REVIEWS IN UROLOGY

Management of Adverse Events From Checkpoint Inhibitors in Urologic Practice: Where Are We Today?

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KEYWORDS:
Urinary bladder neoplasms; immunotherapy; urology

Abstract

Urologic oncology has seen a tremendous impact from the emergence of checkpoint inhibitors in the management of malignant conditions of the urinary tract. These therapies are now in the nonmetastatic setting, and there is ample opportunity to integrate them into urologic practice. The most common barrier to starting a checkpoint inhibitor therapy program is concern about immune-related adverse event management. The evaluation and management of immune-related adverse events can be part of the treatment protocol and centralized to promote safety and success. The key components of implementing an in-office infusion program that includes checkpoint inhibitors are the use of a team-based approach, with a champion physician; appropriate patient education before and during treatment; and timely evaluation and treatment of all adverse events, with subspecialty consultation, if needed.

Members of the urology community are becoming increasingly interested in being more active participants in urologic cancer care. Recent survey data from independent group urology meetings have suggested that 20% of large community-based urology groups are currently administering checkpoint inhibitor therapies in their practice, and up to 50% are interested in doing so in the near future.[1] The most common barrier to starting a checkpoint inhibitor therapy program is concern about immune-related adverse event (irAE) management. Studies of checkpoint inhibitor use in patients with nonmetastatic urologic cancer have found that up to 30% of patients will have high-grade toxic effects, and 11% to 18% of patients will discontinue treatment as a result.[2-4] As these therapies continue to demonstrate significant anticancer effects in late-stage and now early-stage cancers, it is paramount that the contemporary urologist treating patients with genitourinary cancers be proficient with these treatments.

The evaluation and management of irAEs (Table 1) can be set out in protocols and centralized to promote safety and success. The key components of implementing an in-office infusion program are the use of a team-based approach, with a champion physician; provision of appropriate patient education and setting expectations; and timely evaluation and treatment of all AEs, with subspecialty consultation if needed.

Citation: Branch C, Canter D, Jayram G. Management of adverse events from checkpoint inhibitors in urologic practice: where are we today? *Rev Urol.* 2024;23(2):exxx.

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Urologists who are currently positioned to succeed in the delivery of checkpoint inhibitor therapy are likely already heavily involved in advanced prostate cancer care and have dedicated resources to this end. Most urology groups that have demonstrated excellence in this area have built programs with nurse navigation, in-office pharmacy and dispensing service, bone health and nutrition clinics, and clinical trial programs. Extending these same principles and personnel to a more comprehensive genitourinary cancer center is the first step in developing a checkpoint inhibitor therapy program. Although a large investment in a dedicated team is not mandatory, a multifaceted team (usually consisting of a champion physician, advanced practice clinician, and infusion nurse) will significantly improve the efficiency and safety of the program. From an operational standpoint, the day-to-day burden of implementing such a program in a busy practice is fairly low, especially for those practices with advanced therapeutic capabilities. Often, the medication is obtained already compounded, and an infusion nurse reconstitutes the medication and delivers it intravenously in an infusion suite for 30 to 60 minutes after the patient has been interviewed and examined. Advanced practice support from nurse practitioners and physician assistants is instrumental to the provision of timely and quality care. When a urologist is busy in the operating room or conducting procedures, an advanced practice clinician can quickly evaluate an infusion patient in the clinic who may be developing an emerging immunotoxic reaction and provide prompt treatment. Staff must be trained to approach patients' concerns and symptoms while they are receiving immunotherapy, with a champion physician overseeing the process. With experience, physicians and clinicians can develop the necessary skills and internal protocols to quickly identify and manage these unique toxic effects. Management of irAEs is well delineated in existing guidelines, and available algorithms can be followed successfully in the majority of cases (Table 1).[5,6] The most common all-grade toxic effects encountered with checkpoint inhibitor therapy are fatigue, diarrhea, pruritis, arthralgia, hypothyroidism, and rash. The majority of irAEs the urologist will encounter will be low grade, and conservative measures or a corticosteroid taper will be indicated. Of note, irAEs that are refractory to initial corticosteroid treatment likely will

ABBREVIATION

irAE immune-related adverse event

Table 1. General Management Guidelines for irAEs[a]

Grade	Checkpoint inhibitor dosing	General irAE recommendations
1	Continue or hold checkpoint inhibitor	Observation, supportive care
2	Hold checkpoint inhibitor, can consider further checkpoint inhibitor therapy if toxicity resolves to grade ≤1	Oral steroid taper (0.5-1.0 mg/kg/d), often lower steroid doses or observation acceptable
3	Hold checkpoint inhibitor and unlikely to resume further checkpoint inhibitor therapy	High-dose steroids (1-2 mg/kg/d) and slow taper[b,c] over 4-6 wk once toxicity resolves to grade ≤1; consider hospitalization
4	Hold checkpoint inhibitor, permanently discontinue checkpoint inhibitor therapy	Consider hospitalization, high-dose steroids,[b,c] and slow taper over 4-6 wk once toxicity resolves to grade ≤1

Abbreviation: irAE, immune-related adverse event.

[a] Organ-specific management may differ from the recommendations listed here; consultation of guidelines is critical.[5,6]

[b] Prophylaxis for prevention of opportunistic infection should be considered once a patient has received a steroid equivalent of 20 mg or more per day for at least 4 weeks or 30 mg or more per day for 3 weeks.

[c] For high-grade toxicity, additional interventions are often warranted if there is no improvement in 48 hours; consult guidelines for disease-specific treatment.[5,6]

require multidisciplinary or medical oncology assistance because the choice of additional immunosuppressive agents differs by affected organ.

The anti–programmed cell death 1 protein immunotherapies nivolumab and pembrolizumab each have 2 available dosing strategies. Nivolumab can be administered as 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks; pembrolizumab can be administered at 200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks. There are no dose reductions for toxicity, but there is the option to hold or discontinue therapy. Adverse events can occur at any time, but the majority occur within the first 3 months after therapy initiation.[7] For this reason, many clinicians prefer to dose at the shorter interval for the first few infusions, then switch to the longer interval if the patient is tolerating the treatments. There is no reported difference in toxic effect rates between the infusion schedules, and the longer dosing intervals offer logistical benefits for patients as well as for clinic staffing and resources. Notably, a new subcutaneous checkpoint inhibitor injection, sasanlimab, has been studied in non–muscle-invasive bladder cancer, with promising early results. Subcutaneous injection may improve urologic access to immunotherapy because it has a similar AE profile with fewer infrastructural requirements than conventional intravenous delivery.[8]

Suggested Approach to Managing Toxic Effects in the Urology Clinic

At Georgia Urology, a comprehensive strategy has been developed that focuses on monitoring patients for new symptoms and conducting routine laboratory evaluation before each drug administration. A baseline history and physical examination as well as a thorough review of the patient's medications and active medical conditions are critical. A multidisciplinary approach is crucial for patients actively using immunosuppressants, transplant recipients, and those individuals with a complex immunologic history, and such patients should not be among the first patients a new urologist sees. Initial patient education followed by patient monitoring and consistent engagement is paramount. The patient is instructed to report any clinical changes once treatment has started because any new symptom after infusion are considered treatment related until proven otherwise. Furthermore, it is important to explain to patients that irAEs may develop at any time after the initial infusion. It has been observed that patients will discount a new symptom as being related to their checkpoint inhibitor therapy because it started 7 to 10 days after they received an infusion. From a practical standpoint, the Georgia Urology staff call patients 1 to 2 days after each infusion and 1 week before each infusion to check for the development of any new symptoms that could be related to the immunotherapy. The staff specifically ask every patient the following questions at each conversation to monitor for new or developing AEs:

- Are you having shortness of breath, or have you developed a cough?
- Have you noticed a skin rash?
- Are you having anxiety, headaches, palpitations, cold sensitivity, constipation, or muscle cramps?
- Are you having diarrhea or an increase in stool?
- Are you notably more tired or experiencing a lack of energy compared with before you started therapy?

Furthermore, during each infusion, patients are given a handout listing adverse reactions specific to checkpoint inhibitors to help them self-monitor for symptoms during the weeks before their next treatment. Any reported adverse reactions prompt a structured evaluation process wherein the severity and type of reaction determine the intervention strategy.

Routine laboratory evaluation is critical, as well, because patients may develop clinically silent endocrine disorders or hematologic abnormalities. Baseline laboratory values are obtained before the patient's first infusion. Interval blood work is recommended at 2 weeks before each infusion so that any low-grade developing AEs can be identified and addressed

before they progress to a high-grade AE. The following laboratory values are measured according to protocol throughout a patient's treatment course:

- Complete blood cell count
- Comprehensive metabolic panel
- Thyroid-stimulating hormone and cortisol levels

Before practices began providing checkpoint inhibitor infusions, strategic collaborations were forged with consultants, which can be helpful if patients develop irAEs that require more in-depth evaluation and management. Specifically, in consideration of the most common irAEs, dermatology, endocrinology, and gastroenterology practices were engaged to facilitate seamless referrals. This proactive approach to specialty referral has proven instrumental to the success of the program and the safety of patients. Rash is a frequently encountered adverse reaction and most commonly can be resolved without referral by prescribing nondrowsy antihistamines or over-the-counter or prescription steroid creams. Similarly, diarrhea is frequently seen and mostly occurs in self-limited episodes in which antimotility agents suffice. Thyroid disorders are seen frequently, and endocrine abnormalities are the most common reason for referral. Although the urologist can manage these disorders with hormone replacement, patients may require frequent laboratory monitoring or dose modifications. Therefore, collaboration with an endocrinologist has been invaluable in enabling patients to continue immunotherapy safely.

If an AE does occur, the first course of action is to grade the AE and hold or delay immunotherapy doses, depending on the severity of the AE. This approach is typically sufficient to allow the AE to resolve so therapy can be restarted. If the AE does not resolve or worsens, oral steroid therapy should be started without delay, at 1 to 2 mg/kg administered in divided doses twice daily until the AE reaches grade 1 or resolves. It has become apparent with clinical experience that if a patient requires steroid therapy for an AE, then the steroid dosage should be closer to 2 mg/kg to adequately treat and resolve the AE as quickly as possible. Once the AE has resolved, the steroids can be gradually tapered, usually over 3 to 4 weeks to prevent a recurrence of the AE.

Within the authors' collective experience at Georgia Urology and in Nashville, Tennessee, less than 10% of patients receiving checkpoint inhibitor therapy have experienced an AE that has required oral steroid therapy, with the longest duration of steroid treatment being 6 months. Thanks to the implementation of appropriate pretreatment education and constant patient monitoring, no late-night emergency department visits or acute inpatient admissions for irAEs have been observed. In addition, no patients have experienced steroid-refractory AEs that would require more advanced agents (eg, mycophenolate or vedolizumab). These favorable results may be related to patient selection because patients with more comorbidities or those individuals with high frailty scores are usually sent to medical oncology. Using a structured, multidisciplinary approach has been essential to optimize outcomes, the goal being for patients to complete their treatment course safely and with minimal disruptions, thereby improving cancer outcomes.

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Article Information

Published: July 22, 2024.

Conflict of Interest Disclosures: Dr Jayram is a consultant to Bristol-Myers Squibb Company and Merck.

Funding/Support: Dr Jayram received an honorarium from Specialty Networks for time spent on manuscript development. The content, however, is the authors' alone.

Author Contributions: All authors contributed equally to this article.

Data Availability Statement: None.

Article Corrected Online: This article was corrected on July 22, 2024, to specify that the drug is delivered as a subcutaneous injection.