OPEN ACCESS

Saudi Journal of Oral and Dental Research

Abbreviated Key Title: Saudi J Oral Dent Res
ISSN 2518-1300 (Print) | ISSN 2518-1297 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Oral Medicine**

Oral Lesions Associated with Immune Checkpoint Inhibitors in Cancer Therapy: An Emerging Entity Oral Healthcare Professionals Should Comprehend

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DOI: 10.36348/sjodr.2023.v08i10.001 | **Received:** 30.08.2023 | **Accepted:** 03.10.2023 | **Published:** 06.10.2023

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Abstract

Immune checkpoint inhibitors (ICIs) are a new group of drugs that have been recently used as part of antineoplastic therapy targeting the immune system to activate the anti-tumor effect. However, as a result of this immune activity adverse events usually occur that can affect different body parts known as immune related adverse events (irAEs). In the oral and maxillofacial area, irAEs mimic many immune-mediated conditions, including oral lichen planus, mucous membrane pemphigoid, and Sjögren syndrome, among others. The aim of this review is to summarize the irAEs in oral and maxillofacial areas and to enlighten oral healthcare professionals on how to recognize these events and to be a part of the care team for patients treated with ICIs.

Keywords: Immune checkpoint inhibitors (ICIs), antineoplastic therapy, immune activity, Sjögren syndrome.

INTRODUCTION AND BACKGROUND

Surgery, radiotherapy, and chemotherapy have been for many years the mainstay of cancer treatment. However, even with these treatments, recurrence occurs and cancer mortality rates remain high [1]. Recently, immunotherapy using immune checkpoint inhibitors (ICIs) has been met with great promise in the treatment of cancer [2]. ICIs have shown durable antitumor effects and have dramatically improved survival rates of several cancers in an advanced stage such as melanoma, renal cell carcinoma (RCC), cancer with a high degree of microsatellite instability (MSI-H), small-cell carcinoma (SCLC), non-small-cell carcinoma (NSCLC), head and neck cancer, and merkel cell carcinoma (MCC) [3-9]. ICIs are monoclonal antibodies targeting cytotoxic T lymphocyte antigen (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death 1 ligand (PD-L1). Currently, the Food and Drug Administration (FDA) has approved eight ICIs for treating cancer (Table-1) and numerous ones are still in clinical trials [10, 11]. Most tumors provoke an immune response resulting in tumor infiltration by lymphocytes, mainly T-cells, that have the ability to fight against tumor cells and minimize the tumor's growth [12]. However, the cancer cells can inhibit the activated antitumor T lymphocytes by binding with their immunosuppressive molecules overexpressed on their surface. This binding promotes tumor immune escape. Cytotoxic T lymphocyte antigen (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death 1 ligand (PD-L1) are examples of immunosuppressive molecules (immune checkpoint protein) present in the tumor microenvironment. Thus, by blocking the pathways of PD-1/L1, CTLA-4, or both, antitumor T-cells will be activated and the immune system will shift toward anticancer activity [2, 13, 14]. Despite the clinical benefit of this blockade therapy against many cancers, ICIs play with normal immune homeostasis and cause excess immune stimulation that induces an array of inflammatory side effects termed immune-related adverse events (irAEs) [15]. The overall incidence of irAEs is 46.5% [16]. However, it varies according to the agent used and whether the patient is receiving a monotherapy or a combination of ICIs [17]. Anti-CTLA-4 antibodies cause irAEs in 60% of patients, anti-PD-1 or anti-PD-L1 antibodies cause irAEs in about 30% of patients, and combined CTLA-4 and PD-1 or PD-L1 inhibitors cause irAEs in up to 90% of patients [17]. Any organ can be affected by these toxicities, however, the gastrointestinal tract, endocrine glands, skin, and liver are the most involved sites [17, 18]. IrAEs typically occur within the first three months of treatment but can

arise at any time on therapy or even several months after treatment discontinuation [18]. The toxicities can be acute and reversible, chronic and permanent, or rarely fatal [19, 20]. Fatal irAEs occur in approximately 0.4% of patients receiving anti-PD-1/L1 antibodies as monotherapy and in about 1.2% of patients receiving combination anti-CTLA4 and anti-PD-1 regimens [21]. Several clinical grading systems have been proposed to assess the severity of irAEs; the most widely used is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5-a five-point scale from grade 1 (mild) to grade 5 (death) [22]. Recently, the American Society of Clinical Oncology (ASCO), The National Comprehensive Cancer Network (NCCN), and the Society for Immunotherapy of Cancer (SITC) have released clinical practice guidelines for common irAEs the CTCAE framework by taking into account tolerability, duration, and other factors [23-25]. A widely accepted and easy-to-implement grading system is required to appropriately manage patients with lesions secondary to ICIs therapy. Although various systemic immune-related adverse events (irAEs) have been well-recognized, the effect of ICIs on the oral cavity and salivary glands is still less-studied even with an estimated incidence of about 7% [14, 26, 27]. Oral irAEs can appear as isolated lesions or evolve simultaneously with irAEs affecting any part of the body [28-31]. In this review, we summarize the current knowledge on the oral manifestation of irAEs and emphasize the roles of oral healthcare professionals (OHP) in identifying and managing patients with oral irAEs.

Table 1: Approved immune checkpoint inhibitors by Food and Drug Administration

Immune checkpoint inhibitors	Target	Indications
Ipilimumab	CTLA−4	Melanoma
Nivolumab	PD−1	Melanoma, NSCLC, RCC, HCC, CRC, MSI-H/DMMR, Urothelial cancer, HNSCC, cHL, ESCC, Gastric/GEJ cancer
Pembrolizumab	PD−1	Melanoma, NSCLC, RCC, HCC, CRC, MSI-H/DMMR, Urothelial cancer, HNSCC, cHL, ESCC, SCLC, MCC, CSCC, BCC, TMB-H, TNBC, NMIBC, PMBCL, cervical cancer, Endometrial carcinoma, Gastric/GEJ cancer
Atezolizumab	PD-L1	Melanoma, NSCLC, HCC, Urothelial cancer, SCLC, TNBC
Durvalumab	PD-L1	NSCLC, SCLC
Avelumab	PD-L1	RCC, Urothelial cancer, MCC
Cemiplimab	PD−1	NSCLC, CSCC, BCC
Dostarlimab	PD−1	Endometrial carcinoma

Abbreviations: BCC, basal cell carcinoma; cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; CSCC, cutaneous squamous cell carcinoma; dMMR, mismatch repair deficient; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; MPM, malignant pleural mesothelioma; MSI-H, microsatellite instability-high; NMIBC, non-muscle invasive bladder cancer; NSCLC, non-small-cell lung cancer; PMBCL, primary mediastinal large B cell lymphoma; RCC, renal cell carcinoma; SCLC, small-cell lung cancer; TMB-H, tumor mutational burden-high; TNBC, triple-negative breast cancer.

REVIEW

irAEs in advanced HNSCC patients

Many advanced HNSCC patients are treated with anti-PD-1 antibodies. One study showed that in recurrent HNSCC, the overall survival was significantly increased in patients using nivolumab compared to patients treated with standard chemotherapy [32]. In this study, the incidence of irAE induced by nivolumab was 13.1% and the most common side effects were gastrointestinal disorders followed by skin manifestations including rash, pruritus, and dry skin. Pembrolizumab is another drug that shows promising results in treating refractory HNSCC. The overall incidence of irAE associated with pembrolizumab is 63.7% and it involves gastrointestinal disorders, dermatologic disease, liver dysfunction, general disorders, and endocrine diseases [33]. The frequency of serious irAEs was low in both drugs [32, 33]. Oral mucosal diseases secondary to the use of nivolumab and pembrolizumab are generally less than 5% [32, 34].

The role of oral health professionals

History taking and clinical examination Oral health professionals (OHP) should know how to deal with patients planning to take ICIs as a part of cancer therapy starting from history taking. Before initiating ICIs therapy, it is important to know if the patient has any existing immune-mediated conditions since ICIs may aggravate pre-existing immune-mediated conditions. Therefore, it will be difficult to differentiate a de novo irAE from an exacerbation of an underlying disease process [35]. As ICI therapy may be combined with cytotoxic chemotherapy, radiation, other targeted therapies, or even supportive care measures that can introduce additional risk factors/concomitant side effects (e.g., bone marrow suppression, osteonecrosis of the jaw), it is important to obtain a thorough oncologic history that includes any past or ongoing treatments [18].

A comprehensive medical history, a history of present illness, and a review of the systems (ROS) should

be performed for patients with suspected oral irAEs. History of the present illness should include the onset (sudden or gradual), duration (days, weeks, or months), nature (pain, sensitivity, difficulty eating/swallowing, etc.), and severity of symptoms (visual analog scale (VAS) pain/sensitivity score), sites affected (including extraoral sites), and any other irAEs they have experienced. A review of systems (ROS) is done to exclude extra-oral irAEs [14]. Extra-oral and intra-oral examination of these patients should follow the general principles and each site should be examined methodically [26]. In addition, assessment of the salivary gland function should be included in the head and neck examination. Detailed documentation and description of all findings including location, number, size (with measurements if possible), color, and texture of any mucosal abnormality (including that of saliva) should be reported. Clinical photographs can be used as an additional tool to assess lesion's behavior and as a convenient method of communication with other members of the patient's care team.

Orofacial manifestation of irAEs

Orofacial irAEs recapitulate features of many well-known immune-mediated conditions, such as oral lichen planus (OLP), mucous membrane pemphigoid (MMP)/ bullous pemphigoid (BP), erythema multiforme (EM), Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), and Sjögren syndrome, among others [14, 18, 26, 36].

Cutaneous lichenoid reactions are one of the most common dermatologic irAEs [37]. However, OLP-like lesions in patients taking ICI are less common or may be underdiagnosed [14]. OLP-like reactions may present in the oral mucosa only or may be accompanied by skin involvement [14, 37]. White striation, erythema, and/or ulceration are possible clinical manifestations of OLP-like irAEs affecting oral mucosa.

OLP-like irAEs can occur in any mucosal area, however, the ventral tongue and buccal mucosa are the most common locations [14, 26]. Autoimmune cutaneous vesiculobullous diseases (VBDs) are not uncommon and can be seen in 1% of ICIs patients [38]. BP is the most common type of VBDs affecting patients treated with ICIs [39]. However, oral involvement by BP is very rare. On the other hand, oral MMP can be the only manifestation of irAEs [14], presenting as desquamative gingivitis as well as erosions, ulcers, and/or bullae affecting the buccal mucosa, soft palatal mucosa, and tongue [14, 38, 40, 41]. EM-like reaction associated with ICIs is rare and typically present with concurrent mucosal and cutaneous involvement. The clinical features include typical targetoid skin lesions, multiple intra-oral irregularly shaped erosions, and ulcers with hemorrhagic crusted lips [42-44]. SJS and TEN-like irAEs are severe and life-threatening mucocutaneous reactions. Oral lesions of SJS/TEN are similar to those seen in EM, including multiple, large, irregularly shaped, ulcerations/erosions and hemorrhagic crusting of the lips [36, 45]. Systemic lupus erythematosus, oral scleroderma, acute oral GVHD reactivation, and linear IgA disease are rare examples of mucosal lesions described in patients treated with ICIs [36, 46-48]. In addition, IrAEs can affect the salivary gland resulting in sicca syndrome or Sjögren syndrome (SS)-like symptoms that share the same clinical features as these entities [49, 50]. Xerostomia due to polypharmacy or dehydration is not uncommon for patients treated with ICIs. However, a true IrAEs salivary hypofunction typically occurs as an acute onset of severe oral dryness and hyposalivation, with or without dry eyes [49, 50]. Medication-related osteonecrosis of the jaw (MRONJ) has been described in patients treated with ICIs therapies [51-54] Therefore, OHPs should be aware of this possibility in patients taking ICI therapy. Finally, altered taste "Dysgeusia" has been reported in ICIs patients with an incidence of 4.9% [55].

CONCLUSIONS

ICIs have revolutionized the treatment of many types of advanced cancer. OHPs may encounter patients using ICIs as cancer therapy. Therefore, it is crucial that OHPs of all specialties be aware of therapeutic mechanisms and adverse events (irAEs). The main roles of OHPs for ICIs patients are to recognize all possible orofacial irAEs and provide supportive care, communicate with the oncologist in case of positive irAEs findings, provide optimal dental treatment with emphasis on the maintenance of oral hygiene, and participate in the multidisciplinary oncology team for patients treated with ICIs.

Additional Information

Disclosures

Conflicts of interest: The author has declared that no financial support was received from any organization for the submitted work. Financial relationships: The author has declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: The author has declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements: King Saud University for the help and support.

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