycemic control. Admit if symptomatic, concern for DKA, or new-onset T1DM.	
Kidneys	Nephritis	For creatinine increase < 1.5 times ULN, may pause CPI pending evaluation.	Pause CPI. Consult nephrology. Consider prednisone 0.5–2.0 1 mg/kg/d if rule out other AKI etiologies. Taper prednisone over 4–6 wks if improved to < gr 1.	Permanently discontinue CPI. Initiate high-dose corticosteroids. Consult nephrology.	
Cardiovascular	Myocarditis Pericarditis Arrhythmias Impaired ventricular function with heart failure, vasculitis	For all grades: Stop CPI. Rapidly initiate prednisone 1-2 mg/kg. Admit and consult cardiology. Patients with elevated troponin or conduction abnormalities may need immediate transfer to coronary care unit.			

AIHA, autoimmune hemolytic anemia; AKI, acute kidney injury; aTTP, acquired thrombocytopenic purpura; BSA, body surface area; CMV, cytomegalovirus; CPI, checkpoint inhibitor; CT, computed tomography; DKA, diabetic ketoacidosis; DMARD, disease-modifying antirheumatic drug; ICU, intensive care unit; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PEX, plasma exchange; PB, peripheral blood; T1DM, type 1 diabetes mellitus; TH, thyroid hormone; TSH, thyroid stimulating hormone.

microangiopathy) are less common but require immediate intervention [26]. In the phase 3 KEYNOTE-045 study of second-line pembrolizumab (anti-PD-1) therapy in advanced or mUC, 16.9% of pembrolizumab recipients developed irAEs, most frequently hypothyroidism (6.4%), hyperthyroidism (3.8%), pneumonitis (4.1%), and colitis (2.3%) [5]. Fewer than 1% of patients developed nephritis, skin reactions, thyroiditis, or adrenal insufficiency.

Grade 5 irAEs of checkpoint inhibitor therapy are rare. In the KEYNOTE-045 trial, 4.5% of pembrolizumab recipients developed grade 3–5 irAEs, but the only death (0.2%) occurred in a patient with pembrolizumab-emergent myositis, thyroiditis, hepatitis, pneumonia, and myocarditis [5]. In two recent meta-analyses of published trials of checkpoint inhibitors across cancer types, 0% to 1.5% of recipients of anti-PD-1/PD-L1 monotherapy died due to irAEs, most frequently pneumonitis, hepatitis, neurologic events, colitis, and myocarditis [28, 29].

Patients with locally advanced and mUC can benefit from anti-PD/PD-L1 therapy without developing clinically significant irAEs. However, some data suggest that irAEs are associated with a greater likelihood of treatment response. In an exploratory analysis of data from more than 1,700 post-platinum and cisplatin-ineligible patients with mUC enrolled in seven registrational trials, irAEs were documented in 28% of responders versus 12% of non-responders [25]. The development of irAEs requiring corticosteroid therapy was associated prolonged overall survival (hazard ratio, 0.53; 95% CI, 0.43 to 0.66). In the majority (57%) of cases, irAE signs/symptoms occurred before documentation of clinical response.

SURVEILLANCE AND MANAGEMENT

Patients should be assessed for irAE risk prior to starting checkpoint inhibitor therapy [23]. Female patients may be at higher risk of irAEs due to their greater overall risk for autoimmune diseases [30]. Unfortunately, few studies have evaluated biomarkers for irAEs among patients with UC. Studies of PD-1-PD/L1 pathway inhibitors in other tumor types (e.g. melanoma, non-small cell lung cancer, renal cell carcinoma) have identified biomarkers for irAEs including post-treatment increases in circulating IL-6 (nivolumab); a higher rate of change in soluble CD163 and CXCL5 (nivolumab); an absolute lymphocyte count > 2000, and an increased baseline absolute eosinophil count (various anti-PD-1/PD-L1

checkpoint inhibitors) [30–34]. In other studies, treatment-emergent autoimmune type 1 diabetes was associated with the baseline presence of type 1 diabetes autoantibodies, while treatment-emergent thyroid dysfunction was associated with baseline elevations in thyroid stimulating hormone (TSH) and the presence of antithyroid antibodies [35, 36].

Patients should be monitored for irAEs throughout the treatment course by regularly asking about skin, bowel, pulmonary, and neurologic symptoms [37]. Clinicians should regularly evaluate thyroid stimulating hormone (TSH) levels to screen for treatment-emergent thyroid dysfunction and should regularly monitor kidney, liver and pancreatic function, since autoimmunity in these organs is not associated with early symptoms [37].

The American Society of Clinical Oncology (AS CO) recommends taking a graded approach to irAE management (2) [38]. For mild (grade 1) events, patients can usually continue checkpoint inhibitor therapy. The exception is certain neurologic, cardiac, or hematologic toxicities, which may require more careful consideration. For most grade 2 irAEs, it is recommended that patients suspend treatment and initiate corticosteroids, which may be administered either orally or parenterally, although oral administration is usually most amenable (prednisone or equivalent, initially dosed at 0.5 to 1 mg/kg/day). Patients should only resume checkpoint inhibitor treatment without concomitant steroids if irAEs resolve to grade 1 or less. Grade 3 events often require management with high-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day), which should be tapered over at least 4 to 6 weeks. In most cases, these patients should not resume treatment. Grade 4 events require immediate and permanent treatment cessation unless the irAE is an endocrinopathy that is subsequently controlled by hormone replacement therapy. Patients who develop refractory irAEs may require intravenous immunosuppressive therapy with either infliximab or mycophenolate, inpatient hospitalization, and multidisciplinary specialty support. There have been no prospective studies of these treatment regimens; recommendations are based on consensus opinion [26, 27, 38].

Clinicians should be aware that moderate to severe treatment-emergent pneumonitis has affected > 1% of patients receiving PD-1/PD-L1 inhibitors in mUC clinical trials [5, 37, 39]. Very rarely, these cases have been fatal. Patients should be monitored for dyspnea and cough [37, 39]. Worsening pulmonary symptoms require immediate treatment cessation and intervention. Computerized tomography (CT) or bronchoscopy with bronchoalveolar lavage can help distinguish pneumonitis from opportunistic pulmonary infections. Patients with confirmed pneumonitis should immediately be started on high-dose corticosteroid therapy, with close monitoring and frequent pulmonary imaging to assess response. If it is unclear whether a patient has pneumonia or pneumonitis, co-administration of high-dose corticosteroids and antibiotics should be considered.

For pneumonitis and other less common or more severe irAEs, it can be beneficial to consult with endocrinologists, gastroenterologists, medical oncologists, and other medical specialists. I recommend fostering collaborative relationships for this purpose and maintaining a low threshold for consultations and referrals.

Patient education also is key to managing irAEs, especially because many patients are unfamiliar with their signs and symptoms and/or have comorbidities that can mask their onset. Although PD-1/PD-L1 inhibitors often are well tolerated, they are effective because they activate the immune system and thus can cause these aforementioned unique side effects [40]. It is important to counsel patients that these side effects can occur at any time during treatment and must be promptly reported. I recommend developing a handout that lists irAE signs and symptoms by organ system and highlights whom to immediately notify. It is helpful for patients to also know that treating irAEs does not necessarily reduce the efficacy of immuno-oncologic therapy [3]. Indeed, retrospective studies indicate that responses to checkpoint inhibitor therapy may continue even after treatment cessation [27].

USE IN SPECIAL POPULATIONS

The increasing use of checkpoint inhibitors has raised questions about their safety in specific populations. Available data do not support the use of PD-1/PD-L1 inhibitors in solid organ transplant recipients [17]. Elderly patients (aged > 75 years) were not excluded from registrational UC trials, but they were underrepresented and are likely to have had superior performance status and fewer comorbidities than elderly patients in the general population [17]. Retrospective observational studies have produced mixed results regarding whether irAEs disproportionately affect elderly adults; data in the UC setting

are largely lacking [41]. Given the superior safety profile of PD-1/PD-L1 inhibitors compared with chemotherapy, their use in appropriately selected elderly patients is worthy of consideration. A primary care physician or geriatric assessment may help optimize the selection of patients most likely to benefit from treatment.

Should checkpoint inhibitor therapy for UC should be considered in patients with pre-existing autoimmune diseases? Such patients were excluded from relevant phase 1 and registrational trials, although most of these studies did permit the enrollment of patients with diabetes, vitiligo, psoriasis, thyroid disease, or adrenal disease [4, 5, 7–11, 42]. Unfortunately, there is a paucity of post-marketing studies to address this question.

Studies of other tumor types suggest that anti-PD-1/PD-L1 therapy is more likely to cause a flare in pre-existing autoimmunity rather than an entirely new autoimmune disease [43]. In a study of 52 patients with autoimmune diseases who received pembrolizumab or nivolumab for melanoma, 38% experienced flares requiring immunosuppression and 29% developed other irAEs [44]. Flares of rheumatoid arthritis, psoriasis, and polymyalgia rheumatica were most common. Notably, the use of immunosuppressants was associated with a significantly lower rate of response to checkpoint inhibitor therapy (15% vs. 40% among patients who were not on immunosuppressants at baseline). In another small retrospective cohort study, checkpoint inhibitor monotherapy led to irAEs in six of 16 patents with pre-existing rheumatic diseases [45]. These irAEs resolved with corticosteroid therapy and treatment discontinuation, underscoring the need to actively monitor these patients.

CONCLUSIONS

After several decades of stagnancy in advanced urothelial cancer management, therapies for these patients have dramatically expanded over the last four years. Our armamentarium now includes five PD-1/L1 checkpoint inhibitors that are FDA-approved for use in second-line settings, of which two also are available for the first-line treatment of platinum-ineligible patients and one (pembrolizumab) also is approved for the treatment of BCG-unresponsive high-risk NMIBC with CIS in patients who are ineligible for or have elected not to undergo cystectomy. Ongoing studies of combination regimens, as well as of PD-L1 expression and other potential biomarkers of treatment response, are expected to further enhance outcomes and shift the use of checkpoint inhibitors into the management of high-risk earlier-stage bladder cancer.

These novel therapies for UC display unique toxicity profiles that include irAEs that differ significantly from the adverse effects of conventional chemotherapy. Appropriate training and counseling of patients, caregivers, and the entire clinical care team is vital to ensure appropriate surveillance, along with prompt irAE detection and management. Furthermore, the complexity of the therapeutic landscape and the expected advent of multi-modal and combination treatment regimens will necessitate coordination and collaboration amongst urologists, medical and radiation oncologists, pathologists, medical specialists, and nursing expertise to effectively provide care across the entirety of the bladder cancer disease spectrum. Constructing your advanced bladder cancer clinic is essential for optimizing patient access to optimal bladder cancer treatment.

ACKNOWLEDGMENTS

The author thanks Dr. Amy Karon for editorial assistance with the manuscript.

FUNDING

None.

ETHICAL CONSIDERATIONS

As a literature review, this work is exempt from any requirement for Institutional Review Board approval.

CONFLICT OF INTEREST

Consulting fees

Abbvie, Ambry, Amgen, Astellas, Astra Zeneca, Bayer, BMS, Boston Scientific, Clovis Oncology, Dendreon, Exact Imaging, FerGene, Ferring, Foundation Medicine, Invitae, MDxHealth, Merck, Myovant, Myriad, Nymox, Pfizer, PlatformQ, Sanofi Genzyme, Tolmar.

Speaker's Bureau

Astellas, Bayer, Clovis, Janssen, Pfizer.

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