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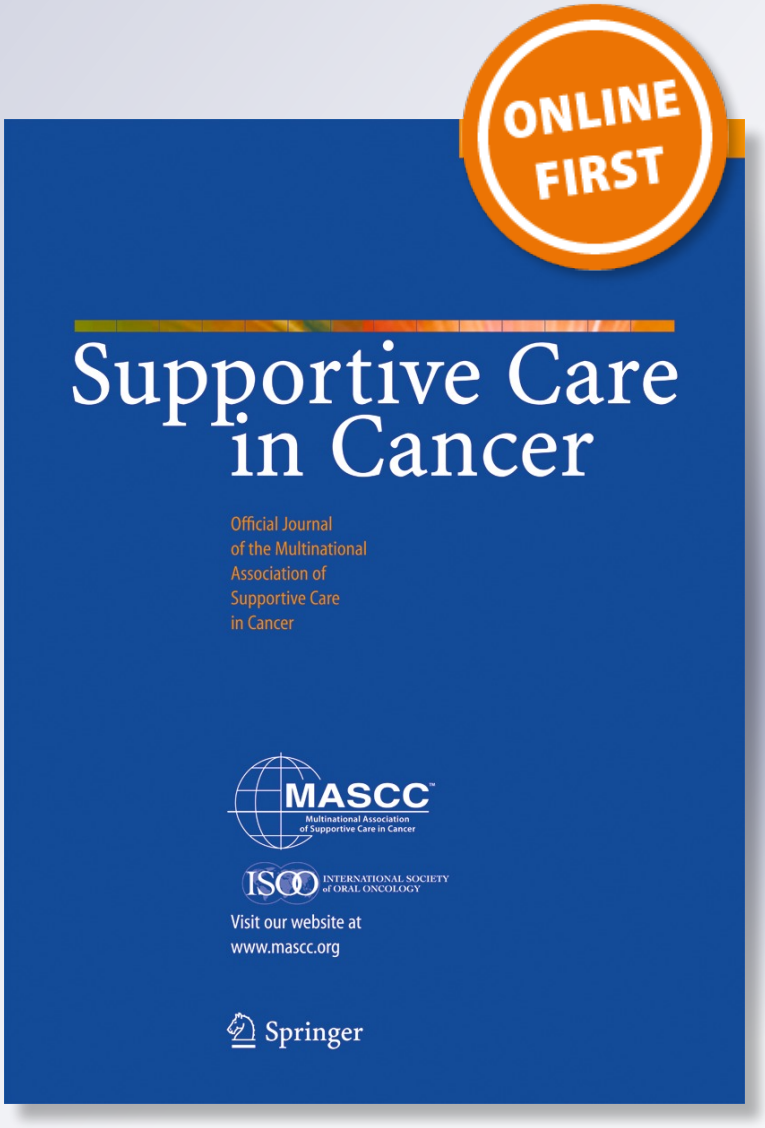

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COMMENTARY

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The overall survival benefit seen with ipilimumab, an anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibody and T cell checkpoint inhibitor, has ushered in a new and exciting era for treatment of metastatic melanoma [1]. Newer antibodies targeting other immune checkpoints like programmed cell death-1 and its ligand (PD-1/PD-L1) have also induced durable tumor regression and stabilization of disease in melanoma, renal cell carcinoma, and non-small cell lung cancer [2]. These and other immune-based therapies are expected to play a significant role in these and other cancers in the future.

Immune-based therapies have a very different spectrum of toxicities compared to cytotoxic agents, and a high level of awareness of potential immune-related adverse events (irAEs) by patients and providers is essential for early recognition and proper and timely management by a multidisciplinary team [3]. Patient education to recognize and manage irAEs is also important to provide safe and effective care [3]. For ipilimumab, irAEs are related to the blockade of CTLA-4, a key negative regulator of T cell-mediated autoimmunity [3]. The most common irAEs are dermatitis, enterocolitis (diarrhea), liver toxicity, endocrinopathies (hypophysitis, thyroiditis), and uveitis [3]. In less than 1 % of patients, other irAEs have been reported, including neurologic events (sensory/motor neuropathy and myasthenia gravis), respiratory tract side effects (alveolitis, sarcoidosis, and atypical pneumonia), and renal toxicity. In the phase III MDX010-20 study, grades 2–4 irAEs resolved by a median of 6.3 weeks [1]. However, delayed onset and chronic irAEs were possible months after treatment, particularly endocrine-related events [3]. Agents targeting PD-1/PD-L1 appear to be better tolerated than ipilimumab, although serious irAEs occur occasionally (notably pneumonitis for anti-PD-1) [4]. Long-term toxicities of these agents have not been well-characterized. In addition, effects on oral health have not been specifically studied either in the acute or chronic setting. Although oral effects of the immune checkpoint inhibitors have not emerged as major acute toxicities in key clinical trials of immune checkpoint inhibitors, there are several reasons to study oral health further in those populations.

Oral effects of immune checkpoint inhibitors have been observed in clinical trials. Grades 1 and 2 dry mouth were reported in 6.5 % of melanoma patients treated with nivolumab and 3 % of those treated with pembrolizumab (MK-3475; anti-PD-1), although this was not further characterized clinically or pathologically [5, 6]. The incidence of oral complications with ipilimumab has not been well defined. Anecdotally, we have observed patients treated with ipilimumab in our clinic who developed a clinical picture resembling Sjogren's syndrome (also in the setting of severe liver, gastrointestinal, and skin irAEs). Potential oral complications may be under-recognized by patients. Oral involvement has been under-recorded by patient reports in other studies of cytotoxic and targeted agents. Potential reasons for this include lack of awareness of the possibility of oral side effects or fear by patients that admitting side effects could lead to withholding of life-saving or life-prolonging immune therapy. Patients might also expect these side effects to improve after therapy and not understand long-term implications of delayed supportive care. Thus, it is important for both

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clinicians and researchers to consider that oral complications could be manifested by T cell-modulating therapies and to investigate this further.

Immune checkpoint inhibitors (particularly ipilimumab) induce toxicities that share many common features with graft-versus-host disease (GVHD). GVHD is a well-characterized model of T cell activation. Toxicities common to both include colitis, hepatitis, and dermatitis. GVHD is the effect of immunologically active donor T cell lymphocytes on an immunosuppressed recipient following allogeneic bone marrow transplantation (alloBMT) [7]. This clinical syndrome may give insight into potential oral sequelae as a result of immune system activation by immune check point inhibitor therapy. Oral effects are briefly reviewed below [7]. Oral GVHD manifestations resemble those of autoimmune diseases: lichen planus (LP), collagen vascular disease, and Sjogren syndrome [8]. Oral GVHD is characterized by erythema, inflammation, atrophy, mucosal lichenoid-hyperkeratotic changes, pseudomembranous ulcerations, mucoceles, fibrosis, changes in taste, and salivary gland dysfunction and dry mouth [8]. Long-standing oral GVHD can result in limited oral opening from sclerotic perioral tissues, LP-like changes, and vasculitis-like appearance of the mucosa [8]. Salivary gland dysfunction increases the risk of dental caries, mucosal infection, mucosal pain, and impairment of speech, taste, mastication, and swallowing [9]. Of note, patients undergoing alloBMT are also exposed to numerous other toxic agents, including chemotherapy and radiotherapy.

Preclinical studies suggest that ipilimumab or anti-PD-1/PD-L1 therapy could induce or accelerate oral complications by aberrant T cell activation similar to what has been seen in GVHD or autoimmune conditions. Oral LP, for example, is a cytotoxic T cell-mediated autoimmune disease of unknown etiology [10, 11]. Mechanisms of immunopathogenesis include antigen-specific killing of basal keratinocytes by CD8 T cells, autoimmune responses, and humoral immunity [11]. In this condition, an increase in expression of PD-L2 (a secondary ligand of PD-1) compared to surrounding tissue has been noted, suggesting that anti-PD-1 could potentially cause or exacerbate LP [7].

Periodontal disease is modulated and controlled by host immune and inflammatory responses, including monocytes/macrophages, dendritic cells, T cells, B cells, and plasma cells [12]. Periodontal disorders represent a chronic infectious/inflammatory condition characterized by the destruction of tooth-supporting tissues with resultant periodontal pocket formation, alveolar bone resorption, and ultimately, tooth loss [12, 13]. T cell dysregulation leads to increased tissue inflammation, alveolar bone and tissue destruction, and eradication of pathogens. T cells help regulate osteoclastic activity. Ipilimumab (anti-CTLA-4) could potentially induce or aggravate existing periodontal disease. Studies of CTLA-4 gene variants have shown increased susceptibility to more severe periodontitis for +49 A/G polymorphism; an association between heterozygosity in −1722 T/C and chronic periodontitis has also been seen [13]. Inflammatory bone resorption has been shown to be mediated by B7/CD28 co-stimulation of the T cell receptor [14]. Further study in this area is warranted.

Immune-based therapies will likely find an expanded role in the treatment paradigm of cancer patients, possibly in earlier lines of therapy or in those who have been treated with radiation therapy in the past. In particular, anti-PD-1/PD-L1 agents are now being evaluated in those with head and neck squamous cell carcinoma, a population already at high risk of oral complications [15]. Mucosal changes such as erythema, inflammation, ulceration, and fibrosis and salivary gland dysfunction and changes in taste could become compounded in this setting. Routine evaluation of the oral cavity should be incorporated into the care of all cancer patients, particularly those already at risk, such as head and neck cancer patients [16]. In addition, patients who respond to immune checkpoint inhibitors are increasingly experiencing extended survival and may be at risk of chronic complications. These populations would be of particular interest to prospectively assess oral effects of immune-based therapies.

Extrapolating from the GVHD literature, a number of effective management options exist for immune-mediated oral conditions. Potential treatments for mild oral (grade I) toxicity include topical steroid such as oral beclomethasone or budesonide and steroid rinses, sprays, inhalers, gels, creams, or ointments [8, 17]. These compounds are active in local mucosa but have little systemic effect (which avoids theoretical blunting of the antitumor effects). Topical nonsteroidal immunomodulatory agents, such as cyclosporine, tacrolimus, azathioprine, or 6-mercaptopurine rinses/gels can be used [8, 17, 18]. Phototherapy, including extracorporeal photopheresis (ECP), ultraviolet B, psoralen plus ultraviolet A (PUVA), low-level laser, and carbon dioxide laser therapy could also be effective [19–21]. High-dose systemic steroids could be used for grade II or worse oral toxicity. Basic oral health maintenance, including brushing with fluoride-containing products, and potentially remineralizing products and dental flossing and xerostomia management should be implemented [19, 20]. Early recognition of trismus is paramount because once present, it is very difficult to treat [22].

Assessing these complications is important due to their implications for quality of life [8, 23]. The use of patient report and general toxicity report has led to under-reporting of oral complications in oncology in general. Oral health outcomes in the setting of immunotherapy have not been well explored; however, the rising use and increased survival of patients treated with immune-based therapies make this a potentially relevant clinical question. There are indications for oral complications after immune therapy. Focused study of the nature, incidence, and severity of oral complications in a prospective manner for patients treated with immune

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checkpoint inhibitors is needed to assess the oral implications of these therapies and to support clinical recognition and management approaches. Integrated oncology teams may be best suited to provide care for these unique complications of these significant advances in oncology care.

Conflict of interest The aforementioned authors have read and approved the manuscript. This manuscript is not under consideration elsewhere. The authors do not have any financial conflicts of interest nor other relationships which may lead to a conflict of interest.

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