Ocular side effects of checkpoint inhibitors

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ABSTRACT

The incidence and impact of ocular side effects in patients treated with checkpoint inhibitors are not clearly defined.

We reviewed prospective phase III clinical trials of checkpoint inhibitors applied in lung cancer, renal cell cancer, and melanoma. Case reports of the occurrence of ocular toxicities in patients receiving immune checkpoint inhibitors were also included. Of the 35 articles corresponding to phase III clinical trials with checkpoint inhibitors, ocular toxicity was described in four. Forty-six clinical cases of ocular toxicity after therapy with checkpoint inhibitors have been reported. The most frequently described ocular toxicities are uveitis, inflammatory orbital disease, and alterations of the ocular surface. Ocular toxicity is underestimated in checkpoint inhibitors clinical trials. Early ophthalmic examination and treatment with corticosteroids may improve the visual prognosis in these patients.

1. Introduction

Checkpoint inhibitors are new immunologic agents that block inhibitory receptors of immune system elements, such as programmed death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA4),[30] altering the immune response of T lymphocytes and promoting the immune response against cancer cells.[42] Since 2010, checkpoint inhibitors have been increasingly used for cancer therapy.[42] Their main indications are in lung cancer, kidney cancer, and melanoma.[31,55,72]

The most used checkpoint inhibitors are atezolizumab, durvalumab and avelumabdhumanized IgG1 monoclonal antibodies that block PDL1[37]; pembrolizumab and nivolumabdhumanized IgG4 monoclonal antibodies that block the PD1 receptor[97,82]; and ipilimumab, immunoglobulin G1 (IgG1)da human monoclonal antibody that acts as a CTLA-4 antagonist.[71] Multiple clinical trials have demonstrated the effectiveness of checkpoint inhibitors as monotherapy and in combination.[31,55,72]

1.1. Checkpoint inhibitors are toxic to multiple organs and systems

Frequent immune-related adverse events include gastrointestinal, endocrine, and dermatologic toxicities. Severe

adverse events include neurotoxicity, cardiotoxicity, and pulmonary toxicity.[96] The efficacy and toxicity of these drugs when used in combination increases, and an increase in toxicity may even be a favorable prognostic factor.[103]

Although systemic toxicity is usually well characterized, this is not the case with ocular toxicity. Dalvin and co-workers[23] have recently described ocular toxicity secondary to checkpoint inhibitors; however, there are no clinical practice guidelines in ophthalmology, and the protocols of phase III clinical trials that lead to the approval of these drugs do not systematically include ocular side effects.

The objective of our study is to define and call attention to the ocular toxicity of checkpoints inhibitors.

2. Findings

We reviewed 35 articles corresponding to Phase III clinical trials of checkpoint inhibitors. All selected articles used checkpoint inhibitors in the treatment of kidney cancer, lung cancer, or melanoma and were the studies responsible for the approval of these drugs in clinical practice. We collected 13 articles on the treatment of melanoma.[20,27,40,51,53,56,59,77,82,83,84,98] Ten articles addressed the treatment of renal cancer.[18,28,64,66,65,79,78,90,91,93] Twelve articles dealt with the treatment of lung cancer.[4,8,10,11,14,29,32,35,73,74,80,85] One Phase II study was included that addressed the ocular toxicity after cemiplimab treatment for cutaneous squamous-cell carcinoma.[61]

Regarding the ocular toxicity reported in the results of these clinical trials, the following data were found: unspecified ocular inflammation with the use of tremelimumab for metastatic melanoma in 13 patients (4%),[8] anterior uveitis in patients who used pembrolizumab for metastatic melanoma in 4 patients (1.5%),[82] increased tearing in 3 patients (1%) treated with nivolumab for lung cancer.[11] Some adverse events were related to atezolizumab in lung cancer as exophthalmos in 1 patient (0.2%), uveitis in 1 patient (0.2%), ocular inflammation in 1 patient (0.2%), optic neuritis in 2 patients (0.3%), and retinopathy in 1 patient (0.2%).[29]

All except optic neuritis and retinopathy were described as grade 1 adverse effects on CTCAE (common terminology criteria for adverse events). These were included as CTCAE grade 3e4 toxicity. Some adverse events were related to cemiplimab in squamous-cell carcinoma as conjunctivitis, dry eye, ocular myasthenia, and diplopia.[61] None of the articles referring to Phase III clinical trials in kidney cancer addressed ocular toxicity. None of the articles reported the management of these ocular toxicities.

The reviewed articles, type of cancer, drugs used, and the report of ocular toxicity are shown in Table 1.

Forty-six clinical cases reported ocular toxicity after the use of checkpoint inhibitors were reviewed. The ocular side effects are reported as mild and occurred in less than 1% of the patients,[25] usually during the first week of treatment.[88] The most frequent side effects described are uveitis (particularly VogteKoyanagieHarada [VKH]-like syndrome) and inflammatory orbital disease.

2.1. *Uveitis*

Uveitis includes inflammation of the iris, vitreous, and choroid.

Anterior uveitis often resolves with topical treatment. Some cases of posterior uveitis required systemic corticosteroids or immunomodulatory therapy. Some authors have associated checkpoint inhibitors therapy with clinical reports of uveitis in relation to pembrolizumab,[1,3,9,21,38,89,106] ipilimumab and[41,48,49,67,70,101] nivolumab.[6,19,24,45,46,81] Sun,[86] in his review of uveitis associated with checkpoint inhibitors, described intraocular inflammation associated with pembrolizumab, ipilimumab, and nivolumab.

The described uveitis was mostly anterior, transitory, and satisfactorily treated with topical corticosteroids. In some cases of posterior uveitis systemic corticosteroid therapy or implantation of an intravitreal dexamethasone device were required.[1,19,21]

VKH is a particular form of uveitis featuring inflammation of melanocyte-containing tissues such as the uvea, the ear, and the meninges. It is characterized by headache, tinnitus, vertigo, and deafness, associated with bilateral granulomatous anterior or multifocal posterior uveitis and exudative retinal detachments. The convalescent phase follows several weeks later with localized alopecia, poliosis, and vitiligo, with focal depigmented fundus lesions (sunset glow fundus) and depigmented limbal lesions.[104]

VKH is described most frequently after the use of ipilimumab,[22,50,52,58,62,76,104] the first FDA-approved treatment in melanoma. Ipilimumab has an affinity with melanocytes, which explains the alteration of choroidal melanocytes and the consequent appearance of uveitis. This secondary effect should be promptly treated with systemic intravenous and oral corticosteroids and with intraocular or topical corticosteroids, followed by immunosuppression. Only in selected cases does VKH justify the withdrawal of treatment.[21] This decision should be taken between the ophthalmologist and the oncologist in considering risk of worsening of the underlying malignancy. Retinal vasculitis (occlusive or not), with its consequent exudation, hemorrhage, or macular edema, is considered as being within the spectrum of posterior uveitis. This rarely requires discontinuation of treatment but should be treated immediately with systemic corticosteroid therapy. This condition has been reported after nivolumab[21,86] and ipilimumab[6,86] treatment.

2.2. *Inflammatory orbital disease*

The inflammatory orbital disease is a heterogeneous entity that can affect the extraocular muscles simulating GraveseBasedow disease.[12,60] Orbital inflammation with the involvement of the lacrimal glands, muscle, orbital fat, and conjunctiva simulating an idiopathic orbital inflammation[54] may occur, or a deep inflammation with the involvement of the cavernous sinus simulating TolosaeHunt syndrome has been described.[95] In these entities, the use of topical and systemic corticosteroids (oral or intravenous pulses) is necessary. In persistent cases, plasmapheresis or immunoglobulins could be used.[57] Most of these toxicities are reported after the use of ipilimumab,[12,54,57,60,95] although they have also

Table 1 e Articles corresponding to phase III clinical trials of checkpoints inhibitors and cemiplimab phase II study

Author (year)	Type of cancer (number of patients)	Drug	Ocular toxicity reported
Weber et al. (2013)	Melanoma (540)	Ipilimumab	No
Eggermont et al. (2015)	Melanoma (475)	Ipilimumab	No
Hodi et al. (2018)	Melanoma (945)	Ipilimumab and/or Nivolumab	No
Lebbe, et al. (2019)	Melanoma (360)	Ipilimumab and/or Nivolumab	No
Larkin et al. (2018)	Melanoma (272)	Nivolumab	No
Long et al. (2016)	Melanoma (210)	Nivolumab	No
Coens et al. (2017)	Melanoma (475)	Ipilimumab	No
Schadendorf et al. (2017)	Melanoma (945)	Nivolumab and/or Ipilimumab	No
McDermott et al. (2013)	Melanoma (676)	Ipilimumab	No
Ribas et al. (2013)	Melanoma (329)	Tremelimumab	Ocular inflammation
Robert et al. (2015)	Melanoma (834)	Pembrolizumab or Ipilimumab	Uveitis
Schachter et al. (2017)	Melanoma (834)	Pembrolizumab or Ipilimumab	No
Weber et al. (2015)	Melanoma (272)	Nivolumab	No
Uemura et al. (2019)	Renal (33)	Avelumab	No
Cella et al. (2016)	Renal (352)	Nivolumab	No
Escudier et al. (2017)	Renal (410)	Nivolumab	No
Tomita et al. (2020)	Renal (550)	Nivolumab and Ipilimumab	No
Motzer et al. (2015)	Renal (410)	Nivolumab	No
Rini et al. (2019)	Renal (432)	Pembrolizumab	No
Motzer et al. (2018)	Renal (550)	Nivolumab and Ipilimumab	No
Motzer et al. (2019)	Renal (442)	Avelumab	No
Rini et al. (2019)	Renal (454)	Atezolizumab	No
Tomita et al. (2019)	Renal (410)	Nivolumab	No
Barlesi (2018)	Lung (396)	Avelumab	No
Bordoni et al. (2018)	Lung (425)	Atezolizumab	No
Govindan et al. (2017)	Lung (388)	Ipilimumab	No
Socinski et al. (2018)	Lung (356)	Atezolizumab	No
Brahmer et al. (2015)	Lung (272)	Nivolumab	No
Gerber et al. (2017)	Lung (275)	Nivolumab	No
Borghaei et al. (2015)	Lung (292)	Nivolumab	Increased tearing
Rittmeyer et al. (2017)	Lung (425)	Atezolizumab	No
Fehrenbacher et al. (2018)	Lung (425)	Atezolizumab	Uveitis, ocular inflammation, exophthalmos retinopathy, optic neutitis
Antonia et al. (2017)	Lung (473)	Durvalumab	No
Planchard et al. (2016)	Lung (700)	Durvalumab	No
Paz-Ares et al. (2019)	Lung (268)	Durvalumab	No
Migden (2018)	Squamous cell carcinoma	Cemiplimab	Conjunctivitis, dry eye, ocular myasthenia, diplopia

been described after durvalumab.[17] Orbital inflammation with muscle involvement can also present with muscle fatigue simulating myasthenia gravis with electromyogram alteration, the elevation of creatine-kinases, but without the presence of acetylcholine receptor antibodies.[44,63,75] This has been described with nivolumab,[75] ipilimumab,[63] and pembrolizumab.[44]

2.3. *Ocular surface*

The ocular surface may be affected in different ways.[16] The most common (2%) is dry eye, usually treated with ocular lubrication or low doses of topical corticosteroids. Topical cyclosporine could be added in severe cases. It has been related to nivolumab,[33,99] pembrolizumab,[39] and ipilimumab.[77,88] There is one case of, ocular perforation from severe dry eyes after ipilimumab that required cessation of immunological treatment and immediate surgery.[68]

Peripheral ulcerative keratitis (PUK) is characterized by severe peripheral corneal infiltration, ulceration, and thinning, resulting in a red eye with decreased vision and pain. In patients with PUK associated with an underlying autoimmune disease, there is an immune complex deposition in the peripheral cornea. There is one case of PUK reported after ipilimumab.[70]

Conjunctivitis has also been reported after pembrolizumab,[106] which remitted with topical corticosteroid therapy, and after ipilimumab, which required the cessation of immunological treatment because of its persistence.[94]

Table 2 e Clinical cases of ocular side effects after checkpoint inhibitors treatment

Ocular side effect	Drug	Author	Management
Uveitis			
Anterior uveitis	Pembrolizumab	Abu Samra,[3] Basilious,[9] Hahn,[36,37] Aaberg,[1] Conrady,[21] Zimmer,[106] Taylor,[89] Sun.[86]	Topical corticosteroids Topical cyclopentolate
	Ipilimumab	Papavasileiou,[70] Weber,[98] Nallapaneni,[67] Kwon,[49] Kiratli,[48] Arai,[6] Sun[60]	Topical corticosteroids Topical cyclopentolate
	Nivolumab	Karlin,[46] de Velasco,[24] Kanno[45] Chan,[19] Sun[86]	Topical corticosteroids Topical cyclopentolate
Posterior uveı´tis			
Chorioretinitis	Pembrolizumab	Aaberg[1]	Checkpoint inhibitor withdrawal Oral corticosteroids Intravitreal corticosteroids
	Nivolumab	De Velasco,[24] Conrady,[21]	Checkpoint inhibitor withdrawal Oral corticosteroids Intravitreal corticosteroids
VKH	Ipilimumab	Wong,[104] Postow,[76] Larkin,[50] Mantopoulos,[58] Crews,[22] Modjtahedi,[62] Lavezzo[52]	Checkpoint inhibitor withdrawal Intravenous and oral corticosteroids
Retinal vasculitis	Nivolumab	Conrady,[21] Sun[60]	Checkpoint inhibitor withdrawal Oral corticosteroids Intravitreal corticosteroids
	Ipilimumab	Arai,[6] Sun[86]	Checkpoint inhibitor withdrawal Oral corticosteroids
Inflammatory orbital disease			
GraveseBasedow-like	Ipilimumab	McElnea,[60] Borodic,[12]	Oral corticosteroids
	Pembrolizumab	Conrady,[21] Sun[86]	Oral corticosteroids
Idiopathic orbital inflammation	Ipilimumab Durvalumab	Lecouflet,[54] Carrera[17]	Oral corticosteroids
TolosaeHunt syndrome	Ipilimumab	Voskens[94]	Checkpoint inhibitor withdrawal Oral corticosteroids Intravenous corticosteroids
Myasthenia-gravis-like	Nivolumab Ipilimumab Pembrolizumab	Polat,[75] Montes,[63]	Checkpoint inhibitor withdrawal Oral corticosteroids Plasmapheresis Immunoglobulins
Ocular surface			
Dry eye	Nivolumab	Cappelli,[16] Gibney,[33] Weber,[99] Herbst[39]	Artificial tears Topical corticosteroids
	Ipilimumab	Hodi,[40] Nguyen[68]	*corneal transplantation
PUK	Ipilimumab	Papavasileioeu[70]	Artificial tears Corticosteroid ointment
Conjunctivitis	Pembrolizumab	Zimmer[106]	Artificial tears Topical corticosteroids
	Ipilimumab	Voskens[94]	Checkpoint inhibitor withdrawal
Episcleritis	Ipilimumab	Weber[97]	Topical corticosteroids
Other ocular side effects			
Neuroretinitis	Ipilimumab	Hahn[36]	Oral corticosteroids
Optic neuritis	Ipilimumab	Yeh[105] Wilson[102]	Checkpoint inhibitor withdrawal Oral corticosteroids
Facial nerve palsy	Ipilimumab	Numata[69]	Oral corticosteroids
Giant cell arteritis	Ipilimumab	Goldstein[34]	Checkpoint inhibitor withdrawal Intravenous corticosteroids
Rosacea	Ipilimumab and Nivolumab	Niels[15]	Corticosteroids ointment Artificial tears

VKH, VogteKoyanagieHarada; PUK, Peripheral.

Episcleritis is an inflammation of the subconjunctival tissue with symptoms similar to conjunctivitis (discomfort, red eye, sensation of inflammation, tearing) that is treated with topical corticosteroids or topical antiinflammatories. There is one case described after ipilimumab.[100]

2.4. Others

Neuroretinitis and optic neuropathy have been associated with ipilimumab. These may require systemic corticosteroids, systemic immunosuppression, and the withdrawal of the

drug.[36,102,105] Facial nerve palsy has also been described after ipilimumab, treated with systemic corticosteroids.[69]

A syndrome resembling giant cell arteritis (headache, jaw claudication, shoulder myalgia, transient monocular visual loss) has been reported after ipilimumab that was treated with intravenous corticosteroid pulses.[95]

Severe ocular rosacea has been associated with nivolumab and ipilimumab and was successfully treated with corticosteroid ointment and lubrication without requiring withdrawal of treatment.[15]

The ophthalmological toxicities reported in the reviewed clinical cases are summarized in Table 2.

3. Discussion

Immunotherapy has changed the way of treating cancer. Checkpoint inhibitors are mainly used in kidney cancer, melanoma, and lung cancer, demonstrating greater survival compared to other types of chemotherapy, but at the risk of various side effects.[92] Currently, the Food and Drug Administration has approved ICIs, including anti-CTLA-4 (ipilimumab), PD-1 inhibitors (pembrolizumab and nivolumab), and PD-L1 inhibitors (atezolizumab, durvalumab, and avelumab).[87] The main side effects are cutaneous, endocrine, gastrointestinal, hepatic, and pulmonary.[2]

The Phase III clinical trials that have led to the approval of checkpoint inhibitors include hardly any mild side effects such as uveitis or nonspecific ocular inflammation[11,59,77] and only collect some isolated reports of serious ocular toxicity that entails the discontinuation of immunotherapy.[29] The protocols of such clinical trials do not include an ophthalmological review.

Clinical oncology guidelines for toxicity management after checkpoint inhibitors therapy pay little attention to the incidence and impact of ocular toxicity.[47]

Recently, Brahmer and coworkers[13] included in their guide the main side effects of checkpoint inhibitors at the systemic and ocular level. This guide, however, only described uveitis, episcleritis, or blepharitis. In addition, its management did not include prior review and follow-up by ophthalmologists of patients receiving this medication and only included the need for an ophthalmological visit if the ocular side effects were severe and disabling. Even some mild degrees of uveitis, however, could cause irreversible long-term ophthalmic effects such as increased intraocular pressure, synechiae, or macular edema leading to sustained vision loss, just as some types of subclinical retinopathy can lead to intraretinal fluid entrapment leading to photoreceptor loss and future vision loss. These side effects must be detected early and treated by the ophthalmologist, often with topical or systemic corticosteroid therapy, to preserve visual acuity as best as possible. The management of checkpoint inhibitor treatment should be discussed between the ophthalmologist and the oncologist, taking into account the risk/benefit ratio[43]

As we have seen, there are multiple cases described in the literature on ocular toxicity after treatment with checkpoint inhibitors. The published cases mainly include various types of anterior and posterior uveitis, including the VKH syndrome.[52]

In reported clinical cases, anti-CTLA-4 agents showed a higher incidence and severity of ocular toxicity than PD-1/PD-L1 inhibitors, and ocular toxicity occurs more often in melanoma than other solid cancers. This observation may be explained through the cross-reactivity between malignant melanoma cells and normal choroidal melanocytes.[5] Uveitis, especially in VKH-like uveitis, is thought to be a marker for a favorable treatment response.[26] These uveitis cases should be treated immediately and specifically with systemic corticosteroids and immunomodulation in chronic cases[52] Other serious side effects described in clinical cases are also included, such as inflammatory orbital involvement,[12,54,60] since if it is severe or maintained over time, it may lead to orbital blockage with consequent chronic pain, diplopia, or visual loss due to compression of the optic nerve.[95]

Therefore, we can see that the ocular side effects described in clinical trials underestimate the ocular side effects in routine clinical practice.[7] Although more and more protocols of these clinical trials include an ophthalmology visit, we would like to emphasize that the description of ocular side effects, especially infrequent ones, increases when drugs are widely used in clinical practice outside the clinical trials.

Some of the ocular consequences may be explained by other effects described at the systemic level, such as the involvement of the extraocular musculature and the described myositis, the presence of subretinal fluid due to extravasation secondary to systemic arterial hypertension, eyelid erythema secondary to skin rash generalized, or involvement of cranial nerves with ocular involvement such as II, III, IV, V, VI, and VII pair as the involvement of the central nervous system.[7]

We propose including systematic ophthalmological reviews in clinical trials of immunotherapy to determine the prevalence and extent of ocular toxicity. We want to familiarize ophthalmologists with the side effects most frequently associated with these drugs so that they can be detected early.

4. Conclusion

In conclusion, we can suppose that the ocular side effects are underestimated in the checkpoint inhibitor clinical trials, and we propose that the ophthalmological visit should be systematized in the evaluation of these patients. With the use of new drugs, there are new side effects. A multidisciplinary approach between oncologists and ophthalmologists is essential for the correct management of these side effects to avoid irreversible visual loss, as well as to improve the quality of life of these patients, who are increasingly experiencing longer survival.

5. Methods of literature search

5.1. Inclusion and exclusion criteria

The criteria for considering studies for this review were as follows: Prospective phase III clinical trials of checkpoints inhibitors applied in lung cancer, renal cell cancer, and melanoma. Clinical cases that reported the occurrence of ocular

toxicities (with a possible immune etiology as judged by the investigators) in the solid tumor of patients receiving immune checkpoint inhibitors were also included.

Phase I or II clinical trials or phase III clinical trial of checkpoints inhibitors in other solid tumors different to renal, lung, or melanoma were excluded except one phase II study about cemiplimab in cutaneous squamous cell carcinoma.

5.2. Search methods

The PUBMED database was searched from January 2010 to March 2020. Search terms for the identification of pivotal clinical trials were “checkpoint inhibitors,” “phase III clinical trial,” “pembrolizumab,” “nivolumab,” “atezolizumab,” “durvalumab,” “avelumab,” “tremelimumab,” “ipilimumab,” “cemiplimab,” “renal cell cancer,” “lung cancer,” “melanoma.” Search terms for the identification of clinical cases were “ocular toxicity,” “checkpoint inhibitor uveitis,” “checkpoint inhibitor ocular inflammation,” “checkpoint inhibitors,” “checkpoint inhibitors adverse events.”

The review was performed according to the PRISMA recommendations. The analysis of data was performed using Review Manager 5.3.

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