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Cancer immunotherapy-induced endocrinopathies: Clinical behavior and therapeutic approach☆

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ABSTRACT

Cancer immunotherapy has proven to be effective in a wide variety of tumors. The use of immune checkpoint blocking monoclonal antibodies has become a standard treatment regimen in some of them as advanced melanoma. However, given the mechanism of action, its use may be associated with immune-related adverse events that may complicate the clinical course and prognosis of patients. Among these are autoimmune endocrine adverse effects, such as hypophysitis, hypo and hyperthyroidism, and adrenal insufficiency. This review focuses on the most relevant and new aspects related to the incidence, clinical presentation, diagnosis and treatment of these adverse effects associated with different types of immune checkpoint inhibitors in cancer immunotherapy.

1. Introduction

Immunotherapy uses different therapeutic approaches to target the immune system against cancer. These include: 1) the use of cytokines (preferably interferon and interleukins); 2) manipulation of T lymphocytes (adoptive cell transfer); 3) therapeutic vaccines; and 4) monoclonal antibodies that bind to specific T lymphocyte receptors to stimulate the immune response against tumor cells (immune checkpoint inhibitors). The use of these monoclonal antibodies has shown important clinical benefits in different types of cancer, including metastatic melanoma, renal carcinoma, non-small cell lung cancer, head and neck cancer, urothelial carcinoma and Hodgkin's lymphoma [1,2]. However, despite its important therapeutic advantages, the use of these antibodies is not free of adverse effects derived from its own mechanism of action, and therefore, associated with an immunological hyperactivity. These immune-related adverse events (irAEs) can become serious and even life-threatening [3,4]. The main irAEs associated with these antibodies, among others, are cutaneous, digestive (gastrointestinal and hepatic) and endocrine (hypophysitis, thyroiditis and adrenal insufficiency) [3–11] (Table 1). The relative risk for developing the endocrine irAEs associated with immune checkpoint inhibitors is 22 for hypophysitis, 8.3 for all forms of hypothyroidism, 5.5 for all forms of hyperthyroidism, and 3.9 for adrenal insufficiency [12]. In the present review, the most novel and relevant aspects related to autoimmune endocrinopathies induced by immune checkpoint inhibitors in the treatment of cancer have been reviewed. For this purpose, all full-text papers and relevant case reports published in Pubmed until May 2017 using "cancer", "immunotherapy", "endocrinopathies", "hypophysitis", "thyroiditis", "adrenalitis", and "type 1 diabetes", as key words, were considered.

2. Immune checkpoints

Immune checkpoints are receptors for T lymphocytes that, after binding to their ligands, modulate the immune system, either by stimulating it (stimulatory checkpoint molecules) or inhibiting it (inhibitory checkpoint molecules) [1]. There are multiple co-stimulatory immune control points, such as CD-28, ICOS, OX40 and CD46. Most of the ligands for these co-stimulatory receptors are induced by the activation/maturation of antigen presenting cells (APCs). On the other hand, the main co-inhibitory immune control points are cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) [1].

CTLA-4 is a molecule that is expressed on the surface of most activated T lymphocytes during the initial activation phase in lymphatic tissue by dendritic cells and by other APCs. Its main action is inhibitory, regulating homeostasis and peripheral immune tolerance, inhibiting the activation of T lymphocytes through mechanisms of negative signaling and competitive antagonism of the CD28/B7-mediated co-stimulatory pathway [1].

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Table 1
Main immune checkpoints antibodies, target molecules, doses, tumor types with demonstrated clinical effects, and main associated autoimmune endocrinopathies.

Immune checkpoint inhibitors	Immunoglobulin type	Target molecule	Dosage	Tumor type	Autoimmune endocrinopathies
Ipilimumab (MDX-010)	IgG-1κ	CTLA-4	3 to 10 mg/kg iv every 3 weeks (4 doses)	Advanced melanoma	Hypophysitis (11%) Hypothyroidism Subclinical (6%) Overt (1–6%) Hyperthyroidism Subclinical (16%) Overt (<2.5%) Adrenalitis (0.3–1.5%) Insulinitis (Ipilimumab + nivolumab) Parathyroiditis (Ipilimumab + nivolumab)
Tremelimumab (CP-675,206)	IgG2b	CTLA-4	15 mg/kg every 90 days up to 4 doses	Renal carcinoma Breast cancer Malignant mesothelioma	Hypophysitis (1–2%) Thyroid dysfunction (2.5%) Adrenalitis (0.3–1.5%)
Pembrolizumab (MK-3475)	IgG-4κ	PD-1	2–10 mg/kg every 2 weeks	Advanced melanoma Non-small cell lung cancer	Thyroid dysfunction (20–40%) Hypophysitis (<1%) Insulinitis
Nivolumab (MDX-1106)	IgG4	PD-1	2–10 mg/kg every 2 weeks	Advanced melanoma Recurrent head and neck squamous cell carcinoma	Thyroid dysfunction (20–40%) Hypophysitis (<1%) Insulinitis Parathyroiditis (Ipilimumab + nivolumab)

PD-1 is another co-inhibitory membrane receptor expressed in T cells activated during the effector phase in peripheral tissues. The binding of PD-1 to its PD-L1 (B7-H1) and PD-L2 (B7-DC) ligands that are expressed in tumor cells and tissue macrophages causes an inhibition of T lymphocyte activation facilitating immunological tolerance, thus preventing tumor rejection by the immune system [1].

3. Immune checkpoint inhibitors

Blocking of immune checkpoints (CTLA-4 and PD-1) with inhibitory antibodies is accompanied by stimulation and proliferation of activated T lymphocytes against tumor cells [1,13,14].

The anti-CTLA-4 (ipilimumab and tremelimumab) and anti-PD1 antibodies (pembrolizumab, nivolumab and pidilizumab) are the main inhibitors of the immune checkpoints that are being used in cancer immunotherapy. Other developing antibodies are anti-PD-L1, such as atezolizumab, durvalumab and avelumab.

Ipilimumab (MDX-010), a recombinant human monoclonal (IgG-1κ) antibody, was the first inhibitor of immune checkpoints that demonstrated its efficacy in advanced melanoma. It was approved in 2011 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of metastatic melanoma given its ability to prolong survival in these patients compared with other therapies, contributing to a plateau in the survival curve that begins at 3 years and lasts up to 10 years of follow-up in some patients [15,16]. In addition, ipilimumab as an adjuvant treatment for stage III high-risk melanoma has been associated with significantly higher rates of relapse-free survival, overall survival, and distant metastasis-free survival compared to placebo [17]. It has also shown its effectiveness in advanced renal cell carcinoma and is being tested in other cancers, such as non-small cell lung cancer [18]. The induction treatment with ipilimumab consists of administration of 3 to 10 mg/kg intravenously in 90 min every 3 weeks, with a total of 4 doses, followed or not by maintenance doses every 3 months.

Tremelimumab (CP-675,206) is a recombinant human anti-CTLA-4 monoclonal antibody (IgG2b) that although has not demonstrated increased survival on chemotherapy in patients with advanced melanoma [19], at the present time it is being evaluated in other tumors such as malignant mesothelioma and renal cell carcinoma [20,21]. The dose of tremelimumab is 15 mg/kg every 90 days up to 4 doses.

In spite of the therapeutic advantage of ipilimumab, its use in advanced melanoma has decreased due to the development of new inhibitory antibodies to the immune checkpoints that have been shown to be more effective and better tolerated, such as anti-PD-1 [22,23].

The main anti-PD-1 antibodies, pembrolizumab (MK-3475) and nivolumab (MDX-1106), are humanized monoclonal antibodies type IgG-4κ e IgG4, respectively. These antibodies have been approved in 2014 by the FDA and in 2015 by the EMA for the treatment of advanced melanoma. In addition, they have shown their efficacy in other tumors such as non-small cell lung cancer [24]; and recurrent head and neck squamous cell carcinoma [25], respectively. Doses of pembrolizumab and nivolumab are 2–10 mg/kg every 2 weeks and 3 mg/kg every 2 weeks, respectively, until progression or unacceptable toxicity. Pidilizumab (CT-011), another humanized antibody anti-PD-1 type IgG-1κ, has shown promising efficacy in phase II trials in patients with diffuse large B-cell lymphoma after hematopoietic stem cell transplantation [26] and combined with rituximab in patients with relapsed follicular lymphoma [27].

Lastly, combined treatment with anti-CTLA-4 (ipilimumab) and anti-PD1 antibodies (nivolumab or pembrolizumab) seems to be an attractive therapeutic alternative in advanced melanoma as it is associated with greater therapeutic efficacy; however, it also presents greater toxicity [28,29].

Other anti-PD-L1 antibodies, such as atezolimumab (MPDL3280A) (IgG-1κ), durvalumab (MEDI4736) (IgG-1κ), avelumab (MSB0010718) (IgG1) and MDX 1105 (IgG4) are being evaluated at the present time in different types of tumors.

4. Hypophysitis

The irAEs associated with the use of anti-CTLA-4 antibodies have been reviewed in a recent meta-analysis of 81 articles, with a total of 1265 patients from 22 clinical trials [3]. The study showed a global incidence of irAEs and an incidence of high-grade irAEs of 72% and 24%, respectively. In addition, the risk of developing irAEs was dose dependent [3]. In the study, autoimmune hypophysitis was the most common endocrine adverse event, documented in up to 13% of clinical trials.

4.1. Hypophysitis induced by anti-CTLA-4 antibodies

Hypophysitis associated with the use of anti-CTLA-4 antibodies is an autoimmune hypophysitis similar to primary lymphocytic hypophysitis

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