MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER (MASCC) 2020 CLINICAL PRACTICE RECOMMENDATIONS FOR THE MANAGEMENT OF IMMUNE CHECKPOINT INHIBITOR ENDOCRINOPATHIES AND THE ROLE OF ADVANCED PRACTICE PROVIDERS IN THE MANAGEMENT OF IMMUNE-MEDIATED TOXICITIES

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Authors' contributions

All of the authors contributed equally to the conceptualization of the manuscript; TC, MG, PG and RG shared sections on endocrinopathies and the role of advanced practice providers, while BLR, TC, MG and DBJ provided clinical input and BLR, DBJ, TC and RA editorial oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

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Abstract

Immune checkpoint inhibitors (ICIs) have emerged as the newest pillar of cancer treatment, transforming outcomes in melanoma and showing benefit in a range of malignancies. Immune-mediated toxicities, stemming from increased activity within the T cell lineage, range from asymptomatic or mild complications to those that are fulminant and potentially fatal. Immune-mediated endocrinopathies include hypophysitis, thyroiditis, and insulin-dependent diabetes mellitus. These presentations, which may be vague and non-specific, can be life-threatening if not diagnosed and treated appropriately. This review considers the work-up and management of immune-mediated endocrinopathies and also considers the role of advanced practice practitioners in the management of immune-mediated toxicities. These state-of-the-art MASCC recommendations represent a comprehensive overview of the management and clinical work-up in those in whom the diagnosis should be considered.

Keywords: APP's (advanced practice providers), corticosteroids, diabetes, hyperglycemia, hypophysitis, thyroiditis.

Introduction

This contribution to the 2020 MASCC recommendations on the management of immune-related toxicities is focused on endocrinopathies and emerging toxicities, specifically the approach to the more severe presentations which require corticosteroids and specialist management. We also consider the role of Advanced Care Practitioners in the management of these toxicities.

Endocrinopathies

Immune-related endocrinopathies from checkpoint inhibitor therapy include most commonly hypophysitis, thyroiditis and, albeit less commonly, insulin-dependent diabetes mellitus and adrenalitis [1]. These can be life threatening if not diagnosed and treated appropriately and thus early recognition is essential [2-5]. ICI treatment often can be continued or resumed after patient stabilization. Diagnosis and management can be complicated by concomitant toxicity of a different organ system.

Hypophysitis

Hypophysitis can present with either hormone defects or mass effect. It is an immune-mediated inflammation of the pituitary gland, usually in the anterior pituitary, and typically results in permanent hypopituitarism of one or more of the pituitary axis with secondary adrenal insufficiency and secondary hypothyroidism; consequently rapid diagnosis is critical [2,6]. In patients with both ACTH and TSH deficiency, glucocorticoid replacement should be initiated prior to, or at the same time as thyroid hormone replacement, in order to prevent precipitating an adrenal crisis.

Hypophysitis is more common in patients treated with CTLA-4 inhibitors and occurs in around 10% of patients [1, 7]. It is rare in patients treated with anti-PD-1 (0.4%) or anti-PDL-1 (<0.1%) treatment alone. [8,9] A meta-analysis of 34 checkpoint inhibitor studies, encompassing 6472 patients, reported 85 cases of hypophysitis of which 34 had severe toxicity [8]. The median onset of time after commencement of checkpoint inhibition is 9 weeks (*i.e.* during the 3rd cycle of treatment), but can occur after the 1st cycle of treatment and is reported to occur up to 19 months after starting therapy [3,4.]

Patients who develop immune-related hypophysitis appear to have superior clinical outcomes from their cancer therapy than those who do not [10]. This correlation could be the result of autoimmunity being indicative of a non-specifically, over-active immune system, resulting in increased anti-tumor efficacy.

CTLA-4 mediated hypophysitis occurs due to type II and type IV hypersensitivity reactions [11]. It may in part relate to antibody-binding CTLA-4 receptors being directly expressed by the pituitary gland, leading to complement activation and an inflammatory cascade alongside direct T cell- mediated cytotoxicity [12]. Autoantibodies targeting the pituitary have been detected in patients presenting with this type of irAE.

Typically, hypophysitis presents with headache and/or fatigue. There is a range of non-specific symptoms including nausea, diarrhea, muscle weakness, malaise and anorexia, which may represent pituitary dysfunction, but are also common complications of cancer itself and a low threshold for clinical suspicion is required. Visual symptoms are rare in immune-related hypophysitis [4].

Multiple informative literature reviews on immune-related toxicities have been performed, with 12 focused purely on endocrinopathies published in the last 2 years. The management of endocrinopathies features prominently in expert opinion guidelines, such as ESMO and ASCO [13]. More recently, the UK [2] and French endocrinology societies [14] have also produced guidance for their management.

There have not been any randomized controlled trials examining the management of immune-related Hypothalamic-Pituitary-Adrenal (HPA) toxicity and, in particular, no studies considering the optimal dose of steroids in these presentations. Classically, high doses of steroids (1-2mg/kg daily of intravenous methylprednisolone) have been initiated in the hope of reducing the need for long-term replacement. However, there is little evidence to support this approach, therefore physiological doses of glucocorticoids are increasingly becoming the accepted treatment of these patients [1, 2,9.10,14]. In patients with severe hypophysitis, intravenous hydrocortisone at a dose of 50-100mg should be given immediately with 50mg administered intravenously every 6 hours for the next 24 hours (see figure 1). Clinically stable patients can be commenced on oral hydrocortisone (20/10/10mg). [2]

Figure 1: Algorithm for emergency management of life-threatening/severe HPA toxicity

In a retrospective analysis of 98 patients with ipilimumab-related hypophysitis, those who received low-dose steroids had improved clinical outcomes both in terms of time to treatment failure and overall survival [10]. Furthermore, this cohort of patients had

equivalent rates of symptom and imaging resolution of their hypophysitis as those receiving high-dose steroids.

High-dose steroids may, however, still be indicated in those patients with the rare presentation of immune-related hypophysitis with visual field defects, cranial nerve palsies, significant pituitary enlargement, severe headache, critical illness, or significant hyponatremia [1, 2,14].

The critical first step in the management of all immune-related toxicities is recognition. In contrast to other immune-related toxicities, hypophysitis tends to be self-limiting and can be safely treated with physiological rather than pharmacological doses of steroids. This necessitates education of emergency care physicians, other health care professionals and the patient, as early intervention can reduce the duration and severity of the complications [15]. This is particularly pertinent in immune-related hypophysitis, where even in life-threatening cases, the presentation can be vague and non-specific.

ICI treatment can be recommenced once the patient is clinically stable on appropriate endocrine replacement therapy. [2] Patients should be re-evaluated once stable to confirm diagnosis and at intermittent intervals to assess for HPA axis recovery.In those with life-threatening HPA axis toxicity, we propose an exemplar algorithm for management as shown in figure 1.

Primary Thyroid Dysfunction

Primary thyroid dysfunction is related to a thyroid gland abnormality, in contrast to secondary hypothyroidism, which can be due to hypophysitis/pituitary dysfunction. Primary thyroid dysfunction can result from both anti-CTLA-4 (~ 5% incidence) [3,16] and anti-PD-1/PD-L1 therapy, although it may be more common with PD-1/PD-L1 blockade [3,17]. Recent studies examining for primary thyroid disorders after PD-1 inhibition report rates as high as 14%–20%, especially following combination ICI therapy [18]. Cases of primary thyroid dysfunction are predominantly related to thyroiditis, which can present initially as thyrotoxicosis due to the release of thyroid hormone from inflamed thyroid tissue [19]. Hypothyroidism from inflammatory

damage to the thyroid gland can subsequently result. The onset of thyroid dysfunction can be as early as three weeks after ICI therapy or as late as 10 months; however, most cases seem to occur within the first 1 -3 months following treatment [17,19].

Baseline Thyroid Stimulating Hormone (TSH) and free T4 are recommended before first treatment and then at least monthly for the first six months for both anti-CTLA-4 and anti-PD-1/PD-L1 therapy. If normal, and the patient is asymptomatic, these investigations can be repeated quarterly for months 6 to 12 and approximately every 6 months thereafter (or until six months post-treatment). If any signs of thyroid dysfunction are noted, thyroid function tests should be undertaken. Clinical and biochemical abnormalities may resolve in two to four weeks in those patients who present initially with thyrotoxicosis from thyroiditis [20]. Thyroid Function Tests (TFTs) should be checked at least every 2-3 weeks in patients with thyrotoxicosis to monitor for progression to hypothyroidism.

ICI-related thyrotoxicosis from thyroiditis is typically transient. If needed, symptomatic management with a beta-blocker can be used. For primary hypothyroidism (high TSH, low free T4), levothyroxine can be started and increased every 4-6 weeks to normalize thyroid function tests [21,22]. If asymptomatic with an elevated TSH less than 10 mIU/L and normal free T4, the patient could be closely followed without thyroid hormone replacement. In those with secondary hypothyroidism related to hypophysitis/pituitary dysfunction [1], low free T4 with a low or low-normal TSH), secondary adrenal insufficiency should be ruled out prior to starting levothyroxine to prevent triggering an adrenal crisis.

Insulin-dependent Diabetes

Insulin-dependent diabetes after anti-PD-1/PD-L1 therapy is uncommon (~0.9% incidence) [23,24] and usually presents with marked hyperglycemia, ketoacidosis, and low C-peptide levels. According to a recent analysis, patients can present with diabetic ketoacidosis or marked hyperglycaemia as early as one week and up to 12 months after treatment initiation with a median of 8.5 weeks following therapy and median glucose of 530 mg/dL [25]. The signs and symptoms of DKA or hyperglycemia include polyuria, polydipsia, blurred vision, and malaise. Serum

glucose measurements are often included as standard laboratory care during ICI therapy, and attention should be made to monitoring glucose trends. Aggressive management of ketoacidosis and individualized insulin regimens are needed. CTLA-4 monoclonal antibody-related insulin-dependent diabetes is even more rare with only a couple of cases reported in the literature [23,26,27]. Once blood glucose levels are controlled with insulin therapy ICI treatment can be recommenced if there are no other contra-indications.[2]

Role of advanced practice provider and patient-provider communication in the management of Immune-related toxicity

Cancer patients receiving immune checkpoint inhibitors require education, early and prompt recognition of emerging IrAEs and prompt management to mitigate any potential long-term consequences.[28,29] Advanced Practice Providers (APPs), specialist nurses and patient navigators trained in the care of irAEs are perfectly positioned to optimize patients' quality of care for the growing number receiving immunotherapy. In this setting, APPs provide patient education, are trained in assessing symptoms of immune-related toxicities, collaborate with consultative services, and develop management strategies.

Patient provider communication

Immunotherapy as a primary treatment for cancer has significantly changed the landscape of cancer care in specific clinical settings. This has impacted on health care professionals, patients and their caregivers. Immunotherapy works differently than traditional chemotherapy and, as such, it is vital that patients and caregivers have accurate and up-to-date education about their treatment, plan of care and the potential for complications.

However, there are challenges to good communication in cancer care. Multiple providers are involved in treatment and they must share potentially life-changing news about diagnoses and complex treatments with patients. Patients and caregivers are often overwhelmed at the time this information is shared and may not be able to grasp the complexity of the information or know the appropriate questions

to ask. Good health care communication is a learned skill and resources are available to help build this skill in oncology. The American Society of Clinical Oncology has issued guidelines on effective communication with a goal to optimize the patient-clinician relationship, as well as patient, clinician and family well-being [30]. Key communication skills include exploring the patient's understanding of their disease, engaging in behaviors that foster trust and collaboration and providing information that is timely and oriented to the patient's preferences and values [29].

APPs need to ensure that patients and caregivers understand the potential complications of immunotherapy, which are different from those of traditional anti-cancer treatments [31]. Patients can have an unusual treatment complication, which can occur at any time in the treatment journey – from early in treatment into survivorship, after completion of treatment. Good communication between the APPs and patients will include regular assessment and dialog about health status, while noting any changes from baseline. The Oncology Nursing Society has developed a Tool Kit, "Recognize It; Report It" as a guide for oncology health care professionals to recognize adverse events early and to learn which symptoms to report and where/who to communicate these adverse events. The tool kit is available on the ONS website at https://www.ons.org/toolkits/recognize-it-report-it.

Immunotherapy has also expanded the oncology health care team as patients may need to be seen by specialists such as endocrinologists, pulmonologists and others. Communication among these different providers and patients is critical and APPs should coordinate these interactions. This is especially important when seeing providers outside of their oncology care team, including their primary care provider or emergency department staff. Wallet cards with treatment details, such as the one from the Oncology Nursing Society (https://www.ons.org/sites/default/files/2019-01/IO%20Card%201-sided_Vertical.pdf) are tools to facilitate effective treatment information. Patients should always keep the card with them and provide it to any health care professional they visit outside of their cancer care team.

Conclusion

Immune-mediated endocrinopathies, particularly those affecting the HPA axis, are potentially life-threatening complications of checkpoint inhibitors. APPs should make learning presentation, communication skills and management of refractory irAEs a priority in their practice.

Conflict of interest

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