Immune-Related Oral, Otologic, and Ocular Adverse Events

17

Akanksha Srivastava, Nagham Al-Zubidi, Eric Appelbaum, Dan S. Gombos, Marc-Elie Nader, Paul W. Gidley, and Mark S. Chambers

Abstract

Emerging immunotherapy agents, such as immune checkpoint inhibitors, have shown remarkable promise in the treatment of various malignancies. These drugs selectively target different steps in the immune response cascade to upregulate the body's normal response to cancer. Due to the novelty of these therapeutic agents, their toxicity profile is less well understood.

Meta-analysis results reveal that the overall prevalence of oral mucositis, stomatitis, and xerostomia is lower with checkpoint inhibitors compared to conventional chemotherapy, and head and neck radiation therapy. However, the widespread use of immunotherapy reveals new oral mucosal barrier adverse events, including bullous pemphigoid, mucous membrane pemphigoid, and lichenoid mucositis. Audiovestibular dysfunction can occur from autoimmune-mediated pathways of immunotherapy (adoptive cell) with limited treatment options. Such auditory complications can lead to speech recognition deficits and sensorineural hearing loss. Ocular toxicities are among the most common adverse events resulting from the use of these agents. The majority of ocular immune-related adverse events (irAEs) are mild, low-grade, non-sight threatening, such as blurred vision, conjunctivitis, and ocular surface disease. Serious and sight-threatening events, including corneal perforation, optic neuropathy, and retinal vascular occlusion, can occur but are infrequent. In this chapter, we review the current evidence on the clinical manifestations of oral, audiovestibular, and ocular immune-related adverse events (i.e., irAEs).

Keywords

Oral adverse events · Hearing loss · Ocular adverse events · Immune-related ocular toxicities · Immune-related otologic toxicities · Immune-related oral toxicities · Checkpoint inhibitors · Ipilimumab · Pembrolizumab · Nivolumab · Anti-PD-1/PD-L1 · CTLA-4 · Atezolizumab

Emerging immunotherapeutic agents, including immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death protein ligand 1 (PD-L1), have revolutionized cancer treatment. The first immune checkpoint inhibitor (ipilimumab), an

A. Srivastava · N. Al-Zubidi · E. Appelbaum
D. S. Gombos · M.-E. Nader
P. W. Gidley · M. S. Chambers (✉)
Department of Head and Neck Surgery, Division of Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: mchamber@mdanderson.org

A. Naing, J. Hajjar (eds.), *Immunotherapy*, Advances in Experimental Medicine and Biology 1244,
https://doi.org/10.1007/978-3-030-41008-7_17

anti-CTLA-4, was approved in 2011. Since then, the U.S. Food and Drug Administration (FDA) has approved more than half a dozen immune checkpoint inhibitors to treat various malignancies. These agents are part of a broader class of chemotherapy agents termed immunotherapy, which selectively target different steps in the immune response cascade to upregulate the body's normal response to cancer. While the effects of traditional chemotherapy are well known, the toxicity profile of emerging immune therapies is not fully elucidated. They have been associated with atypical side effects labeled collectively as immune-related adverse events (irAEs).

Many of these events are related to the same immunologic mechanisms responsible for their therapeutic effects. Among the hypothesized mechanism is a breakdown of peripheral tolerance and induction of organ specific inflammatory process leading to immune dysregulation. Ocular toxicities are among the more common adverse events resulting from these agents with a large spectrum in type and severity [1, 2]. Other common irAEs include dermatologic, endocrine, gastrointestinal, hematologic, renal, and neurologic manifestations of disease. Less understood, perhaps owing to its rarity are audiovestibular irAEs. Similarly, severe oral adverse events are limited to a few case reports.

Immunotherapy and Oral Toxicities

Mucositis and xerostomia are two of the most common oral toxicities encountered with systemic chemotherapy, radiation therapy to the head and neck, and hematopoietic stem cell transplantation (HSCT) [3–5]. The term oral mucositis (OM) refers to ulcerative and erythematous lesions resulting from cytotoxic chemotherapy/radiation therapy-induced mucosal injury [6]. OM is an acute regimen-limiting complication of cancer therapy as the lesions are often painful and lead to compromised nutrition, oral hygiene, and risk for local and systemic infections [3]. The exact pathophysiology of mucositis is not known but is believed to be a result of a complex series of biological cellular events in the submucosal epithelium and connective tissue, which precede epithelial damage [4, 7]. The incidence of oral mucositis/stomatitis, irrespective of severity, has been reported to range from 59.4% to 100% in head and neck cancer patients receiving radiation/chemotherapy, between 70% and 86.6% in HSCT patients, and 14.4–81.3% in patients receiving chemotherapy for solid tumors [8].

Xerostomia, which is the subjective sensation of dry mouth, is an acute but persistent oral toxicity of external radiation therapy to the head and neck resulting from reduced secretory capacity of damaged salivary glands [9, 10]. Patients with reduced salivary secretions have an increased risk of oral infections, carious lesions of teeth, oral mucosal discomfort/pain, declined oral functioning and nutritional state, and an overall poorer quality of life [10]. During radiation therapy, xerostomia has been reported to affect 93% of treated individuals with a slight decrease to 85.3% prevalence 2 years postradiation therapy [10]. Chemotherapy-induced xerostomia has been shown to be much less severe and often reversible at the end of the treatment [11].

Prevalence of Mucositis and Xerostomia with Immunotherapy: A Meta-Analysis

A systematic review and meta-analysis of immunotherapy-based clinical trials registered on clinicaltrials.gov reporting prevalence of mucositis and xerostomia was carried out. A systematic search was conducted on February 2, 2019, and data were extracted from all completed trials (Phases 1, 2, and 3) with reported adverse events data. Oral toxicity data, irrespective of toxicity grading, primary tumor, or drug dosage, were extracted from study arms with administration of a single immunotherapy drug. All adverse events from combination therapies, including chemotherapy, radiation, stem cell transplantation, and other immunotherapy agents, were excluded. The proportion of each oral morbidity along with the 95% confidence

intervals (CIs) was plotted using forest plots. A fixed continuity correction of 0.5 was added to studies where the proportions were 0% or 100% [12]. The studies' heterogeneity was assessed using the I^2 statistic which measures the percentage of total variation that is due to heterogeneity rather than chance. If a statistically significant percentage of the total variation was found to be due to heterogeneity, then the combined proportion from the studies in the meta-analysis was estimated using a random effects model in which each study was weighted equally. Detailed methodology and interpretation are published elsewhere [13, 14].

A total of 20 clinical trials (Table 17.1) were identified, which reported immunotherapy-associated oral toxicities including mucositis, stomatitis, xerostomia, and rare oral adverse events such as dysgeusia, dysphagia, decreased appetite, oropharyngeal or oral pain/discomfort, cheilitis, osteomyelitis, oral candidiasis, and other oral infections. Nine studies reported OM with a weighted prevalence of 5% (95% confidence interval: 2–8%; Fig. 17.1). A higher OM prevalence (10%) was noted with CTLA-4 compared to PD-1 (6%) and PD-L1 (4%) inhibitors. Twelve studies reported stomatitis as a separate entity and yielded a weighted prevalence of 3% (95% confidence interval: 2–4%; Fig. 17.2). PD-1 inhibitors showed a higher prevalence of stomatitis (6%) compared to CTLA-4 (2%) and PD-L1 (3%) inhibitors. Similarly, a higher proportion of individuals taking PD-1 inhibitors had xerostomia (11%) compared to CTLA-4 (2%) and PD-L1 (5%) inhibitors. The overall weighted pooled prevalence of xerostomia was estimated to be 5% (95% confidence interval: 3–7%) based on 10 clinical trials (Fig. 17.3).

Other Immunotherapy-Related Oral Adverse Events: Case Reports

Owosho et al. reported on a 52-year-old male with a history of stage IV, metastatic melanoma of unknown primary with metastases to the left iliac region and pancreatic head, who developed osteonecrosis of the right mandible following administration of ipilimumab at 3 mg/kg intravenous (230 mg) every 3 weeks for a total of 4 doses [15]. The patient presented with a gingival swelling on the lingual aspect of the right mandibular molars following administration of the second dose of ipilimumab. On clinical examination, the patient had localized bleeding on probing, mild discomfort, and a small amount of purulent discharge from the gingival sulcus.

Cases with lichenoid reaction involving the oral mucosa, bullous pemphigoid, and mucous membrane pemphigoid cases have been reported. Naidoo et al. reported 2 cases of patients who developed bullous pemphigoid blisters in the oral cavity [16]. An 80-year-old male previously treated with ipilimumab (3 mg/kg) for metastatic melanoma was treated with second-line nivolumab every 2 weeks. After several dermal lesions, he developed erosions and vesicles on the buccal mucosa after 26 doses of nivolumab. Bullous pemphigoid ELISA was positive, and the oral lesions were treated with oral tacrolimus ointment and dexamethasone swish/spit, while nivolumab was withheld. Another 78-year-old female with metastatic melanoma, treated with first-line ipilimumab (3 mg/kg) with no previous adverse events, developed bullous pemphigoid on her buccal mucosa after a year of durvalumab as second-line therapy. Resolution was achieved with topical steroids alone.

Jour et al. reported another case of a 63-year-old male with a history of recurrent metastatic squamous cell carcinoma of the tongue who was initiated on treatment with nivolumab after progression on the previous radiation, chemotherapy, and erlotinib (150 mg) treatment [17]. The patient developed mucosal blisters that supported a finding of bullous pemphigoid on clinical, histologic, direct immunofluorescence, and immunohistochemistry. Initial management included withholding nivolumab treatment and initiation of topical corticosteroid cream with moderate resolution. Patient developed new oral erosions once he was rechallenged with nivolumab after 21 days. Complete resolution of lesions was achieved with oral prednisolone (10 mg) and cessation of nivolumab.

Table 17.1 Summary of included trials

NCT number	Immunotherapy	Title	Malignancy	Trial phase
Anti-PD-1 checkpoint inhibitors				
NCT02007070	Pembrolizumab	Study of pembrolizumab (MK-3475) in participants with advanced non-small cell lung cancer (MK-3475-025/ KEYNOTE-025)	Non-small cell lung cancer	Phase 1
NCT02179918	Pembrolizumab	A study of 4-1BB agonist PF-05082566 plus PD-1 inhibitor MK-3475 in patients with solid tumors (B1641003/ KEYNOTE-0036)	Advanced solid tumors	Phase 1
NCT02180061	Pembrolizumab	Study of pembrolizumab (MK-3475) in participants with advanced melanoma (MK-3475-041/KEYNOTE-041)	Melanoma	Phase 1
NCT00441337	Nivolumab	A study of MDX-1106 in patients with selected refractory or relapsed malignancies	Non-small-cell lung, malignant melanoma, colorectal, renal, prostate cancer	Phase 1
Anti-CTLA-4 checkpoint inhibitors				
NCT00920907	Ipilimumab	Comparison of Ipilimumab manufactured by two different processes in participants with advanced melanoma	Advanced melanoma	Phase 1
NCT01820754	Ipilimumab	Evaluation of circulating T cells and tumor infiltrating lymphocytes (TILs) during/after Presurgery chemotherapy in non-small cell lung cancer (NSCLC)	Non-small cell lung cancer	Phase 2
NCT01990859	Ipilimumab	Phase 2 study of ipilimumab in Japanese advanced melanoma patients	Melanoma	Phase 2
NCT00162123	Ipilimumab	A companion study for patients enrolled in prior/parent Ipilimumab studies	Melanoma	Phase 2
NCT00094653	Ipilimumab	MDX-010 antibody, MDX-1379 melanoma vaccine, or MDX-010/ MDX-1379 combination treatment for patients with unresectable or metastatic melanoma	Unresectable or metastatic melanoma	Phase 3
NCT01585987	Ipilimumab	An efficacy study in gastric and gastroesophageal junction cancer comparing Ipilimumab versus standard of care immediately following first-line chemotherapy	Locally advanced (unresectable) or metastatic adenocarcinoma of the gastric and gastro-esophageal junction	Phase 2
NCT00623766	Ipilimumab	Evaluation of tumor response to ipilimumab in the treatment of melanoma with brain metastases	Melanoma	Phase 2
NCT00796991	Ipilimumab	Drug–drug interaction—3 arm—carboplatin/paclitaxel, dacarbazine	Advanced melanoma	Phase 1
NCT01057810	Ipilimumab	Phase 3 study of immunotherapy to treat advanced prostate cancer	Prostate cancer	Phase 3
NCT00323882	Ipilimumab	Study of MDX-010 in patients with metastatic hormone-refractory prostate cancer	Metastatic prostate cancer	Phase 1lphase 2

(continued)

Table 17.1 (continued)

NCT number	Immunotherapy	Title	Malignancy	Trial phase
Anti-PD-L1 checkpoint inhibitors				
NCT02008227	Atezolizumab	A study of atezolizumab compared with docetaxel in participants with locally advanced or metastatic non-small cell lung cancer who have failed platinum-containing therapy	Non-squamous non-small cell lung cancer	Phase 3
NCT02031458	Atezolizumab	A study of atezolizumab in participants with programmed death-ligand 1 (PD-L1) positive locally advanced or metastatic non-small cell lung cancer	Non-small cell lung cancer	Phase 2
NCT02302807	Atezolizumab	A study of atezolizumab compared with chemotherapy in participants with locally advanced or metastatic urothelial bladder cancer [IMvigor211]	Bladder cancer	Phase 3
NCT01846416	Atezolizumab	A study of atezolizumab in participants with programmed death-ligand 1 (PD-L1) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) [FIR]	Non-small cell lung cancer	Phase 2
NCT01903993	Atezolizumab	A randomized phase 2 study of atezolizumab (an engineered anti-PD-L1 antibody) compared with docetaxel in participants with locally advanced or metastatic non-small cell lung cancer who have failed platinum therapy–"POPLAR"	Non-small cell lung cancer	Phase 2
NCT02558894	Durvalumab	Phase II study of MEDI4736 monotherapy or in combinations with tremelimumab in metastatic pancreatic ductal carcinoma	Metastatic pancreatic ductal adenocarcinoma	Phase 2

Zumelzu et al. reported a case of mild mucous membrane pemphigoid in an 83-year-old patient after administration of pembrolizumab therapy for metastatic melanoma [18]. The patient developed erosions and blisters 6 months after discontinuation of the pembrolizumab therapy that was administered for 10 months. Complete remission of the oral lesions was achieved with minimal doxycycline therapy.

Schaberg et al. reported a case of a 69-year-old male with history of metastatic urothelial carcinoma refractory to multiple lines of chemotherapy who was started on PD-L1 inhibitor therapy [19]. After 11 weeks of treatment, the patient developed a burning sensation on the tongue, gingiva, and buccal mucosa. Intraoral examination showed symmetric reticulated thin white plaques consistent with Wickham's striae, histopathologically confirmed as lichenoid mucositis with pseudoepitheliomatous hyperplasia and reactive spongiosis. No other contributing factors to a lichenoid reaction could be found. Symptomatic improvement was achieved with a dexamethasone elixir swish and spit.

Immunotherapy and Hearing Loss

Hearing loss is a well-known consequence of cancer treatment. Both radiation therapy and certain chemotherapeutic agents have demonstrated the ability to injure a patient's native inner ear function. Radiation, in the setting of treatment of head and neck malignancies, is known to damage both the inner ear and cause middle ear dysfunction—resulting in both sensorineural and conductive hearing loss, respectively. Traditional chemotherapy modalities, such as carboplatin

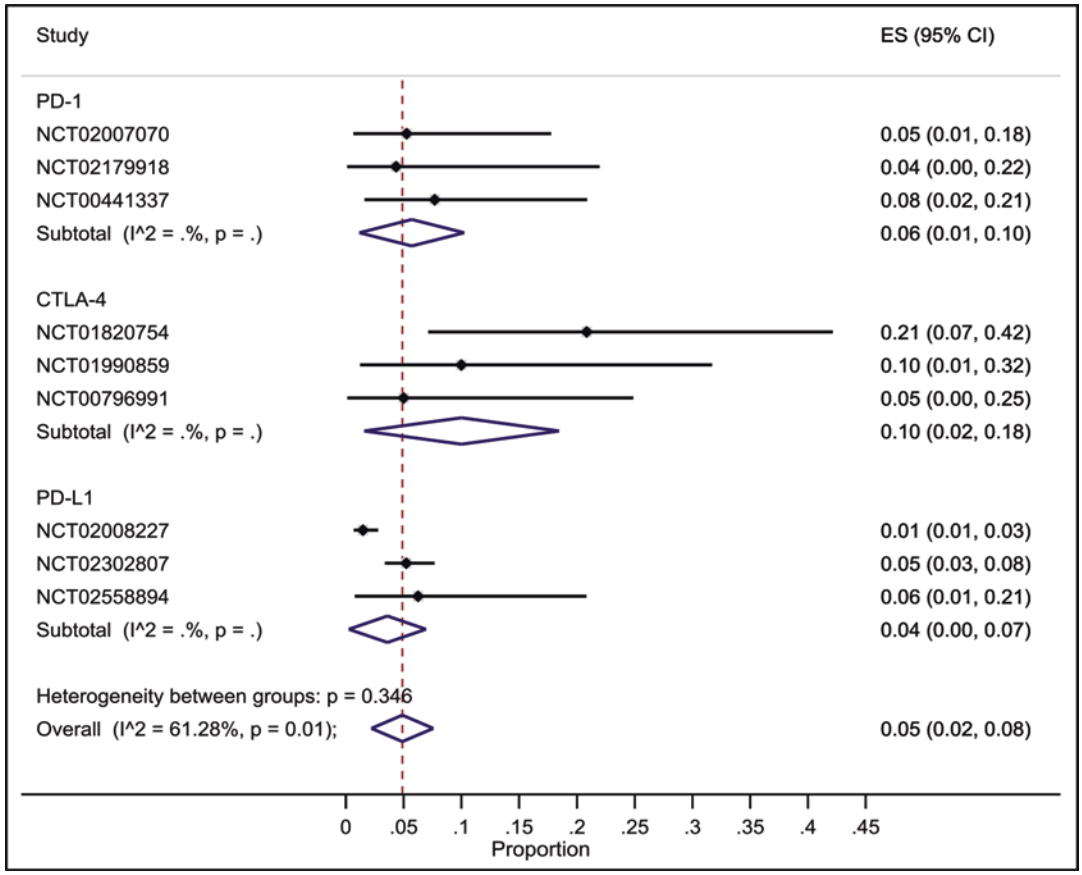

Fig. 17.1 Forrest plot for meta-analysis of prevalence of oral mucositis

and cisplatin, also have well-known and well-studied ototoxicity profiles.

Adoptive Cell Immunotherapy

Autoimmune-mediated complications leading to audiovestibular dysfunction has been previously described in adoptive cell immunotherapy (ACI). In 2009, Johnson and colleagues reported on a series of 36 patients undergoing adoptive cell immunotherapy for metastatic melanoma [20]. Highly reactive T-cell receptors (TCRs) with high anti-melanoma/melanocyte activity were identified via screening of human or murine lymphocytes. Genes encoding these TCRs were then implanted into retroviral vectors and amplified ex vivo prior to transfusion into recipients. All patients underwent baseline audiogram evaluation. While tumor regression was seen in 30% and 19% of human and mouse TCR, respectively, audiometric evaluations demonstrated hearing loss in 10 of 20 patients. This began approximately 1 week following initiation of therapy and was postulated to be related to an inflammatory cytokine surge detected in patients beginning 3–6 days following transfusion. Of those with hearing loss, 70% underwent intratympanic steroid injection with all patients experiencing improvement. Overall, 25% of patients undergoing therapy developed dizziness related to inner ear dysfunction.

Similarly, Seaman and colleagues reported on their experience with 32 patients undergoing ACI with TCRs targeting either gp-100 or MART-1 for metastatic melanoma [21]. All patients underwent pre-intervention audiogram testing for baseline hearing levels. Seventeen of 32 patients

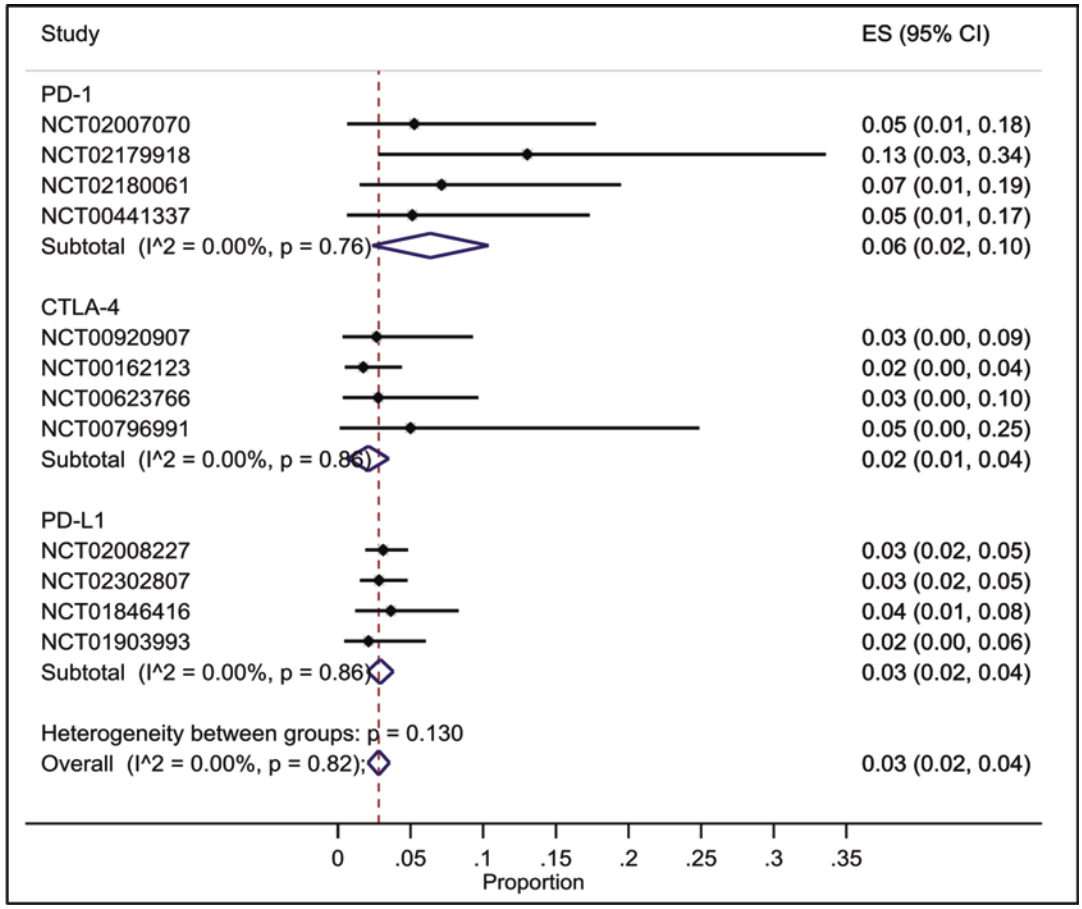

Fig. 17.2 Forrest plot for meta-analysis of prevalence of stomatitis

(53%) showed hearing loss, manifesting an average of 9.5 days following initiation of therapy. Three patients reported dizziness.

In both of the above studies, the proposed mechanism of audiovestibular dysfunction involved aberrant cross reactivity of TCRs to the melanocytes within the stria vascularis of the inner ear. The stria vascularis, a thin, vascularized tissue bed, forms the inner sidewall of the cochlea. It creates and maintains endocochlear ion gradients to provide the electrochemical basis of hearing. Melanocytes, or intermediate cells as they are known in the stria vascularis, are essential contributors to the maintenance of this gradient [22]. Intermediate cells maintain the potassium ion rich milieu of the endolymph within the scala media of the cochlea. It is the electrochemical gradient between the potassium rich endolymph and the potassium poor perilymph within the cochlea that creates the endocochlear potential. This potential is produced by the hair cells in response to the mechanical displacement of the basilar membrane [23]. Absence or dysfunction of stria melanocytes results in sensorineural hearing loss (SNHL). The most common form of non-syndromic, congenital sensorineural hearing loss involves genetic mutations coding for connexin-26, a gap junction protein essential to intermediate cells' ability to recirculate potassium ions [24]. Multiple syndromic causes of congenital hearing loss affect the function of intermediate cells including Tietz Albinism-Deafness Syndrome [25], Craniofacial-deafness-hand syndrome [26, 27], and Waardenburg syndrome [28, 29]. The essential role played by the intermediate cells in hearing supports the hypothesis that their dysfunction or

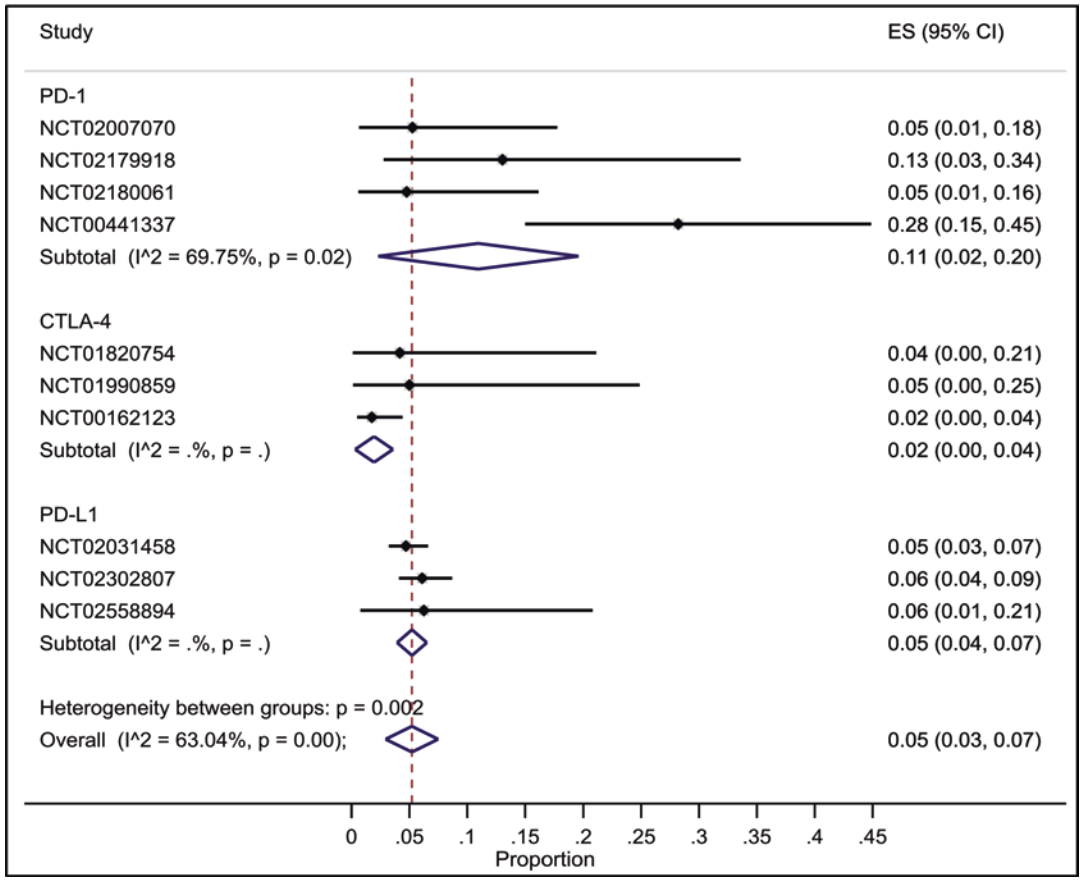

Fig. 17.3 Forrest plot for meta-analysis of prevalence of xerostomia

destruction is the underlying cause of hearing loss following ACI.

Vogt-Koyanagi-Harada Syndrome

Melanocyte destruction within the inner ear has an autoimmune analog in Vogt-Koyanagi-Harada (VKH) syndrome. VHK is a constellation of symptoms including bilateral posterior uveitis, vitiligo, central nervous system deficits, and sensorineural hearing loss. This is thought to be T cell-mediated autoimmune destruction of melanocytes [30]. This condition is more frequently seen in patients with darker skin tone, women, and those aged 20–50 years old. Aggressive treatment with corticosteroids or immunomodulators is the preferred treatment for this disease. Those with uveitis may require intravitreous steroid injection. In the above cases of hearing loss related to adoptive immune therapy, multiple patients also experienced rash, gastrointestinal upset, and changes in visual acuity.

Case Reports

Immune-related adverse events have been reported with the use of ICIs. However, hearing loss appears to be rare and limited to sporadic case reports and to individual patients within larger cohorts of patients with reported irAEs. No clinical trials have evaluated the impact of ICIs on hearing. Only one animal study looked at the impact of anti-PD-1 therapy on a murine animal model [31]. In this study, hearing thresholds were largely unaffected in the group that received immunotherapy alone. When the anti-PD-1 agent

was added to cisplatin, it resulted in minor worsening of hearing compared to the group receiving cisplatin alone.

Case #1

Zibelman et al. reported on an 82-year-old man with metastatic mucosal melanoma who underwent initial treatment with ipilimumab (3 mg/kg), a CTLA-4 inhibitor, before switching to pembrolizumab, a PD-1 inhibitor (2 mg/kg every 3 weeks), due to disease progression [32]. Following his second dose of pembrolizumab, the patient noted bilateral hearing loss.

Audiometry confirmed a mild to moderately–severe symmetric sensorineural hearing loss (SNHL) with word recognition scores (WRSs) of 48% and 44% in the right and left ears, respectively. The patient had not experienced any episodes of meningitis, taken ototoxic chemotherapy agents, or experienced any other obvious etiology for his hearing loss. He underwent intratympanic dexamethasone injections (10 mg/mL), 6 injections on the right and 4 on the left and subjectively noted complete recovery of his hearing. Postinjection audiogram showed recovery of low-frequency hearing thresholds but still with moderate-to-severe SNHL in the higher frequencies. His word recognition scores improved to 88% and 84%. He continued his pembrolizumab therapy and had no further audiovestibular symptoms.

Case #2

Diamantopoulos et al. reported a case of an 81-year-old woman with stage IIIb (T2aN1bM0) cutaneous melanoma who presented 8 months after her initial diagnosis with metastatic lesions to the skin of her left breast and axillary lymph nodes [33]. Imaging showed an additional metastatic pulmonary lesion. She was started on encorafenib 300 mg daily, and binimetinib at 45 mg twice daily as part of a phase III clinical trial.

Six months after initiation of therapy, the patient experienced a 10-day course of headaches, light sensitivity, and worsening visual acuity. She underwent a detailed ophthalmological exam, which revealed bilateral panuveitis. In addition to her ocular symptoms, the patient also experienced bilateral sudden hearing loss with elevation of pure tone thresholds to 60 dB in the right and 40 dB in the left consistent with an asymmetric bilateral SNHL. The patient did not have a pre-intervention audiogram for comparison. Other causes of sudden onset SNHL, including infectious and autoimmune etiologies, were excluded based on testing.

Encorafenib and binimetinib were both immediately discontinued, and the patient was started on 64 mg of methylprednisolone daily for 7 days along with dexamethasone eye drops. Her vision gradually improved; however, no data are given regarding resolution of her hearing loss.

Case #3

Tampio et al. reported a case of a 67-year-old man with a history of sarcoidosis with widely metastatic melanoma [34]. Testing revealed BRAF and PDL-1 markers and it was decided to proceed with nivolumab monotherapy with a plan for 12 cycles of 240 mg administration. Approximately 2 months after starting therapy, the patient presented to the emergency department for bilateral light sensitivity. He was seen the following week in the Ophthalmology Clinic and was noted to have findings consistent with intraocular inflammation. Concern for an autoimmune reaction to his current immunotherapy regimen led to a cessation of ICI therapy and initiation of corticosteroid eye drops.

Approximately 2 weeks after the above events, the patient noticed bilateral ear fullness, subjective hearing loss, and brief episodes of vertigo with head movement. Audiogram showed a bilateral mild to severe sloping, high-frequency SNHL with word recognition scores of 100% bilaterally. Because of the bilateral sudden SNHL and bilateral panuveitis, this presentation was felt to be part of broader, ICI agent-induced autoimmune reaction, and a 60 mg daily prednisone burst was initiated and tapered over 5 weeks. The patient had received 4 cycles of nivolumab, and repeat MRI and PET/CT at this time showed resolution of neoplastic disease. At 6 weeks follow-up, the patient noted completely resolved ocular symptoms and improved hearing. Repeat audio-

gram at the 4 months follow-up showed normalization of the speech reception thresholds.

Immunotherapy and Ocular Toxicity

The majority of described ocular irAEs are mild, low-grade, non-sight threatening, such as blurred vision, conjunctivitis, and ocular surface disease (dry eye). Serious and sight threating events such as corneal perforation, optic neuropathy, and retinal vascular occlusion can occur but are infrequent. Knowledge and awareness of ocular side effects is imperative to guide the proper treatment plan. A multidisciplinary approach between the medical and ocular oncologist is essential in the identification and management of these events [1, 35, 36].

Fu et al. conducted a study of ocular toxicities associated with all FDA approved oncologic immune therapies through March 2015. The review included 32 independent reports that met the inclusion criteria. The severity of ocular events was graded according to common terminology criteria for adverse events (CTCAE) grade (Version 4.0). The study concluded that the most commonly reported events were conjunctivitis and blurred vision; reported in nine (19.6%) and ten (21.7%) agents of the total reviewed. Imatinib was found to have the highest incidence of grade 3 or higher toxicity. Overall imatinib and crizotinib had the highest incidence of any ocular events. Acute serious and sight threating ocular events were rare, and accounted for <1% including retinal vascular occlusion, retinal pigment epithelial detachment, corneal ulceration and perforation, and blindness. Devastating vision-threatening ocular irAEs were reported with only five classes of agents (10.9%): EGFR inhibitors (erlotinib and gefitinib), MEK inhibitors (trametinib), V600E mutated BRAF inhibitors (vemurafenib), anti-CTLA4 inhibitors (ipilimumab), and targeted antibodies [37–43].

Abdel-Rahman et al. conducted a systematic review to assess the incidence of ocular irAEs. Eleven prospective trials were analyzed included one trial for ipilimumab and tremelimumab, three for nivolumab, five for pembrolizumab, and one comparing pembrolizumab to ipilimumab. The incidence of uveitis ranged from 0.3% to 6%, whereas the incidence of dry eyes ranged from 1.2% to 24.2%. Among the four randomized studies comparing immune checkpoint inhibitors agents versus nonimmune checkpoint inhibitors, the pooled analysis for odds ratio of all grade is 3.40 [95% CI: 1.32–8.71; $P = 0.01$]. This suggests that these toxicities are more common with immune checkpoint inhibitors compared to control [44–46].

Antoun et al. conducted a systematic review to evaluate ocular and orbital irAEs of checkpoint inhibitors. They suggested that irAEs may occur as early as 1 week after initial dose with the median occurrence of 2 months after initiation of therapy. Common ocular events included peripheral ulcerative keratitis (PUK), uveitis, and Vogt-Koyanagi-Harada (VKH) syndrome. Peripheral ulcerative keratitis, severe peripheral infiltration, and ulceration were reported with ipilimumab. In addition uveitis has been reported with nivolumab and bilateral uveitis and papillitis with pembrolizumab. Vogt-Koyanagi-Harada syndrome has been reported in one case with combination of ipilimumab and anti-PD1 inhibitors [47, 48].

Bitton et al. reviewed 745 patients from a single center and national registry between June 2014 and March 2018, identifying patients with moderate-to-severe ocular toxicity following anti-PD-L1 administration. Dry eye was the first and most frequently reported event. In total, three patients had moderate-to-severe ocular events, with an overall prevalence of 0.4% and an incidence of 0.7 per 1000 patient-months of treatment. In addition to the cases reported through the national registry, five presented with intraocular inflammation, two with ocular surface disease, and one with orbital myopathy; five (62.5%) developed exophthalmos [49].

Fang et al. looked at the association between immune checkpoint inhibitors and ophthalmic adverse effects using data from U.S. FDA's Adverse Events Reporting System (FAERS) database from 2003 to 2018. The study identified 113 ocular events including dry eye, uveitis, ocular myasthenia, and "eye inflammation." Nivolumab showed the highest number of ocular

events. It also had the highest association with ocular myasthenia followed by pembrolizumab. Atezolizumab had the highest association with "eye inflammation," while ipilimumab had the highest association with uveitis. Nivolumab was also associated with these two toxicities. No cases were reported for other checkpoint inhibitors including avelumab, cemiplimab, and durvalumab [36, 40, 50].

Management

Many mild ocular toxicities are managed with topical corticosteroids and/or lubrication. Severe side effects may require systemic corticosteroids and/or termination of the drug. The decision regarding continuation or withdrawal of treatment should be evaluated on a case-by-case basis, depending on the severity of toxicity and the response to treatment. Detailed recommendations with clinical practice guidelines based on evidence from a rigorous systematic review, published medical literature and expert consensus for management of ocular (irAEs) have been recently published. In general immunotherapy should be continued with close monitoring for grade 1 toxicities, with few exceptions. Therapy may be held or reduced for grade 2 toxicities. For grade 3 toxicities or above, treatment should be held and high-dose corticosteroids considered. Rechallenge can be considered with extreme precaution after a grade 3 toxicity. Permanent discontinuation should be considered in all grade 4 cases [51–54].

Summary

Immune-based cancer therapy has revolutionized the treatment of various malignancies. Clinicians should be familiar with likely adverse events associated with immune therapies. Ocular toxicities are among the most common adverse events resulting from the use of these agents. The majority are mild, and not sight threating; however, serious events can occur and lead to blindness. Acute visual changes always necessitate an immediate ophthalmologic assessment.

The overall prevalence of commonly encountered oral toxicities, including oral mucositis, stomatitis, and xerostomia, was found to be lower with checkpoint inhibitors compared to conventional chemotherapy and head and neck radiation therapy. However, the widespread use of immunotherapy reveals new oral mucosal barrier adverse events, including bullous pemphigoid, mucous membrane pemphigoid, and lichenoid mucositis. Auditory and vestibular dysfunctions have also been reported in patients treated with immunotherapy directed toward melanocytes.

A multidisciplinary approach with good communication is crucial for prompt referral and management of such complications. At present, there is a lack of standardized surveillance guidelines for all patients potentially at risk. Establishing an ophthalmic, otolaryngology and audiology, and oral surveillance protocol with baseline screening is ideal. The specific frequency and exam parameters may be dependent on the agent and its toxicity profile.

Further research is needed to establish prevalence/incidence of immunotherapy-induced oral, ocular, and audiovestibular toxicities as well as their pathophysiology and management.

References

1. Centerwatch Database of FDA Approved Drugs. [Available from: http://www.centerwatch.com.
2. Fraunfelder FT. Clinical ocualr toxicology. Saunders Elvevier; 2008.
3. Lalla RV, Peterson DE. Oral mucositis. Dent Clin N Am. 2005;49(1):167–84.. ix
4. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004;100(9 Suppl):1995–2025.
5. Treister N, Sonis S. Mucositis: biology and management. Curr Opin Otolaryngol Head Neck Surg. 2007;15(2):123–9.
6. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. Dent Clin N Am. 2008;52(1):61–77.. viii

7. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer. 2004;4(4):277–84.
8. Berger K, Schopohl D, Bollig A, Strobach D, Rieger C, Rublee D, et al. Burden of oral mucositis: a systematic review and implications for future research. Oncol Res Treat. 2018;41(6):399–405.
9. Pinna R, Campus G, Cumbo E, Mura I, Milia E. Xerostomia induced by radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage. Ther Clin Risk Manag. 2015;11:171–88.
10. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer. 2010;18(8):1039–60.
11. Jensen SB, Pedersen AM, Reibel J, Nauntofte B. Xerostomia and hypofunction of the salivary glands in cancer therapy. Support Care Cancer. 2003;11(4):207–25.
12. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014;72(1):39.
13. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001;54(10):1046–55.
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
15. Owosho AA, Scordo M, Yom SK, Randazzo J, Chapman PB, Huryn JM, et al. Osteonecrosis of the jaw a new complication related to Ipilimumab. Oral Oncol. 2015;51(12):e100–1.
16. Naidoo J, Schindler K, Querfeld C, Busam K, Cunningham J, Page DB, et al. Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1. Cancer Immunol Res. 2016;4(5):383–9.
17. Jour G, Glitza IC, Ellis RM, Torres-Cabala CA, Tetzlaff MT, Li JY, et al. Autoimmune dermatologic toxicities from immune checkpoint blockade with anti-PD-1 antibody therapy: a report on bullous skin eruptions. J Cutan Pathol. 2016;43(8):688–96.
18. Zumelzu C, Alexandre M, Le Roux C, Weber P, Guyot A, Levy A, et al. Mucous membrane pemphigoid, bullous pemphigoid, and anti-programmed death-1/programmed death-ligand 1: a case report of an elderly woman with mucous membrane pemphigoid developing after pembrolizumab therapy for metastatic melanoma and review of the literature. Front Med (Lausanne). 2018;5:268.
19. Schaberg KB, Novoa RA, Wakelee HA, Kim J, Cheung C, Srinivas S, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. J Cutan Pathol. 2016;43(4):339–46.
20. Johnson LA, Morgan RA, Dudley ME, Cassard L, Yang JC, Hughes MS, et al. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood. 2009;114(3):535–46.
21. Seaman BJ, Guardiani EA, Brewer CC, Zalewski CK, King KA, Rudy S, et al. Audiovestibular dysfunction associated with adoptive cell immunotherapy for melanoma. Otolaryngol Head Neck Surg. 2012;147(4):744–9.
22. Steel KP, Barkway C. Another role for melanocytes: their importance for normal stria vascularis development in the mammalian inner ear. Development. 1989;107(3):453–63.
23. Kim HJ, Gratton MA, Lee JH, Perez Flores MC, Wang W, Doyle KJ, et al. Precise toxigenic ablation of intermediate cells abolishes the "battery" of the cochlear duct. J Neurosci. 2013;33(36):14601–6.
24. Wingard JC, Zhao HB. Cellular and deafness mechanisms underlying connexin mutation-induced hearing loss – a common hereditary deafness. Front Cell Neurosci. 2015;9:202.
25. Izumi K, Kohta T, Kimura Y, Ishida S, Takahashi T, Ishiko A, et al. Tietz syndrome: unique phenotype specific to mutations of MITF nuclear localization signal. Clin Genet. 2008;74(1):93–5.
26. Asher JH Jr, Sommer A, Morell R, Friedman TB. Missense mutation in the paired domain of PAX3 causes craniofacial-deafness-hand syndrome. Hum Mutat. 1996;7(1):30–5.
27. Drozniewska M, Haus O. PAX3 gene deletion detected by microarray analysis in a girl with hearing loss. Mol Cytogenet. 2014;7:30.
28. Pingault V, Ente D, Dastot-Le Moal F, Goossens M, Marlin S, Bondurand N. Review and update of mutations causing Waardenburg syndrome. Hum Mutat. 2010;31(4):391–406.
29. Chaoui A, Watanabe Y, Touraine R, Baral V, Goossens M, Pingault V, et al. Identification and functional analysis of SOX10 missense mutations in different subtypes of Waardenburg syndrome. Hum Mutat. 2011;32(12):1436–49.
30. Greco A, Fusconi M, Gallo A, Turchetta R, Marinelli C, Macri GF, et al. Vogt-Koyanagi-Harada syndrome. Autoimmun Rev. 2013;12(11):1033–8.
31. Spielbauer K, Cunningham L, Schmitt N. PD-1 inhibition minimally affects cisplatin-induced toxicities in a murine model. Otolaryngol Head Neck Surg. 2018;159(2):343–6.
32. Zibelman M, Pollak N, Olszanski AJ. Autoimmune inner ear disease in a melanoma patient treated with pembrolizumab. J Immunother Cancer. 2016;4:8.
33. Diamantopoulos PT, Stoungioti S, Anastasopoulou A, Papaxoinis G, Gogas H. Incomplete Vogt-Koyanagi-Harada disease following treatment with encorafenib and binimetinib for metastatic melanoma. Melanoma Res. 2018;28(6):648–51.
34. Tampio A DS, Sivapiragasam A, Nicholas B. Bilateral sensorineural hearing loss and panuveitis in a man with stage IV malignant melanoma after nivolumab immunotherapy. Poster presentation presented at the: Combined Otolaryngology Spring Meetings 2019; May 3, 2019; Austin, TX. https://www.

researchposterscom/display_postersaspx?code=cosm2019.
35. Basti S. Ocular toxicities of epidermal growth factor receptor inhibitors and their management. Cancer Nurs. 2007;30(4 Suppl 1):S10–6.
36. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. Retina (Philadelphia, PA). 2018;38(6):1063–78.
37. Fu C, Gombos DS, Lee J, George GC, Hess K, Whyte A, et al. Ocular toxicities associated with targeted anticancer agents: an analysis of clinical data with management suggestions. Oncotarget. 2017;8(35):58709–27.
38. National Cancer Institute (U.S.) Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE). 2009.
39. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. 2008;26(4):626–32.
40. Draganova D, Kerger J, Caspers L, Willermain F. Severe bilateral panuveitis during melanoma treatment by Dabrafenib and Trametinib. J Ophthal Inflamm Infect. 2015;5:17.
41. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006;6(10):803–12.
42. Perez-Soler R, Chachoua A, Hammond LA, Rowinsky EK, Huberman M, Karp D, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. J Clin Oncol. 2004;22(16):3238–47.
43. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353(2):123–32.
44. Abdel-Rahman O, Oweira H, Petrausch U, Helbling D, Schmidt J, Mannhart M, et al. Immune-related ocular toxicities in solid tumor patients treated with immune checkpoint inhibitors: a systematic review. Expert Rev Anticancer Ther. 2017;17(4):387–94.
45. Robert CSJ, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521–32.
46. Eltobgy M, Oweira H, Petrausch U, Helbling D, Schmidt J, Mehrabi A, et al. Immune-related neurological toxicities among solid tumor patients treated with immune checkpoint inhibitors: a systematic review. Expert Rev Neurother. 2017;17(7):725–36.
47. Antoun J, Titah C, Cochereau I. Ocular and orbital side-effects of checkpoint inhibitors: a review article. Curr Opin Oncol. 2016;28(4):288–94.
48. Papavasileiou E, Prasad S, Freitag SK, Sobrin L, Lobo AM. Ipilimumab-induced ocular and orbital inflammation – a case series and review of the literature. Ocul Immunol Inflamm. 2016;24(2):140–6.
49. Bitton K. Prevalence and clinical patterns of ocular complications associated with anti-PD-1/PD-L1 anticancer immunotherapy. Am J Ophthalmol. 2019.
50. Fang T, Maberley DA, Etminan M. Ocular adverse events with immune checkpoint inhibitors. J Curr Ophthalmol. 2019;31(3):319–22.
51. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36(17):1714–68.
52. Brahmer JR, Lacchetti C, Thompson JA. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline summary. J Oncol Pract. 2018;14(4):247–9.
53. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with Ipilimumab at memorial Sloan Kettering Cancer center. J Clin Oncol. 2015;33(28):3193–8.
54. Liu Y, Liu ZG. [Role of epidermal growth factor and its receptor family in ocular surface wound healing]. [Zhonghua yan ke za zhi]. Chinese J Ophthalmol. 2007;43(10):953–6.