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Clinical Reviews

MANAGEMENT OF IMMUNE CHECKPOINT INHIBITOR TOXICITIES: A REVIEW AND CLINICAL GUIDELINE FOR EMERGENCY PHYSICIANS

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☐ **Abstract—Background: Immune checkpoint inhibitors (ICIs) are a novel class of drugs used in cancer immunotherapy that are becoming more commonly used among advanced-stage cancers. Unfortunately, these therapies are sometimes associated with often subtle, potentially fatal immune-related adverse events (irAEs). Objectives: We conducted a review of relevant primary research and clinical guidelines in oncology, pharmacology, and other literature, and synthesized this information to address the needs of the emergency physician in the acute management of irAEs. Discussion: Although the antitumor effects of immunotherapies are desirable, the inhibition of immune checkpoints may also lead to loss of peripheral tolerance and a subsequent unleashing of the immune system on nontumor cells, leading to unintended tissue damage, which manifests as multisystem organ dysfunction. This tissue damage can affect nearly every organ system, with the dermatologic, gastrointestinal, endocrine, and pulmonary systems being the most commonly affected. Treatment may range drastically, depending on the severity of the irAE, starting with supportive care and moving toward high-dose steroids and additional immune modulators such as infliximab or intravenous immunoglobulin. Conclusion: With the increasing success and popularity of ICIs, emergency physicians will inevitably encounter increasing numbers of patients on these medications as well as the associated side effects. It is important that emergency physicians become aware of these irAEs and improve the detection of these processes to prevent inappropriate discharges, emergency department revisits, and downstream complications.** © **2018 Elsevier Inc. All rights reserved.**

☐ **Keywords—oncology; cancer; oncologic emergencies; checkpoint inhibitor; toxicity; toxicities; chemotherapy; immunotherapy; pneumonitis; colitis; thyroiditis; hypophysitis; dermatitis; immune checkpoint inhibitor; immunotherapy-related adverse events; irAEs; ICPI; ICI**

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are a novel class of drugs used in cancer immunotherapy that rapidly gained popularity due to their initial success in improving overall survival in patients with metastatic melanoma (1). Over the past few years, the indications for use of ICIs have expanded beyond melanoma to other advanced-stage cancers (2). Currently, the U.S. Food and Drug Administration has approved ICIs for use in ovarian cancer (CA), urothelial carcinoma, metastatic non-small-cell lung cancer, and more (3). Table 1 includes ICIs with each designated ICI class, as well as each ICI indication, and associated clinical trial investigations (1,2,4–6). Extrapolating from this trend, one can anticipate an increase in the approval and use of ICIs to treat a wide variety of cancers in the near future (7). The administration of ICIs, however, carry the risk of immune-related adverse events (irAEs) such as dermatitis, diarrhea, colitis, endocrinopathy, hepatotoxicity, neuropathy, and pneumonitis (8). Although irAE-related fatalities are

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Table 1. List of Current ICIs and Their Indications*

Drug Class	Drug Name	Indications and Status	Most Common Toxicity of Any Grade (1–4)	Most Common High-Grade (3 or 4) Toxicity
CTLA-4 Inhibitor	Ipilimumab† (1)	Approved melanoma after surgery Late stage melanoma	Dermatologic (43.5%) Gastrointestinal (29.0%) Hepatic (3.8%) Endocrine (7.6%)	Gastrointestinal (7.6%)
	Tremelimumab (2)	Mesothelioma	Diarrhea (30–40%) Rash/pruritis (30–34%)	Diarrhea (5–10%)
PD-1 Inhibitor	Nivolumab (5)	Hodgkin's lymphoma HNSCC Advanced lung cancer Metastatic renal cell carcinoma Advanced melanoma High microsatellite instability tumors Merkel cell carcinoma	Dermatologic (29.1%) Gastrointestinal (11.2%) Endocrine (7.8%)	Hepatitis (2–3%)
	Pidilizumab	Under trial	NR	NR
	Pembrolizumab† (6)	Recurrent or metastatic HNSCC Metastatic NSCLC Advanced melanoma Renal cell carcinoma Merkel cell carcinoma	Dermatologic (10.7%) Gastrointestinal (8.1%) Endocrine (6.9%)	Pneumonitis (1.8%)
	Atezolizumab (2)	Melanoma HNSCC Renal cell carcinoma Classical Hodgkin's lymphoma High microsatellite instability tumors Merkel cell carcinoma Metastatic NSCLC Urothelial carcinoma	Diarrhea (18–20%)	Diarrhea (1–2%)
	Durvalumab (2)	Melanoma HNSCC Renal cell carcinoma Classical Hodgkin's lymphoma High microsatellite instability tumors Merkel cell carcinoma	Diarrhea (9–10%)	NR
	Avelumab	Melanoma HNSCC Renal cell carcinoma Classical Hodgkin's lymphoma High microsatellite instability tumors	NR	NR

ICI = immune checkpoint inhibitor; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1/PD-2 = programmed death receptor-1 and -2; PD-L1 = programmed death-ligand 1; NR = not reported; HNSCC = head and neck squamous cell carcinoma; NSCLC = non-small-cell lung cancer.
* Current ICIs, their indications, most common associated toxicities reported as of December 2017.
† Drugs with dose-dependent toxicity.

rare, their associated morbidity can be quite high. Especially with higher-grade irAEs, complications can often be mitigated by timely identification and treatment, which generally includes high-dose systemic steroids, resuscitative efforts, and potential discontinuation of the ICIs (9). As established, ICIs are continually being approved for use in additional cancers, and as novel ICIs are brought to market, emergency physicians will undoubtedly see a concomitant rise in irAEs. Additionally, momentum is building to employ these agents in the treatment of HIV and other infectious diseases, which would further increase their use and secondarily, the incidence of irAEs (10,11). It is therefore critical to raise awareness within the emergency medicine (EM) community of the potential for irAEs–both smoldering and fulminant–and to equip emergency physicians with the knowledge to treat them appropriately. Although there is a large body of literature on irAEs from the oncology perspective, the aim of this article is to inform the emergency physician of irAE-associated toxicities of ICIs and to provide a streamlined approach to diagnosis, management, and follow-up for affected ED patients (12).

MATERIALS AND METHODS

Although there is a wealth of literature on ICIs, their associated irAEs, and relevant management algorithms, to our knowledge there is no comprehensive review directed toward physicians in the emergency department (ED) setting. We conducted a review of relevant primary research and clinical guidelines in oncology,