

Research Article

Highlights on Ocular Toxicity of Immune Checkpoint Inhibitors at a US Tertiary Cancer Center

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ABSTRACT

Introduction: Immune checkpoint inhibitors (ICIs) have improved prognosis in advanced malignancies; however, they may be associated with extensive ocular immune-related adverse events (irAEs) that are sight threatening. Our study aimed to identify the presentation, characteristics, management, and clinical outcomes of ocular irAEs.

Methods: In this retrospective, observational case series, we reviewed the medical records of 1280 patients at a large US tertiary cancer center between 2010 and 2020. **Results:** We identified 130 patients who presented with ocular irAEs (10%) with 69 males (53%) and 61 females (47%). The mean time to toxicity was 6.1 months. Adverse events include corneal toxicity (31%), neuro-ophthalmic (14%), uveitis and scleritis (13%), retinopathy (13%), periocular disorders (11%), and others. IrAEs occurred most frequently with nivolumab (26%). Most ocular irAEs were treated with topical therapy. Advanced cases required systemic corticosteroids and even cessation of ICIs. **Conclusion:** Our cohort is a large case series highlighting the increased potential of ocular toxicity associated with ICIs. Prompt recognition and management of ocular irAEs can minimize their effect.

Keywords: immune checkpoint inhibitors, ocular immune-related adverse events, nivolumab, ocular toxicity, immunotherapy side effects

INTRODUCTION

Immunotherapy has transformed the field of oncology. Traditionally, cancer has been treated by chemotherapy, radiotherapy, and surgical removal.^[1] Immunotherapy is a modern treatment modality that uses the patient's own immune system to overcome cancer.^[1] Immunotherapy works successfully on previously difficult-to-treat tumors, leading to improved prognosis in advanced cancer.^[2]

Immune checkpoint inhibitors (ICIs) are the most common type of immunotherapy and block tumor cells from deactivating the immune system.^[3,4] This allows antigen presenting cells (APCs) and T cells to continue attacking tumor cells. The primary targets of checkpoint

inhibition are cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), program cell death receptor 1 (PD-1), and programmed cell death ligand 1 (PD-L1).^[3] The current United States Food and Drug Administration (FDA)-approved ICIs include ipilimumab (CTLA-4), nivolumab (PD-1), pembrolizumab (PD-1), atezolizumab (PD-L1), avelumab (PD-L1), durvalumab (PD-L1), and combination therapy ipilimumab-nivolumab.^[4] Cemiplimab, another PD-1 inhibitor, was recently approved by the FDA.

Despite their success, ICIs have been associated with a broad spectrum of side effects called immune-related adverse events (irAEs).^[5,6] Ocular irAEs are quite rare, occurring in approximately 1% of treated patients;

Table 1. Common terminology criteria of adverse events grading of immune-related adverse event severity

	Grade 1, Mild	Grade 2, Moderate	Grade 3, Severe	Grade 4, Life (or Site) Threatening	Grade 5, Death
Description	Asymptomatic or mild symptoms	Symptomatic with moderate decrease in VA BCVA > 20/40 or < 3 lines of decreased vision from baseline	Symptomatic with marked decrease in VA BCVA < 20/40 or > 3 lines of decreased vision from baseline (up to 20/200)	Life-threatening consequences BCVA < 20/200	Death
Intervention indicated	None	Medical	Invasive	Urgent	

Based on information from [8].

BCVA: best-corrected visual acuity; VA: visual acuity.

however, they are becoming more relevant as indications increase and the demand for immunotherapy rises.^[7] Ocular adverse events range from transient blurred vision to permanent vision loss.^[4] Ocular toxicity may be sight-threatening and can significantly affect a patient's quality of life.^[7]

As the use of ICIs increases, it is necessary to understand the ocular irAEs better to diagnose and manage patients undergoing treatment appropriately. This study aimed to identify the presentation and characteristics of ocular irAEs. We detail the management and clinical outcomes related to checkpoint immunotherapy.

METHODS

In this retrospective cohort study at a tertiary cancer center, 1280 patients treated with ICIs were reviewed between 2010 and 2020. The institutional review board approved this study and informed consent was obtained from all patients. Patients taking the following ICIs were identified: ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab. In addition, combination regimens were incorporated. Cemiplimab was not included in the study because the FDA approved it in 2021, after we had collected data. We then investigated all patients on ICIs who underwent an ocular examination at the institution by an optometrist or ophthalmologist. Both inpatient and outpatient referrals were included. Most protocols involving ICIs at the institution (total, 135) required an ophthalmology consult as part of routine screening. Patients that received a new ocular diagnosis were detected. Those who had existing ocular pathology before starting ICIs were excluded. For example, a patient with optic neuropathy from brain metastasis before starting an ICI was not included.

Categorization

We categorized the irAEs and recorded the severity according to the National Cancer Institute's Common Terminology Criteria of Adverse Events (CTCAE).^[8] This compendium provides descriptive terminology to report adverse events, such as grading for the severity of ocular

pathology. Only ocular irAEs listed in the CTCAE were reported.^[8] The severity of irAEs is based on Grades 1 to 5 described in the CTCAE (Table 1).

Data Analysis

Patient demographics, including age and sex, were included in the study. The cancer diagnosis, ICIs used for treatment, frequency, and severity of ocular irAEs were reported. We included the time to presentation, management, and ultimate clinical outcome. Statistical analysis was performed using Statistical Analysis System (SAS) version 9.4 (SAS Inc., Cary, NC). Categorical variables were presented as counts and percentages. Clinical patterns associated with increasing severity of irAEs were determined using the Cochran-Armitage and the Fisher exact tests. Statistical significance was defined as $p < 0.05$.

RESULTS

Of the 1280 patients on ICIs, 170 of them underwent ocular examination, and 130 met the criteria for data analysis. These patients represented 10% of the study population on ICIs. Of ocular irAEs, 180 were documented in 130 patients. All patients were on ICIs at the time of developing symptoms. Patients could have more than one irAEs, such as dry eye and retinopathy. The mean age of the patient population was 61 years (SD, 12.6 years; range, 25–88). Among the patients identified, 97 were White (75%), 15 were Hispanic (12%), 10 were Black or of African American descent (8%), and 8 were Asian (6%). At the time of the study, 47 patients were deceased. Sixty-nine males reported ocular irAEs (53%) compared with 61 females (47%). The mean time to develop ocular toxicity related to an ICI was 6.1 months based on the first dose of the ICI administered. The minimum time was 6 days, and the maximum was 36 months.

In our study, the most common treated malignancy with ICIs that resulted in ocular irAEs was metastatic melanoma in 27 patients (28%). This was followed by renal cell carcinoma in 12 patients (10%) and lung cancer in seven patients (8%).

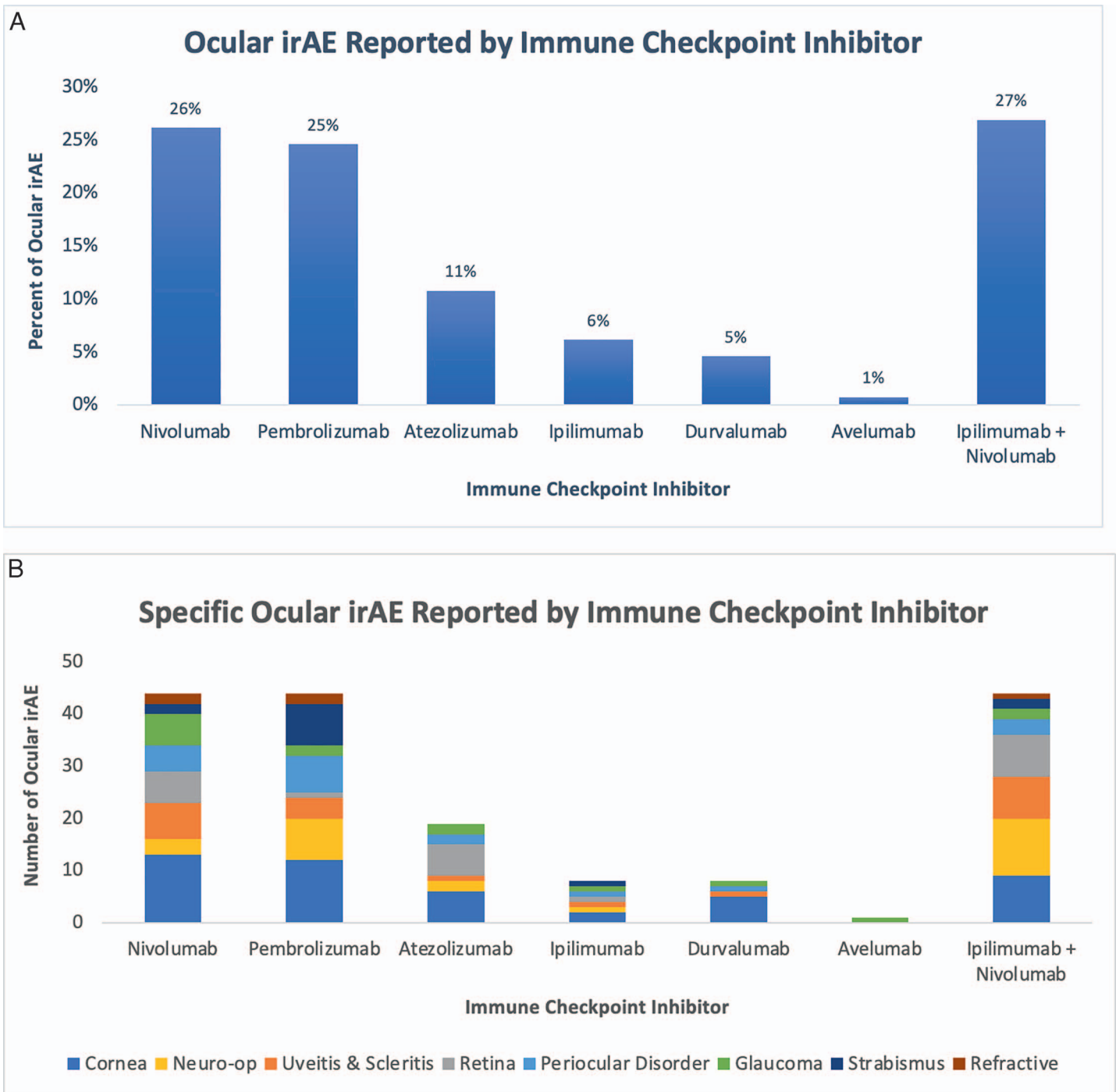


Figure 1. (A) Ocular immune-related adverse events (irAEs) reported by immune checkpoint inhibitor (ICI). (B) Specific ocular irAEs reported by ICI.

Ocular irAEs were most frequently described with nivolumab in 34 patients (26%), followed by pembrolizumab in 32 patients (25%), atezolizumab in 14 patients (11%), and ipilimumab in eight patients (6%) (Fig. 1A). Patients taking durvalumab and avelumab accounted for a lower proportion of patients with ocular adverse events. Ocular toxicity occurred in six patients on durvalumab (4%) and one on avelumab (1%). Combination therapy ipilimumab-nivolumab found irAEs in 35

patients (27%). There was a variable distribution of ocular irAEs found with most ICIs (Fig. 1B).

Corneal toxicity was the most common ocular irAE in 55 patients (31%) (Fig. 2). This was followed by neuro-ophthalmic disorders in 25 patients (14%). Retinopathy developed in 23 patients (13%). Other common toxicities were uveitis and scleritis with a total of 24 patients (13%), and periocular complications in 20 patients (11%).

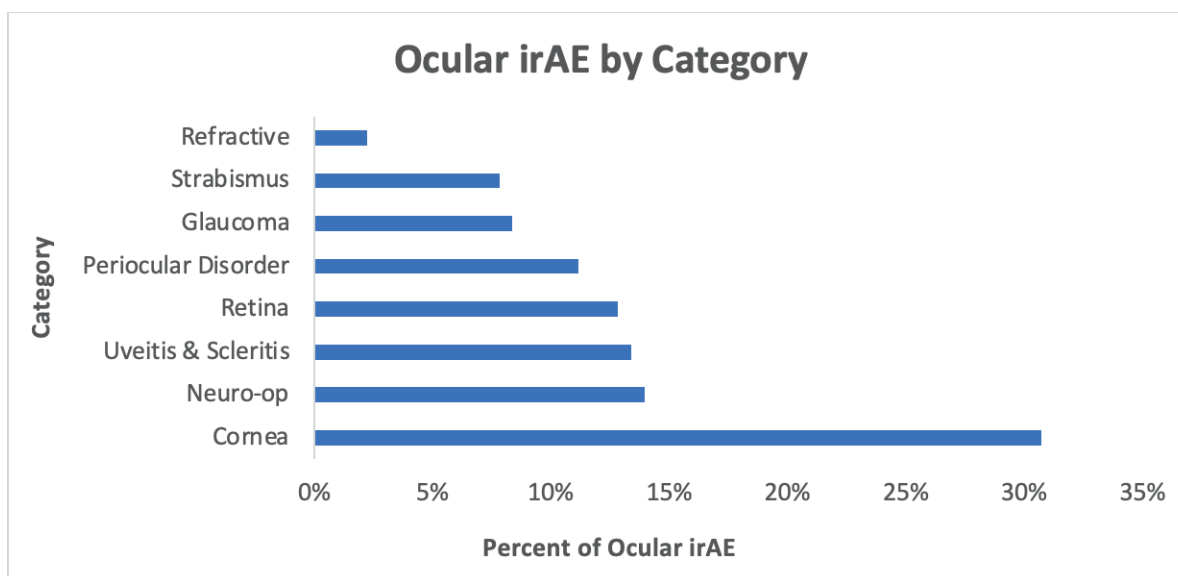


Figure 2. Ocular immune-related adverse events (irAEs) by category.

Table 2. Specific irAEs within broad categories

Specific irAE	Events, <i>n</i>
Cornea	
Corneal ulcer	1
Conjunctivitis	15
Keratitis	11
Dry eye syndrome	28
Glaucoma	
Glaucoma or elevated IOP	15
Retina	
Flashing lights or photopsias	3
Floaters	1
Retinal vascular disorder	3
Retinopathy	14
Retinal detachment	1
Vitreous hemorrhage	1
Refractive	
Blurred vision	4
Neuro-ophthalmic	
Myasthenia gravis	7
Papilledema	4
Optic nerve disorder	13
Nystagmus	1
Strabismus	
Extraocular muscle paresis	14
Periocular complications	
Periorbital edema	9
Periorbital infection	2
Eye pain	2
Eyelid function disorder	1
Hypertrichosis	3
Stevens-Johnson syndrome	3
Uveitis and scleritis	
Uveitis	19
Scleritis	5

irAE: immune-related adverse event; IOP: intraocular pressure.

Dry eyes were the most common specific ocular irAE in 28 events (15%) (Table 2). One patient developed a corneal ulcer without a history of contact lens wear or trauma. Optic nerve pathology was the most common neuro-ophthalmic diagnosis with 13 events (7%). This could include optic neuritis or optic nerve atrophy. This was closely followed by immune-related myasthenia gravis (3%). Fifteen patients had a documented rise in intraocular pressure with a corresponding loss of nerve fiber thickness on optical coherence tomography. There were 14 instances (8%) of retinopathy, such as central serous retinopathy or macular edema. Three patients had nonspecific symptoms of flashing lights in the periphery without any secondary dryness, inflammation, retinal tears, or holes. Photopsias can be associated with several conditions in the general population; however, these patients described the symptoms only after starting their ICIs. Similarly, four patients noted blurred vision secondary to changes in refraction after initiation of ICIs.

In addition, our study showed that most irAEs were Grade 1 (51%) and managed with observation or topical treatment (Fig. 3). Topical treatment included lubrication, nonsteroidal anti-inflammatory drugs, or empiric antibiotic eye drops in the case of potential infection. It did not include topical corticosteroid therapy. Most moderate to advanced cases (Grades 2–4) in patients required some form of corticosteroids (either topical, systemic, or combination). Patients with Grade 3 to 4 toxicity frequently required cessation of ICIs. Some patients with Grade 4 toxicities underwent procedures. One patient required a pars plana vitrectomy for non-clearing vitreous hemorrhage. There was no prior history of trauma, diabetes, or hypertension in the patient. Another patient required a tarsorrhaphy for severe noninfectious keratitis. None of our patients suffered death (Grade 5 toxicity) from an ocular irAE.

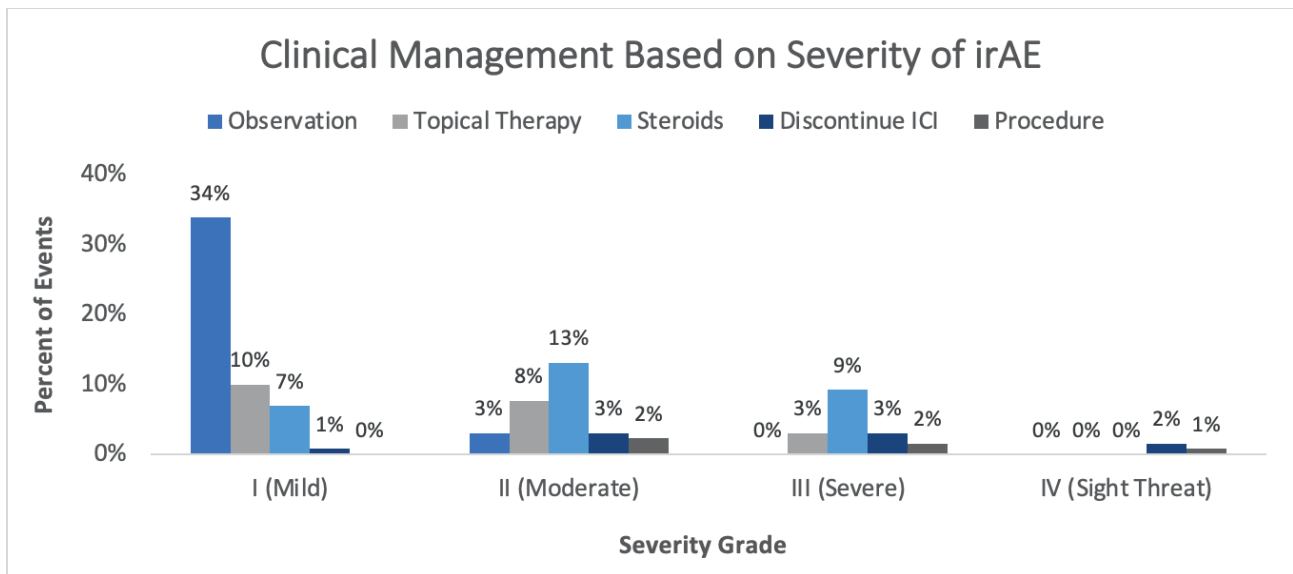


Figure 3. Clinical management based on severity of immune-related adverse events (irAEs).

We hypothesized that the more severe the toxicity, the more likely therapy was stopped. Figure 4 demonstrates the distribution of ocular irAE severity and the percentage of patients that discontinued the ICIs from ocular irAE. Of patients who developed Grade 4 toxicity, 67% required discontinuation of ICIs compared with 1% of patients who developed Grade 1 toxicity. This was statistically significant using the Fisher exact test ($p = 0.0007$) and Cochran-Armitage trend test ($p = 0.0001$). Therefore, we can conclude that the more severe the toxicity, the more likely the immunotherapy was discontinued.

DISCUSSION

This is one of the larger English literature cohorts to date to investigate the ocular toxicities of ICIs at a single

tertiary cancer center. Ten percent of the patients on ICIs developed ocular irAEs. This is more than prior studies, showing a 1% to 3% prevalence of ocular irAEs.^[7] Most ocular irAEs are limited to individual case reports and single-digit case series.^[7,9,10] The frequency of ocular irAEs may be underestimated because of insufficient attention and documentation. As the use of ICIs increases, ocular adverse events are becoming more relevant in clinical practice.

The mean time to develop an ocular irAE was 6.1 months from the first administration of ICIs. This is consistent with another report of ICI use in lung cancer, for which the mean onset of ocular irAE was 6.5 months.^[11] Ophthalmologists should know that patients on ICIs do not have to develop toxicity immediately after administration but may develop months to years

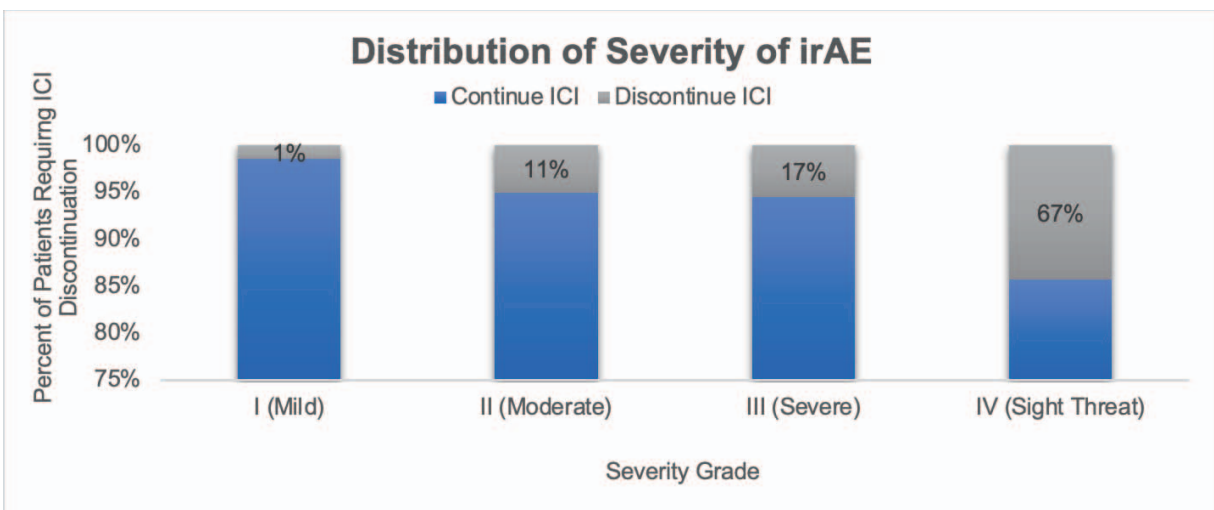


Figure 4. Increasing severity of immune-related adverse events (irAEs) more likely to lead to immune checkpoint inhibitor (ICI) discontinuation.

later. Although complications can arise after stopping the ICIs, especially during the washout period, all reported irAEs in our cohort occurred while patients were on treatment.

IrAEs are believed to arise from the enhancement of the immune system.^[6,12] Historically, CTLA-4 inhibitors were associated with a higher frequency of irAE.^[11] This was thought to be secondary to the upstream effect of CTLA-4. One study proposed that CTLA-4 inhibitors impair the survival and function of T cells, which yields to the formation of autoimmune inflammatory disorders.^[13] Although CTLA-4 inhibition occurs at T-cell initiation, PD-1 inhibition occurs more downstream. In our study, the most common ICI implicated in ocular toxicity was nivolumab, which is a PD-1 inhibitor (34 patients [26%] nivolumab alone or with combination therapy with ipilimumab in 35 patients [27%]).

Of note, PD-1 and PD-L1 play a role in ocular immune privilege.^[14,15] PD-1 is constitutively expressed in the eye by retinal pigment epithelial cells.^[14] When blocked, this can trigger an immune response against intraocular tissues. In a mouse model that underwent corneal transplantation, the transplants developed rejection when PD-1 or PD-L1 were blocked.^[14] It is thought that because of PD-1 involvement in immune privilege, blockade of PD-1 is more likely to trigger irAEs.

The most common specific ocular irAE was dry eyes with 28 events (15%). Clinical trial reports of CTLA4 and PD-1–targeting antibodies showed that the incidence of dry eye is 1–24%.^[4] Shahzad et al^[7] suggested that dry eye occurred in one in four patients treated with ICIs. Dry eye is a challenge because it is often underreported in clinical trials and practice.^[4]

Because ICIs enhance the immune system, it is not surprising that many ocular toxicities are related to exaggerated immune responses. For example, ICIs have been shown to trigger myasthenia gravis.^[16] In our study, there were seven events (4%) of immune-related myasthenia gravis with ocular irAEs. Similarly, uveitis is one of the more well-known irAEs.^[17] Uveitis and scleritis were among the more frequent irAEs in our study with 24 events (13%).

The most common severity was Grade 1—mild and required little to no intervention. Only one patient with Grade 1 ocular irAE stopped therapy, but this was because of other more severe systemic adverse events. Most of the patients with Grade 1 toxicity did not need to discontinue treatment. Corticosteroids were the primary treatment for many moderate to advanced ocular irAE. In doing so, many patients returned to baseline visual acuity. Some cases, such as optic neuropathy, resulted in permanent vision loss. Recognition of ophthalmic irAE allowed for improved overall visual prognosis. Fortes et al^[18] showed that most ocular irAEs were either well controlled or resolved with the treatment of topical therapy or corticosteroids. The more severe the ocular irAE, the more likely the patient was to discontinue immunotherapy. A consideration for rechall-

enge was managed on a case-by-case basis depending on recovery and risk. For instance, a patient with ischemic optic neuropathy or central retinal artery occlusion would not be considered for rechallenge given the high risk for recurrence, and the patient would require alternate therapy.

Because there are no prospective trials to guide the treatment of irAEs, treatment is based on clinical experience, expert opinion, and knowledge. The Society for Immunotherapy of Cancer (SITC) established the Toxicity Management Working Group ASCO guidelines to help standardize counseling and management.^[19] These guidelines would serve as an excellent resource to help providers treat ocular irAEs depending on the severity and grade of toxicity.^[19] Ongoing communication between oncologists, ophthalmologists, and primary care providers can help determine if systemic irAEs require the discontinuation of ICI therapy.^[18] Specialized and multidisciplinary care is critical to managing adverse events related to immunotherapy to minimize its effect and help preserve vision.^[20]

A limitation of our study design is that this is a retrospective study, and thus the reporting of adverse events is based on prior medical records. In this study, the patients identified were clinical trial participants and could have a lower threshold for primary physicians to request an ophthalmology consultation. This could contribute to the increased incidence of irAE. Another limitation is that the power of the study is low. Furthermore, systemic adverse events could have played a role in discontinuing ICIs. Current studies at our institution are investigating the correlation between systemic and ocular irAEs. Larger cohorts will continue to refine the frequency of irAEs while using ICI therapies.

CONCLUSION

Checkpoint immunotherapy uses the body's immune system to target cancer and has dramatically improved outcomes in advanced cancer. However, enhancing the immune system can unleash a broad spectrum of ocular immune-related adverse events. Our study highlights the increased potential of ocular toxicity in up to 10% of the study population. Prompt recognition with specialized and multidisciplinary care is critical to managing adverse events related to immunotherapy to minimize their effect.

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