CANCER EDUCATION DAY

Endocrine Toxicities of Cancer Immunotherapy

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- To provide a practical approach for clinicians regarding the management of patients with immune checkpoint inhibitor (ICI)mediated-endocrinopathies
- References:
- American Association of Clinical Endocrinology Disease State Clinical Review Evaluation and Management of Immune Checkpoint Inhibitor-Mediated Endocrinopathies – Elsevier, 2022
- Endocrine toxicity of cancer immunotherapy: Clinical challenges Endocrine Connections, 2021

Immunotherapy for Malignancies

- In recent years, increasing nr. of cancer patients are being treated with immunotherapies/immune checkpoint inhibitors
- Immune checkpoint inhibitors (ICI) = monoclonal antibodies that BLOCK T cell signaling pathways that otherwise SUPPRESS immune responses to cancer cells
- The result is an ACTIVATION of the T cells which will create an ANTI-TUMOR immune response resulting in destruction of the cancer cells
- BUT... this also results in an enhanced auto-immune & destructive response towards *normal* tissues

Immune checkpoint inhibitors

- First line treatment for metastatic melanoma, non-small cell lung cancer and renal cell carcinoma
- Multiple other cancers bladder cancer, hepato-cellular cancer, etc
- The drugs more often implicated:
- CTLA-4 inhibitors Ipilimumab
- PD-1 or PDL-1 inhibitors Pembrolizumab, Nivolumab, Durvalumab
- Combination CTLA 4 + PD-1

Endocrinopathies as Adverse Effect

- Endocrinopathies are among the more common immune AE of immunotherapies can affect skin, lung, liver, CVS, kidneys, eyes, etc
- Diagnostic challenge can present with subtle & nonspecific symptoms – fatigue
- Are generally persistent and require life-long hormonal replacement
- Development of an endocrinopathy is associated with longer survival versus in those patients without
- The pattern of endocrinopathy tends to be different between the 2 classes of drugs

M. R.

- 62 y old woman first seen Nov 2023
- Metastatic renal cell Ca with lung mets 2022 right nephrectomy
- Tx: Nivolumab D/C Aug 2023 due to severe skin reaction/sepsis and hospital admission
- October: C/o nausea, vomiting, no appetite, 20 lb weight loss and "slow mind"
- TSH 49.3 (0.3-5), free T4 2 (9-21)
- Cortisol 19 (135-537), ACTH <0.7, Estradiol <55, FSH 46 (menopausal >16), Hb A1C 5.4, Na 138, creatinine 92
- ? Diagnosis

- 65 y old woman seen at MET Campus Aug 2021
- Metastatic malignant melanoma lymph nodes, brain, bones
- Immunotherapy with Ipilimumab and Nivo
- Normal BG/labs July 2021 no hx of diabetes
- 3 w later Presents in critical condition with severe nausea, vomiting, severe metabolic acidosis, altered LOC
- BG > 80, Ph <7, K 7.6, high anion gap, serum ketones
- ? Diagnosis

Endocrinopathies

- Thyroid dysfunction hypothyroidism and hyperthyroidism
- Isolated Central adrenal insufficiency
- Pituitary dysfunction/Hypophysitis (more rare)
- Insulin-dependent Diabetes Mellitus

Thyroid dysfunction

- Most commonly seen endocrinopathy
- Hypothyroidism more common than hyperthyroidism
- Can occur in up to 30% patients
- More commonly seen with PD-1 inhibitors Pembro and Nivo
- Generally the immunotherapy does not have to be interrupted

Hypothyroidism

- More common in women
- Symptomatic fatigue, weakness, cold intolerance
- Or more commonly detected on routine blood work
- TSH and free T4 at baseline and every 1-2 cycles
- Elevated TSH and low or normal Free T4 and Free T3
- Onset is variable 5-9 months or anywhere 3 weeks-3 years
- Elevated Thyroid antibodies: Anti-TPO and anti-Tg
- Replacement with levothyroxine max 1.5 mcg/kg ideal body weight

Hyperthyroidism/Thyrotoxicosis

- Palpitations, heat intolerance, tremors, tachycardia, weight loss, etc.
- Same principles as in non-cancer pts: Low-suppressed TSH and elevated Free T4
- 2 types:
- **1. Thyroiditis** destructive inflammation of the thyroid gland release of thyroid hormones in bloodstream
- 2. Graves-like picture overproduction of thyroid hormones
- Treatment is DIFFERENT

Thyrotoxicosis

- THYROIDITIS is more common
- Hyperthyroidism followed by hypothyroidism destruction of thyroid tissue
- Low or zero uptake on I-131 scan
- GRAVES-LIKE PICTURE less common, also less typical eye findings
- Elevated I-131 Uptake
- *Positive TSH-receptor antibodies*
- Ultrasound not very helpful "inflammation/thyroiditis"

Thyroiditis treatment

- Beta blockers if symptomatic
- Short course of glucocorticoids
- No role for anti-thyroid drugs the thyrotoxic phase is SELF-LIMITED
- Patients will then become hypothyroid treatment with Levothyroxine

Graves disease treatment

- Beta blockers symptomatic treatment
- Antithyroid drugs : Methimazole preferred over PTU (liver toxicity)
- Thyroid storm is rare treatment is per standard guidelines

Pituitary disease

- 10-25% patients
- Isolated ACTH deficiency more common PD-1 or PDL-1 inhibitors
- Adrenal insufficiency of central (pituitary) origin
- *Hypophysitis* more rare CTLA-4 inhibitors Ipilimumab
- Headache, fatigue and pituitary enlargement causing visual deficits seen on MRI imaging
- Multiple hormonal deficiencies

Central Adrenal Insufficiency

- Nausea, vomiting, lack of appetite, fatigue, weakness
- Low 8 am morning CORTISOL NOT accurate if pt received Steroids/Dex
- Low ACTH
- If ACTH is high: PRIMARY adrenal problem bilateral adrenal mets/adrenalitis
- ACTH stimulation test is not useful in acute situations
- Treatment:
- Replacement dose of Hydrocortisone 15-25 mg daily or Prednisone 5-7.5 mg daily
- 20 mg Hydrocortisone = 5 mg Prednisone (1:4 ratio)
- Treatment of adrenal crisis

Hypophysitis

- More generalized PITUITARY inflammation
- Central AI
- Central Hypothyroidism
- Central Hypogonadism
- Check 8 am serum cortisol, ACTH, TSH, Free T4 all low
- Estrogen, testosterone levels low, also low FSH and LH
- Electrolytes, serum and urine osmolarity DI is very rare
- MRI for pituitary imaging

Hypophysitis

- Treatment with high-dose steroids Solumedrol did not help recover pituitary function
- Melanoma patients treated this way had worse oncological outcomes
- High dose steroids is reserved for patients in *adrenal crisis or with significant pituitary enlargement*
- Replacement dose glucocorticoids Hydrocortisone 15-25 mg daily in divided doses
- Thyroid replacement
- Estrogen and testosterone replacement (not acutely)
- ! Always replace glucocorticoids first to avoid adrenal crisis
- Generally irreversible

Diabetes

- Insulin dependent Type 1 DM-like picture
- Rare 1-2% patients
- Mostly/only seen with PD-1 inhibitors Pembro or Nivo
- Tends to occur in the first 3 months of immunotherapy
- Rapid onset of severe hyperglycemia in a matter of days!!
- DKA acute & profound insulin deficiency "fulminant presentation"
- Patients require insulin therapy as in DM1
- The need for insulin is irreversible

Diabetes

- Immunotherapy can also worsen glycemic control for patients with pre-existing DM
- Also Steroids effect! High dose Dexamethasone
- 1/3 patients on immunotherapy require high dose steroids for management of non-endocrine side-effects
- Fasting glucose and HbA1C should be done before immunotherapy and repeated with every cycle
- Patients should be informed and educated regarding the negative effects of cancer treatment on BG

Our patients

- M.R.
- Combined hypothyroidism and central adrenal insufficiency (isolated ACTH deficiency)
- Started on Prednisone 5 mg am and 2.5 mg pm
- Synthroid 125 mcg daily
- Regular F/UP
- C.C.
- Severe DKA secondary to newly dgn insulin-dependent DM
- Started on insulin 4 injections/daily, DM education, Referral to Diabetes Wellness and regular follow-up

Summary

- The success of immunotherapy has transformed the oncological treatment of various cancers in recent era
- This frequently results in immune-mediated endocrinopathies that can cause acute and persistent morbidity and rarely death
- Patients benefit from a HIGH INDEX OF CLINICAL SUSPICION by all the health-care providers when it comes to diagnosis and a MULTIDISCIPLINARY approach for evaluation and treatment