Management of Immunotherapy-Related Toxicity in Genitourinary Cancers

Subjects: Oncology

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Genitourinary (GU) malignancies are among the most common types of cancer. The use of immune checkpoint inhibitors (ICIs) is rapidly increasing as more combinations and clinical indications are approved in the field of genitourinary malignancies. Most immunotherapeutic agents being approved are for the treatment of renal cell carcinoma and bladder cancer, which mainly involve PD-1/PD-L1 and CTLA-4 pathways. There is an ongoing need for recognizing and treating immunotherapy-related autoimmune adverse effects (irAEs).

genitourinary cancer | immunotherapy | immunotherapy-related toxicity | immune checkpoint inhibitor | immunosuppression | immunotherapy rechallenge

1. General Principles

The incidence of adverse events is highly variable across different clinical trials, with a reported incidence of any-grade toxicity ranging from 15 to 90% [1]. Intensification of treatment is one factor contributing to this variability in reported toxicity. The estimated rate of treatment discontinuation is less when monotherapy is used (13%) compared with combination therapy (43%) [2]. It is highly probably that given the nature of irAEs, and their novelty, the reported rates underestimate the actual incidence [1]. Bertrand et al. studied a total of 1265 patients receiving anti-CTLA-4 antibodies from 22 clinical trials and reported an all-grade irAEs incidence of 72%, and high-grade irAEs observed in 24% of patients [3]. Similarly, in patients receiving anti-PD-1/PD-L1 agents, the reported high-grade irAEs range from 5 to 8% [4]. The incidence increases significantly upon combining the anti-CTLA-4 antibodies and anti-PD-1/PD-L1 agents, with reported high-grade events as high as 55–60% [5][6][7].

A thorough history taking and clinical examination during each clinic visit is essential for early detection to mitigate the risk for morbidity and mortality. The National Cancer Institute/National Institute of Health has defined grading for the adverse events using the standardized Common Terminology Criteria for Adverse Events (CTCAE) grading system [8]. Notably, this system does not separate irAEs from pre-existing autoimmune diseases (**Table 1**). Key oncology societies have proposed comprehensive guidelines (The American Society of Clinical Oncology, ASCO; The European Society for Medical Oncology, ESMO; and The National Comprehensive Cancer Network, NCCN) to assist oncologists in irAE management [1][9][10].

Table 1. Common terminology criteria for adverse events (CTCAE) and grading system for irAEs, and management with immunosuppression.

CTCAE Grading	Setting of Treatment	Treatment	Immunotherapy
I (Asymptomatic or mild)	Outpatient	Observation	Close monitoring Immunotherapy to continue
II (Moderate)	Outpatient	Low dose steroids (0.5–1 mg/kg/day)	Temporary discontinuation
III (Severe)	Inpatient	High dose steroids (1–2 mg/kg/day)	Consider permanent discontinuation
IV (Life threatening)	Inpatient (likely ICU level)	High dose steroids (1–2 mg/kg/day)	Permanent discontinuation

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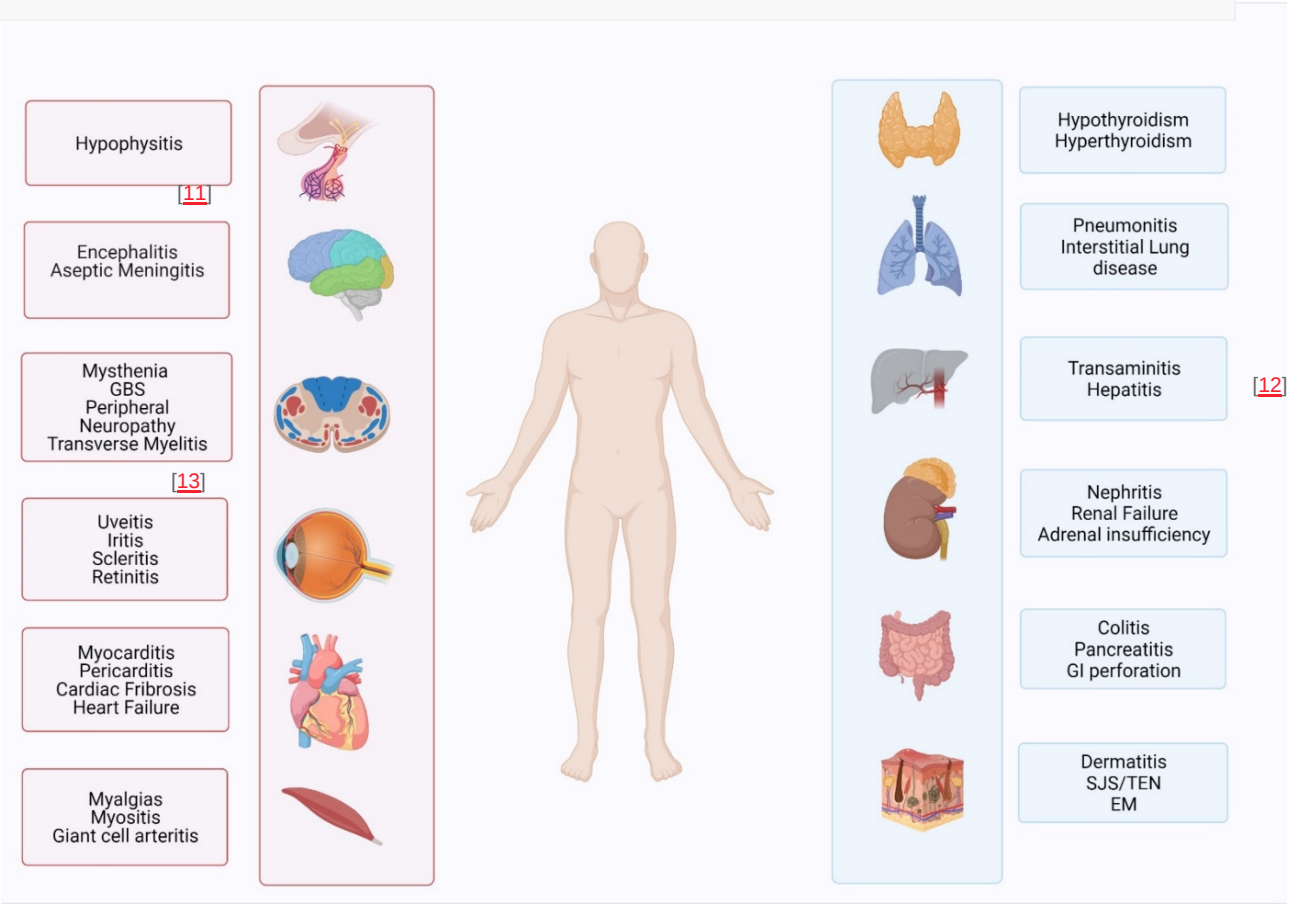

Figure 1. Various organ systems affected by immune-related toxicities.

2. Dose Modification of ICIs

- Grade 1 toxicity (mild): Usually does not require dose modification. The patient needs close monitoring for any change in the symptoms or worsening of the symptoms.

- Grade 2 toxicity (moderate): Treatment with ICIs should be temporarily withheld until the toxicity improves to grade 1 or resolves. An exception to this is grade 2 immune-mediated endocrinopathies in which ICI should be held until hormone replacement has been initiated. Patients with immune-mediated endocrinopathies may need a prolonged taper/maintenance of low dose oral steroids (10 mg of prednisone per day or less) only if

symptomatic from a treatment flare (e.g., symptomatic hyperthyroidism). Generally, hormone replacement alone is sufficient without concurrent immune suppression for endocrinopathies. Endocrine dysfunction from irAE typically is a permanent complication with life-long hormone replacement needed.

- Grade 3 and grade 4 toxicity (severe): ICIs are recommended to be permanently discontinued with grade 4; they can be restarted with some grade 3 toxicities after resolution of toxicity to grade 1 or less. High-dose steroids are given with close monitoring for the response. Once toxicity subsides to grade 1 or less, gradual tapering of steroids is recommended over at least 1-month duration.

- Rapid and aggressive treatment of irAE helps to minimize the incidence of permanent organ injury and severe complications.

- Corticosteroids are typically the first-line therapy for irAE management.

- Certain irAEs are treated with upfront combination therapy instead of steroid monotherapy. These typically involve organs associated with a high mortality rate (e.g., cardiomyositis) or organs that easily lead to permanent organ impairment such as ophthalmitis, myasthenia gravis or motor neuropathies.

For additional reading please review [1].

3. Immunosuppressive Agents to Treat irAEs

- Corticosteroids: Steroids remain the backbone of the treatment for irAEs and are usually dosed as 1–2 mg/kg/day of prednisone equivalent. Generally, some clinical improvement is expected within 48–72 h. If no clinical improvement is observed over this duration, then consideration of either intensification of immune suppression or further diagnostic workup for another etiology should be considered. A tailored approach may be required for specific organ involvement with assistance from an organ specialist (**Table 1**). In the case of steroid-refractory disease alternative immune suppressants are used. Other immune modulators, such as infliximab, mycophenolate, anti-thymocyte globulin (ATG), calcineurin inhibitors, methotrexate, intravenous immunoglobulin (IVIG), and plasmapheresis may be considered on a case-to-case basis [14][15].

- Infliximab: Infliximab (IFX), a monoclonal antibody functions by binding with high affinity to soluble and transmembrane TNF-alpha which prevents stimulation of TNF-alpha cognate receptors. This reduces pro-inflammatory cytokine levels (IL-1, IL-6). IFX is usually given as a single dose of 5 mg/kg after the failure of oral steroids. Repeat dosing can be administered if needed after 2 weeks of first dose [16][17]. IFX has been found very effective against immune-related colitis and inflammatory arthritis.

- Vedolizumab: In contrast to the infliximab's broadly dampening TNFα's role, vedolizumab (VDZ) is a gut-selective humanized anti-$\alpha_4\beta_7$ monoclonal antibody [18]. VDZ blocks the interaction between $\alpha_4\beta_7$-integrin and mucosal addressing cell adhesion molecule 1 (MAdCAM-1) which in turn inhibits the lymphocytic infiltration to the gut [19]. Zou et al. in their observational study compared the efficacy and safety of VDZ and IFX in patients

suffering from immune-mediated diarrhea and colitis (IMDC). The study showed encouraging results with fewer hospitalizations (16% vs. 28%, $p = 0.005$), shorter duration of steroid use (35 vs. 50 days, $p < 0.001$), (lower recurrence 14% vs. 29%, $p = 0.008$) while maintaining comparable clinical remission rate (resolution of symptoms to grade 1 or less) in the VDZ arm as compared to the IFX arm (88% vs. 89%, $p = 0.785$). However, the onset of action of VDZ is slower than IFX [17.5 vs. 13 days, $p = 0.012$] [19]. Real-world data also corroborate these findings [18][20].

- Mycophenolate mofetil: IFX can be hepato-toxic, and hence contraindicated to use in immunotherapy-related hepatitis. In cases of steroid-refractory hepatitis, mycophenolate mofetil (MMF) is typically recommended for steroid-refractory or steroid-dependent drug-induced hepatitis with the usual dose of 500–1000 mg twice daily. MMF is a well-established immunosuppressant used to prevent graft rejection, and autoimmune conditions (autoimmune hepatitis, lupus nephritis, and others) [21][22]. MMF has been successfully used in a variety of irAEs involving nephritis, hepatitis, ophthalmitis, and pancreatitis [23][24][25].

- Tocilizumab: Tocilizumab is an IL-6 receptor antagonist that has been widely used in treating autoimmune diseases. Retrospective studies suggested that tocilizumab is a viable option for steroid-refractory irAEs [26]. An ongoing prospective trial is assessing the safety and effectiveness in patients who develop steroid refractory irAEs.

- Intravenous immunoglobulin: IVIG is a pooled IgG derived from healthy donors and is commonly used in a variety of autoimmune conditions. It has a wide range of immune modulation effects on both the B and T cell lymphocyte functions. Its use has been especially explored in neurological irAEs such as Guillain–Barre syndrome (GBS), myasthenia gravis, neuropathies, and hematological irAEs that are thought to be largely antibody mediated [27][28]. There are institutional experiences that have reported better outcomes with upfront IVIG use as first-line therapy when compared to receiving steroids alone [29]. In addition, IVIG has been used to manage autoimmune pneumonitis [30]. A small case series reported seven cases of IVIG-treated steroid-refractory pneumonitis. It suggested a superior efficacy in both oxygenation requirement and mortality, when compared to infliximab treatment [31].

- Plasmapheresis: The use of plasmapheresis is considered mostly in neurological irAEs, like GBS and myasthenia gravis as second-line therapy in steroid-refractory cases. The reported clinical response is variable in patients with moderate to severe neurological irAEs [14][32][33].

4. Safety and Risk of Using Immunosuppression

Patients receiving prolonged duration of immunosuppressants are at risk of various secondary complications such as hyperglycemia, hypertriglyceridemia, osteoporosis, and opportunistic infections. Many immunosuppressants have organ-specific complications. For instance, calcineurin inhibitors can cause nephrotoxicity, hypertension, and neurotoxicity [34]. The most common complications with mycophenolate involve the gastrointestinal tract resulting in nausea, vomiting, diarrhea, abdominal cramps, or the bone marrow causing leukopenia and anemia. IVIG and anti-thymocyte globulin can cause infusion reactions, flu-like symptoms, or cytokine release syndrome [35]. The FDA

has provided a black box warning for IFX regarding the potential to cause reactivation of tuberculosis and invasive fungal infections [36]. Hence, while it is essential to start immunosuppression immediately for treating irAEs, it is also important to limit the prolonged exposure to immunosuppression. Chronic management of these patients should be conducted under the guidance of a physician experienced with prescribing these medications, such as an organ specialist of an oncologist with significant experience treating steroid refractory irAEs. Currently there are not any prospective clinical trials demonstrating clear benefit of one treatment modality over another in the management of patients with steroid refractory irAEs. The choice of steroid sparing therapy is determined based on clinical factors such as toxicity of the immune suppressive therapy, patient comorbidities and treatment paradigms for related autoimmune disorders (e.g., Crohn's Disease guidelines for managing patients with immune mediated colitis).

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