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REVIEW ARTICLE

Immune-related endocrine disorders in novel immune checkpoint inhibition therapy

Le Min

Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA, 02115, USA

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Abstract Immune checkpoint inhibition against advance malignancies was named breakthrough discovery by the science magazine in 2013. In numerous clinical studies, monoclonal antibodies against the immune checkpoints, CTLA4, PD1 and PD1 ligand PDL1 have shown promising tumor response in different type of metastatic malignancies. The adverse events are autoimmune-related. The endocrine disorders, hypophysitis and thyroiditis are among the most common side effects associated with immune checkpoint inhibition treatment. Hypophysitis, a very rare endocrine disorder occurs in about one tenth of the patients receiving anti-CTLA4 treatment. Thyroiditis, on the other hand, is more commonly seen in patients receiving anti-PD1 treatment. In addition, both thyroiditis and hypophysitis are common in patients receiving combination treatment with anti-CTLA4 and anti-PD1 treatment. The time to onset of hypophysitis and thyroiditis is short. Most of the endocrine disorders occur within 12 weeks after initiation of the immune checkpoint inhibition therapy. Hypophysitis can manifest as total anterior pituitary hormone deficiency or isolated pituitary hormone deficiency. Diabetes insipidus is rare. TSH and gonadotropin deficiencies may be reversible but ACTH deficiency appears permanent. Thyroiditis can present as hypothyroidism or thyrotoxicosis followed by hypothyroidism. Hypothyroidism appears irreversible. Early identifying the onset of hypophysitis and thyroiditis and proper management of these endocrine disorders will improve the quality of the life and the outcome of this novel immunotherapy.

E-mail address: lmin@bwh.harvard.edu.
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Introduction

Immune system regulation is through immune checkpoints expressing on the T lymphocytes to stimulate or inhibit T cell activity.[1] Alternation of the checkpoint function results in disruption of the balance between co-stimulator and inhibitory signaling in T cells leading to change T cell activity. For instance, knockout cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), an inhibitory immune checkpoint, in mice caused T cell activation and lymphoproliferative disorders.[2] CTLA4 null mice die at an age of 2–3 weeks due to massive lymphoproliferation. In contrast, the phenotype of program death-1 (PD-1) deletion mice appears more mild. The mice developed and grew normally.[3] Although the thymus was apparently normal, PD-1 deletion mice had splenomegaly. Biochemical tests show increased levels of subset of immunoglobulins, IgG2b, IgA and most strikingly IgG3. The phenotype of PD-1 deletion mice supports the role of PD1 in the negative regulation for subset of B cell proliferation and differentiation including class switching.[3]

Over a century's efforts[4] searching for immunotherapy to augment our own immune system to fight against cancer have finally reach a breakthrough discovery when a humanized monoclonal antibody against immune checkpoint CTLA4, ipilimumab demonstrated effective and durable anticancer activity in patients with metastatic melanoma.[5] In 2011, FDA has approved ipilimumab as the first immune checkpoint inhibitor to treat metastatic melanoma. In 2013, the Science Magazine name cancer immunotherapy "the breakthrough of the year".[6] Following the success of anti-CTLA4 therapy in melanoma, the clinical trials exploring the anticancer efficacy by anti-PD1 and anti-PDL1 demonstrated promising outcome. In 2014 and 2015, two anti-PD1 agents nivolumab and pembrolizumab received FDA approval to treat metastatic melanoma and other metastatic malignancy. More clinical trials are undergoing to explore the combination anti-PD1 and anti-CTLA4 therapy. Not surprisingly, combination therapy resulted in higher tumor respond rate.[7]

Immune checkpoint blockade therapy represents a major success in cancer therapy, yet this novel treatment is associated with a unique spectrum of adverse events that are mostly immune-related adverse events (irAEs). Among irAEs, immune-related endocrinopathies including hypophysitis and thyroid disorders are common.[8] Early recognition and proper management of these endocrinopathies are important for the oncologists, endocrinologists and other clinicians to safely use these immune checkpoint inhibitors. The goal of this review is to describe the clinical manifestations and management of hypophysitis and thyroid disorders associated with anti-CTLA4 and anti-PD1 as monotherapy or combination therapy. The rare endocrine disorders such as autoimmune diabetes as well as hypercalcemia will be briefly discussed.

Hypophysitis

Hypophysitis, the inflammation of the pituitary, emerged to be one of the most common irAEs in patient receiving anti-CTLA4 treatment. The incidence of hypophysitis ranged from 0 to 17% in earlier studies.[9] Recent cohort studies from our institution,[10] Massachusetts General Hospital,[11] and Memorial Sloan Kettering Cancer Center[12] show consistent high incidence (8–13%). The higher incidence reported in recent studies suggests the increased awareness of this rare disease that occurs in 1 per 9 million per year[13] in general population. The incidence of hypophysitis is low in patients receiving anti-PD1 treatment, less than 1% in most of the clinical studies.[8,14] On the other hand, the incidence of hypophysitis in the combination therapy is higher[8] or comparable to the incidence in patients receiving anti-CTLA4 treatment.[12] Unlike sporadic hypophysitis, anti-CTLA4-related hypophysitis is more commonly reported in male patients. In our study, the incidence of hypophysitis in patients received ipilimumab treatment was 16% in male and 8.7% in female respectively.[10] A higher male to female ratio (11:8) was reported in a different study.[12] The mechanism underlying anti-CTLA4-related hypophysitis remains to be elucidated but a recent study displayed that pituitary glands expressed CTLA-4, particularly in a subset of prolactin- and thyrotropin-secreting cells. These cells became the site of complement activation, featuring deposition of C3d and C4d components and an inflammatory cascade similar to that seen in type II hypersensitivity.[15]

Since anti-CTLA4-related hypophysitis is a manageable adverse event, early identification of this potential life threatening condition warrants timely initiation of the proper management to improve the outcome and quality of life in patients receiving anti-CTLA4 treatment and developed hypophysitis. The symptoms of hypophysitis are nonspecific. Fatigue and headache are most common symptoms as initial manifestation of hypophysitis.[11] The median onset of hypophysitis after initiation of anti-CTLA4 treatment is 8–9 weeks.[10–12,16] Because anti-CTLA4 treatment is usually given every 3 weeks, most anti-CTLA4-related hypophysitis occur after 2–3 cycles of the treatments.

Pituitary is the master gland that secrets hormones to regulate the downstream endocrine organ function and the hormone production from the targeted endocrine organs. Anterior pituitary secrets corticotropin (ACTH) to regulate cortisol production from the adrenal glands, thyrotropin (TSH) to regulate thyroxine production from thyroid, gonadotropins (LH and FSH) to regulate the function of gonads, and growth hormone (GH) to regulate muscle, adipose and bone metabolism; prolactin to regulate milk production. Posterior pituitary produce arginine vasopressin to regulate fluid volume homeostasis and oxytocin to regulate labor process. Anti-CTLA4-related hypophysitis mainly causes anterior pituitary hormone deficiency,[10,16] while posterior hormone deficiency as manifestation of diabetes insipidus is rarely reported. Ipilimumab-related hypophysitis can manifest as either isolated or pan-anterior pituitary hormone deficiency.[9,10,16,17] Among the anterior pituitary hormones, ACTH and TSH deficiencies are most common.[10,16,17] The mechanisms of selective damage to subgroups of pituitary cells remain to be decoded but the high incidence of destructive injury to pituitary corticotrophs and thyrotrophs secondary to anti-CTLA4-related hypophysitis underscores the importance of vigilant monitor of adrenal and thyroid functions after the patients are initiated with anti-CTLA4 therapy. It is important to