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EDITORIAL

MASCC 2020 recommendations for the management of immune-related adverse events of patients undergoing treatment with immune checkpoint inhibitors

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Oncoimmunotherapy with immune checkpoint inhibitor–targeted antibodies has developed as the most significant advance in the management of cancer in recent years [1]. The concept that the immune system was unsuccessful in protecting humans against the development of cancer has changed over the last decade. Checkpoint molecules are inhibitory (PD-1, PDL-1, CTLA-4, TIM-3, LAG-3, BTLA, and HEVM) and stimulatory (CD27, CD40, OX40, GITR, ICOS, and CD137) co-receptors expressed mostly by T cells, but also by other immune cells including antigen-presenting dendritic cells. The basic function of these inhibitory co-receptors is to negatively regulate T cell activation, which is critical in the maintenance of peripheral self-tolerance. The co-inhibitory receptor ligands for these immune checkpoint molecules are, however, also significantly upregulated in various types of cancers, resulting in evasion of anticancer immunity.

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Recent advances in immunotherapy include the discovery of the inhibitory immune checkpoint molecules, programmed cell death protein 1 (PD-1), and cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), discovered by Tasuku Honjo and James P. Allison in 1992 and 1996, respectively [2, 3]. In acknowledgment of this pioneering research, these scientists received the 2018 Nobel Prize for Physiology and Medicine. The significant and often durable clinical responses seen with monoclonal antibodies targeting CTLA-4 and PD-1 have resulted in new standards of care in a variety of malignant diseases [1–4], following FDA approval of checkpoint inhibitors that included pembrolizumab [5], nivolumab [6], cemiplimab [7], atezolizumab [8], durvalumab [9], and avelumab [10]. These agents are approved for several indications including melanoma, lung cancer (small and non-small cell types), bladder cancer, renal cell carcinoma, and Hodgkin's disease [5–10]. Other co-inhibitory molecules under clinical evaluation include T cell immunoglobulin and mucin domain–containing molecule-3 (TIM-3) [11], lymphocyte activation gene-3 (LAG-3) [12], V domain Ig–containing suppressor of T cell activation (VISTA) [13], and B and T lymphocyte attenuator (BTLA) [14]. Additionally, numerous clinical trials are also investigating combinations of immune checkpoint inhibitors with other anticancer treatments such as chemotherapy, radiotherapy, targeted therapy, and antiangiogenic agents (small molecules or monoclonal antibodies), with several of these combinations already approved and in routine clinical use.

Monoclonal antibodies that target inhibitory immune checkpoint molecules are generally well tolerated and are significantly less toxic than standard chemotherapy regimens. These agents do, however, have toxicities related to overactivation of the immune system. These are referred to as immune-related adverse events (IrAEs) [15]. IrAEs include fatigue, skin, gastrointestinal, liver, pulmonary, endocrine,

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ocular, neurological, and rare toxicities such as type 1 diabetes and those of cardiac and hematological origin.

Dermatological toxicities can emerge following the first treatment with immune checkpoint inhibitors (ICIs). Skin rashes are frequently maculopapular and mild in nature [16]. Rash and pruritus occur more commonly with anti-CTLA-4 compared with anti-PD-1 inhibitors [17]. Serious skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are seen in a minority of patients [18]. Vitiligo occurs in a small number of patients receiving ICIs and is generally associated with clinical benefit and long-term survival [19].

Gastrointestinal side effects include ulcers, mucositis, gastritis, colitis, and abdominal pain. Diarrhea, occasionally with bloody or mucus stool, is the most common gastrointestinal manifestation and usually accompanies enterocolitis. In severe cases, these complications are associated with toxic megacolon and perforation [20].

Endocrine IrAE symptoms are generally nonspecific and include fatigue, mental status changes, headaches, and dizziness [21]. Hypothyroidism is the most common endocrinological abnormality; hypophysitis or adrenal insufficiency (more often seen with anti-CTLA-4) and type 1 diabetes may present with severe acute symptoms [21]. Clinicians should screen for thyroid abnormalities and baseline thyroid function tests, while adrenal function assays may be indicated in some patients.

Other, less frequent IrAEs may also occur. Ophthalmological IrAEs in the form of episcleritis, uveitis, or conjunctivitis have also been reported [22]. Neurological IrAEs include myasthenia gravis, aseptic meningitis, encephalitis, motor and sensory neuropathies including Guillain-Barre syndrome, and other rare events such as enteric or autonomic neuropathies and transverse myelitis [23]. Musculoskeletal IrAEs include inflammatory arthritis, myositis, polymyalgia rheumatica-like presentation, and rarely osteitis. Other rare IrAEs include anemia related to red cell aplasia, neutropenia, acquired hemophilia A, thrombocytopenia [24, 25], pancreatitis [26], renal insufficiency [27], nephritis [27], and myocarditis [28].

MASCC established the MASCC Subgroup on Immuno-Oncology (IO) in 2018 under the auspices of the Neutropenia, Infection, and Myelosuppression Study Group (SG). The IO subgroup comprises members from numerous medical specialties with an interest in IrAEs. Represented disciplines include, but are not limited to, gastroenterology, dermatology, neurology, immunology, hematology, rheumatology, endocrinology, nephrology, and emergency medicine.

The first initiative of the new MASCC subgroup on IO was to update current treatments for the management of patients undergoing checkpoint inhibition who experienced these unique toxicities. It must be emphasized, however, that the management of these IrAEs is primarily based on clinical recommendations from experience based on clinical trials, general clinical consensus, and daily clinical practice. There are no prospective randomized trials to assess whether one treatment strategy is superior to another. Although these recommendations are widely accepted, the level of evidence is too low to constitute a "Guideline." Additionally, some of these recommendations are based on only clinical case series, particularly for those patients experiencing infrequent or rare toxicities.

MASCC appointed a multidisciplinary team of experts from different parts of the world including North America, South America, the UK, and South Africa and to develop these recommendations. In line with MASCC as a multidisciplinary professional association, the team was comprised of basic scientists and clinical investigators, including medical oncologists, emergency physicians, internal medicine subspecialists, and professional nurses.

The main difference between the guidelines developed by other professional organizations like ASCO [29], NCCN [30], ESMO [31], and SITC [32] and the MASCC recommendations is that the MASCC recommendations focus on the updated management of patients with severe and refractory toxicities.

IrAEs are typically low-grade and controllable, especially with use of single agent immune checkpoint inhibition; however, the reporting of these IrAEs outside a clinical trial setting is generally suboptimal [33]. Early recognition of IrAEs and proactive management by clinicians remain critical to lower morbidity and mortality associated with these treatments. Anti-CTLA-4 and anti-PD-1/anti-PD-L1 have different mechanisms of action, and several clinical trials investigating combination therapies in a multiplicity of cancers, including metastatic renal cell cancer and metastatic melanoma, have been reported. In these studies, the incidence of severe grade 3 and grade 4 IrAEs due to the combination of ipilimumab and nivolumab was present in approximately 50% of patients. The occurrence of these severe toxicities was significantly higher compared with either antibody administered as a single agent, resulting in treatment interruption and discontinuations in approximately one-third of patients [34].

Clinicians and healthcare professionals treating these patients and managing IrAEs should be aware that there is a wide range of additional distinctive toxicities and side effects that can be unpredictable and severe in nature. As these agents are increasingly being administered in combination with targeted therapies, vaccines, chemotherapy, radiation therapy, or other treatment modalities, the incidence and severity of these toxicities may evolve. These changes in toxicity patterns will require ongoing efforts to update our recommendations to achieve better management of these IrAEs. Identifying biomarkers to categorize patients who will benefit from treatment with ICI-based treatment is imperative. Thus far, predictive biomarker research has concentrated on various tumor

signatures including PD-L1 expression, microsatellite instability, and tumor mutational burden. Biomarkers to identify patients at risk of severe toxicity would also be clinically useful. Somewhat paradoxically, however, there is a growing body of evidence that the presence of IrAEs also is associated with a better outcome, making this a more challenging task [35].

Authors' contributions All of the authors contributed equally to the conceptualization of the manuscript; BLR and RA shared equally drafting of the manuscript, while TC and DBJ provided additional expert input and editorial oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

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