

REVIEW

Endocrine toxicity of cancer immunotherapy: clinical challenges

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Abstract

Immune checkpoint inhibitors are now widely used in the treatment of multiple cancers. The major toxicities of these treatments are termed immune-related adverse events and endocrine dysfunction is common. Thyroid disease, hypopituitarism and a form of diabetes resembling type 1 diabetes are now all well described, with different patterns emerging with different checkpoint inhibitors. We review the presentation and management of the common endocrine immune-related adverse events, and discuss a number of recent advances in the understanding of these important, potentially life threatening toxicities. We also discuss some remaining dilemmas in management.

Key Words

- ▶ checkpoint inhibitor
- ▶ cancer
- ▶ thyroiditis
- ▶ hypophysitis
- ▶ diabetes

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Introduction

Immunotherapy with immune checkpoint inhibitors (CPI's) has been revolutionising the management of advanced malignancies with their success in improving overall patient survival (1, 2). CPI's are antibodies that block T-cell signalling pathways, that otherwise suppress immune responses to cancer cells, thereby acting to promote an anti-tumour immune response. Current agents are monoclonal antibodies targeting either cytotoxic T lymphocyte antigen 4 (anti-CTLA4), programmed cell death-1 (anti-PD-1) or its ligand PD-L1 (anti-PD-L1) to potentiate anti-tumour immune responses. Such is their success, they have now become first-line therapy for metastatic melanoma, non-small cell lung cancer and renal cell carcinoma (3). They are now licensed for use in multiple other cancers, including Head and Neck cancers.

Unfortunately superior clinical response is often associated with treatment toxicity termed immune-related adverse effects (IRAEs) and can involve multiple organs including skin, lung, liver and bowel (4). Whilst the exact mechanism of these toxicities is not yet fully understood, it is thought to involve a reduction in tolerance, through inhibition of the immune

checkpoints, resulting in autoimmunity towards normal tissues (Fig. 1). Side effects can range from mild to life threatening. The latter can include severe colitis, pneumonitis and cardiomyopathies (5). Whilst in mild cases treatment can often continue, the mainstay of moderate and severe IRAE's involves cessation of CPI therapy and immunosuppression with glucocorticoids as first-line agents (5).

Adverse effects have been reported more frequently with CTLA-4 inhibitors (e.g. ipilimumab) vs PD-1 inhibitors (e.g. pembrolizumab, nivolumab). Whilst it has been shown that combination therapy with both agents show superior response rates, but also carries a greater risk of such IRAE's (6).

Endocrinopathy has emerged as an important group of IRAEs. Importantly, whilst most IRAE's are reversible with prompt treatment cessation and glucocorticoids treatment, endocrinopathies usually persist and often require lifelong hormonal replacement. Untreated endocrinopathy can be life threatening. Whilst both CTLA-4 and PD-1 inhibitors are associated most commonly with thyroid dysfunction, hypophysitis resulting in adrenal insufficiency, and insulin-dependent

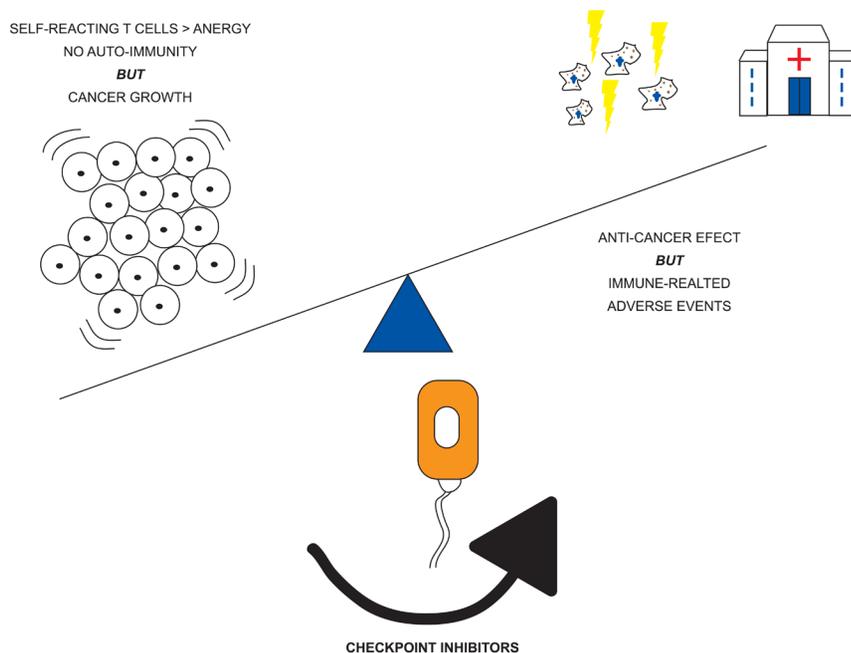


Figure 1

Graphic illustrating checkpoint inhibitor action to shift immune response. Without treatment self and tumour reacting T-cells are driven to anergy and unchecked tumour growth. Following treatment, the anti-cancer immune response is upregulated leading to controlled tumour growth, but increased risk of self-reacting T cells contributing to immune-related adverse events.

diabetes also occur (7). Detection of endocrinopathy can be difficult given their subtle, non-specific symptoms such as fatigue and may be a challenge to distinguish them from pre-existing comorbidities. Therefore clinicians need to be vigilant to ensure rapid recognition and treatment, especially in those individuals with increased risk of autoimmune reactions. The major endocrine toxicities from checkpoint inhibitors and their management are summarised in Table 1.

This review will focus on recent advances in our knowledge of endocrinopathy following checkpoint inhibitor therapy. Current areas of clinical uncertainty, ongoing controversies and changes in the management approaches will be discussed.

Pituitary

Two distinct patterns of pituitary involvement have been described. Patients treated with the CTLA-4 inhibitor Ipilimumab can develop hypophysitis in around 10% of cases, which can present with the classical features of headache, fatigue and pituitary enlargement seen on brain imaging (8, 9, 10, 11, 12). Pituitary dysfunction is variable but ACTH deficiency seems essentially universal (13, 14). In contrast, the PD-1 and PD-L1 inhibitors result less commonly in pituitary involvement (~1%), and are reported to result in isolated ACTH deficiency, without other features of hypophysitis (15, 16). However the literature can be confusing, as hypopituitarism and hypophysitis are

frequently used interchangeably (17) and there is a need for standardised case definitions (16).

Role for high dose steroids and management of hypopituitarism

By extrapolation from other inflammatory pituitary conditions, initially patients presenting with ipilimumab-induced hypophysitis were initially treated with high dose glucocorticoids (typically 1mg/kg of methylprednisolone). In addition, early case reports frequently described pituitary enlargement on MRI associated with headache (18, 19, 20, 21, 22), so glucocorticoids may have been indicated to prevent further pituitary enlargement. When patients present with signs or symptoms of adrenal insufficiency, stress doses of glucocorticoids are also indicated (23).

However, there is now evidence that treatment with high dose glucocorticoids does not improve pituitary function (24). More concerning, melanoma patients with ipilimumab-induced hypophysitis treated with high dose glucocorticoids had worse oncological outcomes than those receiving replacement doses. There was a shorter time to treatment failure and overall survival in those receiving high dose steroids (25). This is notable as studies in patients with non-endocrine immune-related toxicity have not shown an association with the use of high dose steroids and oncological outcomes (26).

Therefore current practice is to reserve high dose corticosteroids for those presenting with adrenal crisis

Table 1 Summary of checkpoint inhibitor-induced endocrinopathy.

Endocrinopathy	Incidence + timing of onset	Precipitating therapies	Symptoms	Investigations	Indications for treatment	Treatment
Pituitary	11–24% (8, 9, 81) (with anti-CTLA4)	Predominantly anti-CTLA4 (8, 9, 81)	Headache, fatigue, weakness, nausea, weight loss, temperature intolerance, arthralgia	Pituitary hormone profile, sodium level, visual fields Pituitary MRI	Severe headache, hyponatraemia, hypopituitarism or pituitary enlargement seen on MRI (18, 19, 20, 21, 22)	High dose glucocorticoids if pituitary enlargement (24, 25)
Thyroid dysfunction	<1% (8, 9, 44, 49) (with anti-PD-1) Usually 6–14 weeks after treatment	Rarely seen with anti-PD-1 – mostly cause ACTH deficiency (8, 9, 44, 49)	May present with hyperthyroidism symptoms prior to becoming hypothyroid (lethargy, constipation, cold intolerance, etc.)	Thyroid hormone profile	Hypothyroidism Thyrototoxicosis	Hormone replacement (24, 25) (hydrocortisone or prednisolone ± levothyroxine/oestrogen/testosterone) Thyroid hormone replacement Consider beta blockers for palpitations (23) Anti-thyroid drugs only in Graves' disease (51, 52, 53, 54, 55) High dose steroids if severe thyroiditis seen (49)
Hyperglycaemia and new-onset diabetes	5.2–8% overall (8, 9, 49, 50) 5.2–5.9% (8, 9) (with anti-CTLA4) 5–8% (49) (with anti-PD-1) 14–20% (combined therapy) (49, 50)	More commonly seen in anti-PD-1 or anti-PD-L1 therapies (49, 50) Seen less commonly in anti-CTLA-4 therapy (8, 9)	Polydipsia, polyuria, weight loss	Hyperglycaemia on fasting and random glucose samples, HbA1c	Persistent hyperglycaemia, diabetic ketoacidosis	Exogenous insulin replacement (usually lifelong) (62)
Primary Adrenal insufficiency	Usually 1–3 months after treatment Approximately 1% (59) Presents usually within 3 months of therapy Very rare, only a few case reports published (16, 23, 36, 40)	Anti-PD-1/PD-L1 (58, 61, 62) Not reported with anti-CTLA therapies (58) Anti-CTLA-4 therapy or Anti-PD-1 (16, 40)	Typical Addisonian symptoms	Cortisol, ACTH, plasma renin	Treatment indicated in all cases	Hydrocortisone + Fludrocortisone (23, 27)

or with significant pituitary enlargement. Other patients can be commenced directly on replacement doses of corticosteroids (e.g. hydrocortisone 20 mg daily in divided doses or prednisolone 3 mg once daily (27)). Indeed there are now reports of the safety of managing such patients on an out-patient basis (28).

Thyroxine is replaced by standard approaches, following glucocorticoids, and testosterone or oestrogen replacement may also be required. Notably growth hormone replacement is contra-indicated in those with active or recent history of cancer (29), so assessment of growth hormone levels is not recommended.

Prediction of hypophysitis

Given the potentially severe impact of hypopituitarism and adrenal insufficiency, early detection of hypophysitis is vital. There has therefore been interest in biomarkers to predict its onset. The summary of product characteristics for checkpoint inhibitor recommend regular testing of thyroid function during treatment. Attempting to predict the onset of hypophysitis with subtle changes to thyroid function tests has been examined. Two studies have described a fall in TSH in the cycle of treatment prior to the onset of ipilimumab-induced hypophysitis (9, 30), although a larger series showed that a fall in free T4 at cycle 3 of ipilimumab had the best predictive value for subsequent hypophysitis (13). The later study used a clinical definition of hypophysitis that required at least one other feature apart from secondary hypothyroidism, confirming that a fall in T4 levels may precede hypophysitis. However, as pituitary involvement in PD-1/PD-L1 inhibitor therapy is usually limited to ACTH deficiency, thyroid function would not be expected to be a useful predictor in this cohort.

The development of autoantibodies has been described in a number of IRAEs, including diabetes and hypophysitis (31, 32, 33). Two studies have now reported the development of auto-antibodies in hypophysitis (34, 35), although notably there was no common antibodies described, and both studies included patients with both ipilimumab hypophysitis and the more limited ACTH deficiency with nivolumab or pembrolizumab. A further study suggested that hypophysitis was more common in certain HLA types, most notably DR15 (36), although again the hypophysitis cohort was heterogeneous.

Currently, there are no reliable biomarkers for risk of hypophysitis, and given the protean presentation of hypopituitarism, adrenal insufficiency and hypophysitis, careful clinical assessment is required (9, 23, 37).

Longer term prognosis of hypophysitis

To date, most series have not reported recovery of ACTH function, although recovery of other pituitary axis is reported (9, 37, 38). As discussed previously, high dose steroids do not improve pituitary function recovery (24). Nevertheless there have been occasional reports of spontaneous recovery of pituitary function, including ACTH secretion (39, 40), so clinical and biochemical assessment over time is advised.

A third of patients receiving a CPI will require high dose glucocorticoids for management of non-endocrine IRAs, at doses associated with adrenal suppression (26, 41). Therefore, caution is also required when stopping glucocorticoids in these patients in case of the development of ACTH deficiency.

Thyroid

The thyroid is the most common endocrine gland to be affected by checkpoint inhibitors, with PD-1 and PD-L1 inhibitors showing a higher rate of clinically overt disease than ipilimumab (42, 43, 44). Hypothyroidism is common, as is transient thyrotoxicosis, usually, but not always, followed by subsequent hypothyroidism. Hypothyroidism is managed with levothyroxine replacement as per standard practice. Hyperthyroidism can usually be managed symptomatically with beta blockers, although steroids are occasionally required, with close monitoring for progression to hypothyroidism (23).

Although symptoms should prompt assessment, thyroid dysfunction is usually detected on routine treatment monitoring blood tests. Both a higher patient BMI or a higher baseline TSH may be associated with an increased risk of thyroid dysfunction (43, 45). Prior use of a tyrosine kinase inhibitor also increases the risk of thyroid dysfunction (46). Raised levels of cytokines including IL-1 β and IL-2 pre-treatment, as well as an early rise in thyroglobulin have been reported to predict thyroiditis (47), although the clinical utility of these markers is unclear. FDG-PET uptake in the thyroid is also associated with subsequent hypothyroidism (48).

Notably, whilst onset can occur as early as 3 weeks post therapy initiation, most cases present 1–2 months following but it has been shown to present as late as 3 years (49, 50).

Thyroiditis vs Graves'

The main clinical challenge in thyroid practice is detecting the rare patient with Graves' disease and distinguishing

this from the more common thyroiditis (51, 52, 53), which has been described with both PD-1 and CTLA-4 inhibitors. Those with thyrotoxicosis should therefore be investigated with TSH Receptor antibodies and clinicians should consider an uptake scan to distinguish Graves' from destructive thyroiditis, taking into account that many patients will have received recent intravenous iodine contrast. However, as the thyrotoxicosis in thyroiditis is usually short lived, these investigations may only be required in prolonged thyrotoxicosis (23). The presence of thyroid eye disease may also alert the clinician to the possibility of Graves' as a cause of thyrotoxicosis (54, 55). First-line management is with anti-thyroid drugs such as carbimazole.

Diabetes

A form of insulin-requiring diabetes is described in around 1–2% of patients receiving PD-1 or PD-L1 inhibitors, alone or in combination with ipilimumab (33, 56, 57, 58, 59). Features closely resemble Type 1 diabetes, with low c-peptide levels, whilst GAD antibodies are present in around 50% of cases, a notably lower proportion than in spontaneous type 1 diabetes (59, 60).

Several case studies demonstrate that patients given anti-PD-1 therapy present with either severe hyperglycaemia or more commonly, diabetic ketoacidosis (DKA) (58, 61). A large scale review of 71 case reports found that 76% presented with DKA with a mean capillary blood glucose of 33.4 ± 11.5 mmol/L and HbA1c of 62 ± 0.3 mmol/mol (62). 71% of cases developed within 3 months of first exposure to anti-PD-1 or anti-PD-L1 therapy. However, this review found no correlation between HbA1c and time of diabetes diagnosis.

Notably the onset is frequently rapid, with some showing features compatible with fulminant type 1 diabetes, progressing from euglycaemia to DKA in a matter of days (63, 64, 65, 66, 67, 68, 69, 70, 71). Whilst those with very rapid onset are less likely to have classical diabetes autoantibodies, and frequently show elevations of pancreatic enzymes (60), other case series have suggested that autoantibodies were in fact associated with a shorter onset of diabetes (62). Therefore the clinical utility of autoantibodies is unclear, and close attention to any red flag symptoms such as fatigue, thirst or polyuria is required, with prompt assessment of glucose and ketones to try to avoid missing a diagnosis of DKA. Pre-existing type 2 diabetes may be a risk factor for CPI-induced diabetes,

- Checkpoint inhibitors (CPIs) are now widely used in oncology treatment however, their use is often associated with treatment toxicity termed ‘immune related adverse events’ (IRAE).
- Endocrinopathies are amongst the more common IRAEs and usually result in long term hormone deficiencies.
- Detection of endocrinopathy may be challenging due to subtle, non specific symptoms (see Table 1).
- **Pituitary dysfunction** can either be seen as an isolated ACTH deficiency or a more classical hypophysitis (hypopituitarism, headaches, ± pituitary enlargement) with PD-L1 and CTLA4 inhibitors respectively.
- High dose glucocorticoids do not improve immunotherapy-induced hypophysitis and may result in worse oncological outcomes versus those receiving only physiological replacement.
- **Hypothyroidism and transient thyrotoxicosis**, followed by hypothyroidism, is the most common endocrinopathy caused by CPIs.
- Distinguishing between thyroiditis associated with CPIs and Grave’s disease can be challenging and may require TSH receptor antibody levels and uptake scans to determine diagnosis.
- **Insulin-requiring diabetes** has been described with anti-PD1 therapy and may first present with rapid onset diabetic ketoacidosis (DKA).
- A third of patients receiving CPIs require high dose steroids for non-endocrine IRAEs and therefore deteriorating hyperglycaemia needs careful evaluation to determine whether it is steroid-induced or CPI-induced.
- Development of endocrinopathy is associated with longer overall survival versus those patients without and therefore, lifelong hormonal treatment with specialist care from both endocrinologists and oncologists is required.

with 7–10% of those with type 2 diabetes showing deterioration in control, often requiring insulin (56).

Corticosteroids do not prevent progression to insulin deficiency (72), although insulin deficiency is not universal with one case describing preservation of insulin secretion after cessation of the checkpoint inhibitor (73), and one patient with prior IA2 antibodies able to come off insulin (32).

Steroids and CPI diabetes

A potential confounder is that around 30% of patients receiving CPIs will require high dose steroids for non-endocrine IRAEs (26, 41), with studies suggest that 6–8% of CPI treated patients go on to develop steroid-induced hyperglycaemia (41, 74). As such, patients with new-onset or deteriorating hyperglycaemia after CPI treatment need careful evaluation, including a history of steroid use and assessment for ketosis to ensure that CPI-induced diabetes is not missed, placing patients at particular risk of DKA.

Clinical presentation

Importance of fatigue as red flag

Fatigue is a common symptom in cancer, also being frequent with conventional treatments such as cytotoxic chemotherapy. Close to 40% of patients treated with

PD-1/PD-L1 inhibitors have been reported to have fatigue (75), most of whom will not have endocrinopathy. However, fatigue can also be a presentation of adrenal insufficiency (either primary or due to pituitary involvement), thyroid dysfunction and diabetes. As adrenal insufficiency and diabetes leading to DKA can be life threatening, it is vital that onset of fatigue in patients who have received a checkpoint inhibitor leads to prompt investigation for endocrinopathy.

Equally though, it is important to recognise that fatigue can occur, as a result of cancer or its treatment, without endocrine dysfunction, so a thorough evaluation is required before starting hormone replacement.

Long term implications

Unlike most other IRAEs, endocrinopathy is usually non-reversible and is expected to require long term hormone replacement. Hypopituitarism is associated with reduced quality of life, although careful avoidance of over-replacement with glucocorticoids improves this (76). Type 1 diabetes is also well known to be associated with reduced quality of life (77). Both conditions need life long specialist care.

This is particularly important as it is now emerging that the development of endocrinopathy, specifically hypophysitis or thyroid dysfunction, is associated with

better cancer outcomes and longer overall survival than controls without endocrinopathy (78, 79, 80). Therefore the cohort of long term survivors is likely to include many with endocrinopathy, with the associated need for hormone replacement, impact on quality of life and need for specialist follow up.

Conclusions

Endocrine dysfunction is among the more frequent immune-related adverse events following checkpoint inhibitor treatment, usually resulting in life long hormone deficiencies. The presentation can be subtle, and a careful endocrine assessment of patients presenting with red-flag symptoms including fatigue is required. Those with confirmed endocrinopathy, especially adrenal insufficiency and diabetes, need ongoing endocrine input to optimise treatment.

Declaration of interest

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