Endocrine toxicity

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Immune checkpoint inhibitors (ICI) including anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) agents have shown antitumor activity by enhancing adaptive immune response against cancer cells, resulting in significant long-lasting responses. Although the toxicity profile of the immune checkpoint inhibitors is more favorable than conventional chemotherapy, immune-related adverse events (irAEs) can occur as a result of enhancing immune response in normal tissues. IrAEs induced by ICI can potentially affect every organ in the body, but gastrointestinal tract, skin, liver, and endocrine system are the most commonly involved sites.

The endocrine system is a common target for irAEs. Patients treated with ICI are at risk of developing hypophysitis, thyroiditis and less common, primary adrenal insufficiency and autoimmune diabetes. It is mandatory monitoring hormonal function with an "endocrinological blood assessment" containing TSH; Free T4, baseline serum cortisol, sodium, potassium and baseline glucose, before and during treatment with immunotherapy.

Along the treatment, the patient and the oncology team should be educated on recognizing clinical signs and symptoms suggestive endocrinopathies in order to detect and treat them promptly:

- Fatigue / hypotension / sudden headache / abdominal pain /nausea / vomiting -> suspected diagnosis of: hypophysitis / adrenal insufficiency. Contact with endocrinologist and assess baseline pituitary hormones and baseline cortisol.
- Tachycardia/ tremor/ weight loss/ sweating -> suspected diagnosis of: hyperthyroidism. Assess TSH, free T4. If abnormal, contact with endocrinologist.
- Fatigue/edema / constipation / cold / drowsiness -> suspected diagnosis of: hypothyroidism. Assess TSH, free T4. If abnormal, contact with endocrinologist.
- Polyuria / polydipsia / hyperglycemia -> suspected diagnosis of diabetes/ hypophysitis. Contact with endocrinologist. Assess baseline pituitary hormones, baseline cortisol and monitoring glucose.

Immune induced hypophysitis

Hypophysitis induced by ICI appears most often in men over the age of 60 years and in patients treated with anti CTLA4 (ipilimumab) alone or in combination with nivolumab. The prevalence varies between 4-20%, increasing in combined therapy. The pathophysiological mechanisms are not completely understood. In mice models of

hypophysitis treated with anti CTLA-4, lymphocyte infiltration of pituitary gland and the expression of CTL4-antigen on pituitary cells have been reported.

Clinical manifestations are often non-specific. The most frequent signs are headache and fatigue. Hyponatremia is present in almost 50% of the patients. Polyuric-polydipsic syndrome (diabetes insipidus) is very rare. Hormonal deficiencies are often multiples at the time of diagnosis: central hypothyroidism and central hypogonadism almost in 100% of the patients, hypoprolactinemia in 96%, ACTH insufficiency with adrenal insufficiency in 50% and GH insufficiency in 17% of cases. Recovery from hormonal deficiencies is variable and new deficiencies can appear along the follow up. ACTH insufficiency with chronic adrenal insufficiency persists in 86-100% of the cases, and patients require chronic therapy with hydrocortisone.

Pituitary RMI is the most sensitive imaging for diagnosis. In 30-100% of cases shows a moderate increase in pituitary volume and enlargement of the pituitary salk suggestive of hypophysitis. These findings are transitory and after 4-12 weeks pituitary RMI return to normality.

High-dose corticosteroids are not systematically recommended to treat hypophysitis. (It may be suggested in patients presenting with major headaches, visual aberrations or other severe symptoms).

Treatment of hormonal deficiencies:

- Acute adrenal insufficiency -> In case of signs of acute adrenal insufficiency (dehidratation, hypotension, tachycardia, hyponatremia…) emergency therapy with endovenous hydrocortisone + fluid therapy should be started.
- Chronic adrenal insufficiency -> (Low cortisol value with minor signs of no signs of adrenal insufficiency), therapy with oral hydrocortisone 15-30mg/day should be started.
- Hypothyroidism -> New assessment of thyroid function after 1-2 months, then treatment with levothyroxine should be considered on a case-to-case basis.
- Hypogonadism -> Assess gonadal function after 2-3months and then consider replacement therapy in the absence of oncological contraindication.

Thyroid dysfunction induced by immunotherapy

The thyroid gland is a common site for irAEs. The risk of thyroid dysfunction (TD) is higher in patients treated with antiPD1 alone or in combination with antiCTLA4, with an overall incidence of TD ranging from 4 to 21%. The TD includes hypothyroidism and thyrotoxicosis, which are generally mild to moderate. The cause of TD induced by targeting PD-1, as well as the timing, pattern of the TD and prognosis of patients who develop TD remain unclear. The most common TD consists of silent inflammatory thyroiditis with a transient thyrotoxicosis followed by hypothyroidism. Most of the cases are mild and do not require replacement therapy. Treatment of TD depends on the clinical severity and etiological diagnosis and it must be decided on agreement between the

endocrinologist and the oncologist. Assessment of thyroid function (TSH; free T4) at baseline and before each cycle during the first 6 months and then every 3-6 months is recommended.

large number of immunotherapy drugs approved as single agents in many different tumor types, but it is expected that there will be more new approvals of combinatory regimes in a forthcoming future. Indeed, combinations of immunotherapies with other agents have already been approved in melanoma, renal cell carcinoma or non-small cell lung cancer. Therefore, it is crucial that any healthcare professional involved in the care of cancer patients treated with immunotherapy is aware of these side effects and have enough knowledge to treat them or to refer the patient where appropriate.

The usual first treatment of severe immune-related adverse events is the administration of steroids, initially orally or intravenously in case that the toxicity is not improved or resolved after 48-72 hours of oral treatment. If toxicity persists in spite of several days of intravenous treatment, more potent immunosuppression drugs such as infliximab, mycophenolate or tocilizumab should be considered. Given the complexity of the management of some of these side effects and the potential life-threatening consequences of some of them, the involvement of a wide array of different medical specialities other than medical oncologists is essential in order to provide an optimal care to our cancer patients treated with immunotherapy.