Endocrine Care of Oncology Patients

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Endocrine Neoplasia and Hormonal Disorders
MD Anderson Cancer Center
AACE PNW Annual Meeting
10/14/2017
Disclosures

• Nothing to Disclose
Endocrinology and Cancer – a management spectrum

• Primary endocrine tumors
  • Hormone secreting or non-secreting
• Glands resected/damaged by cancer/treatment
  • Hypothyroidism, hypoparathyroidism, adrenal insufficiency, etc.

   • Endocrine Effects of Cancer Therapy
     • Fertility, hyperglycemia, hyperlipidemia, hypothyroidism, bone health

• Paraneoplastic Syndromes from non-endocrine cancers
  • Hypercalcemia of malignancy, SIADH, Cushing’s syndrome
Endocrinologist’s role for a cancer patient

• Patient’s focus is usually cancer & treatment not their endocrine disorder
• Depends on overall goals of cancer care
• Improve quality of life without excessive burden of treatment
• Improve patient safety
• Take time/burden of management off of oncology team
• Keep in clinical trials
Case 1

- 54 y/o man with a longstanding cheek mole which became ulcerated
- Diagnosed as melanoma, resected without evidence of disease at margins
- 1 year later new lung nodule noted on chest x-ray
- Referred for CT: 1.6 cm R lower lobe nodule. CT guided biopsy confirms metastatic melanoma
- Diagnosed with type 2 diabetes and hypertriglyceridermia during this time
- What is his likely therapy?
Melanoma Therapy

- Historically few options
  - Immune modulation with cytokine therapy – IL-2, Interferon alfa
  - Cytotoxic chemotherapy
- New targeted therapies show promise but still significant toxicity
- Immunotherapy has been revolutionary
  - Relatively low toxicity compared to prior treatments
  - Treating at earlier stages than in the past
Case 1

• Enrolled in a clinical trial using epacadostat (IDO1) and durvalumab (anti PDL-1) every 2 weeks.
• On enrollment he had blood glucose of 290, had discontinued his diabetes medications, told to restart.
• 1 month later presents for cycle 3 with blood glucose 422 mg/dL
• Referred for urgent evaluation
Diabetes history

- Diagnosed ~1 year ago when he had high blood glucose and triglycerides at PCPs office
- Started on saxagliptin/metformin XR 5/1000 mg combination and vascepa 2 capsules twice daily
- Reports on this his blood glucose trended down to low to mid 100s, rarely 200s
- Ran out of medication the past week, he was taking twice daily instead of daily and ran out early
- Ate a carbohydrate heavy dinner (with beers) the night before
In office

- Repeat finger stick glucose: 299 mg/dL
- Point of care hemoglobin A1c: 8.2%
- Asymptomatic, feels these BG are out of the ordinary but they have been this high off of treatment in the past
- Last blood glucose on prior visit: 182 mg/dL
What would you do?

- A. Admit for observation and treatment
- B. Start basal/bolus insulin this visit
- C. Check c-peptide and insulin levels
- D. Restart home medications and discharge
Labs

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BG spontaneously decreased to 260
Insulin: 18.4 mIU/mL (2-29.1)
C-peptide: 2.6 ng/mL (0.9-7.1)

Should his treatment be held?
Case 1

• No outside records available
• Given insulin in clinic for acute hyperglycemia, new prescription for maximum dose saxagliptin and metformin
• Told to start today, contact us if BG don’t normalize
• Warned about DKA symptoms
• Blood sugars improved the following day and received his scheduled treatment
10 days later

- Presented to local ED with persistent nausea vomiting
- Bicarbonate: 9 mEq/L
- Anion Gap: 34
- 4 + urine ketones
- Given fluids, IV insulin and 10 units of glargine
- Discharged home with metformin and glipizide (didn’t fill)
2 days later

- Returned to local Emergency Department
- Bicarbonate: 5 mEq/L
- Kept on insulin drip and discharged home with Determir 10 units twice daily
- Returned for follow-up 1 week later
- C-peptide: <0.1 ng/mL
- Anti-GAD65: 0.12 nmol/L (<0.02)
- Anti-IA-2: negative
- Repeat C-peptide 10 months later: <0.1
Immunotherapy Induced Diabetes

• More typical case:

• Working definition: rapid onset of insulin requirement with or without history of diabetes

• Our case: LADA accelerated by immunotherapy?
  • On follow-up (with wife) BG not well controlled on oral therapy, frequent post-prandial spikes, relatively rapid onset
• T-cell needs co-stimulation to activate. Suppressive signals prevent autoimmunity

• By inhibiting this signal we can increase response to cancer “neoantigens”
Currently Available agents

• CTLA-4
  • Ipilimumab (Yervoy) – FDA approved: malignant melanoma
  • Tremelimumab – In studies for melanoma and mesothelioma (orphan)

• PD-1
  • Pembrolizumab (Keytruda) – NSCLC, Head and Neck SCC, Hodgkin’s lymphoma, Gastric. 5/2017: any tumor with high microsatellite instability.
  • Nivolumab (Opdivo) – melanoma, NSCLC, RCC, Hodgkin’s lymphoma, urothelial, H&N SCC

• PD-L1
  • Durvalumab – Pending FDA approval for urothelial
  • Atezolizumab (Tecentriq) – Urothelial and NSCLC (Failed some Phase 3 trials)
  • Avelumab (Bavencio) – Merkel cell carcinoma
Immune related adverse events

• Induction of autoimmunity due to decreased self tolerance
  • Normal proteins become antigens
  • Analogues of many autoimmune diseases have been reported
• Wide variety of IRAEs with more cases still being reported
• Most treated with holding treatment and courses of steroids
  • Colitis
  • Arthritis
  • Dermatitis
More on the way!

The history of PD-1 signal

- 1992: Discovery of PD-1
- 1999: PD-1 KO mouse → autoimmunity
- 2002: PD-1 blocking → anticancer effect in mice
- 2006: FIM Nivolumab
- 2007: FIM Pidilizumab
- 2009: FIM BMS-936559
- 2011: Kyoto Nivolumab trial
- 2011: FIM Pembrolizumab
- 2014: approved Pembrolizumab
- 2014: approved Nivolumab
- 2016: approved Atezolizumab

PD-L1, PD-L2
Reported cases

• Multiple small case series/case reports
• Seen only with PD-1, PD-L1 therapy, no reported cases with CTLA-4
• Infrequent, rarely identified in the initial clinical trials
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<tr>
<th>Study</th>
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<th>Endocrinopathy</th>
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Risk Factors

- Positive GAD65 antibodies in roughly half of currently reported cases
  - Titers highly variable
- HLA haplotypes associated with type 1 diabetes presents in most tested
  - A2.1, DR4
- No known practical screening test to estimate risk
- Were cases missed/misdiagnosed in initial studies?

Common trends

• Small uptrend prior to severe hyperglycemia

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- 93 *
- 113 *
- 103 *
- 91 *
- 100 *
- 117 *
- 285 *

• Most progress rapidly to undetectable c-peptide regardless of whether therapy is held

• One case report of a patient able to discontinue insulin after 55 days
  - Never developed undetectable c-peptide

What don’t we know?

• Do other agents amplify risk?
  • Immunotherapy often given in combination, new agents in development

• Should we screen for positive antibodies or high risk HLA haplotype prior to therapy?
  • Limited options at this time – more immunotherapy agents in the future

• Does holding therapy influence outcome?

• Does presence of an IRAE increase risk of having another or change cancer outcome?
Other Endocrine IRAEs

• Seem to be divided by medication class:
  • CTLA-4
    • Hypophysitis/Adrenal insufficiency
    • Hypothyroidism/Thyroiditis
  • PD-1/ PD-L1
    • Thyroiditis/hyperthyroidism
    • Type 1 Diabetes
• Other rare reports
  • Hypoparathyroidism, Immune mediated insulin resistance
• Initial classification not always consistent – potential underreporting
Most common presenting symptom of immunotherapy induced hypophysitis?

- A – Headache: 85%
- B – Fatigue: 66%
- C – Incidental MRI finding: 79% (total)
- D – Diabetes Insipidus: 0%

Faje et al “Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights”; Pituitary 2016
Other Endocrine IRAEs

• Hypophysitis
• Seen primarily with CTLA-4 agents
  • Ipilimumab & tremelimumab
• Typically presents with anterior pituitary deficiencies and headache
• Now a leading cause of Lymphocytic hypophysitis
CTLA-4 Mediated Hypophysitis

• Routine TSH/free T4 monitoring for patients on CTLA-4 recommended
• Unclear if high dose steroids helpful
  • Recommended for adrenal crisis or severe headache/vision changes
• Hormonal recovery can be variable
  • ACTH least likely to recover
• Pituitary enlargement always resolves

Faje et al “Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights”; Pituitary 2016
Immunotherapy induced thyroid disease – which would you expect?

• A – Sudden onset hypothyroidism
• B – Transient symptomatic thyroiditis with resolution to euthyroid state
• C – Transient mild hyperthyroidism with rapid progression to hypothyroidism
• D – Persistent hyperthyroidism until therapy held or thionamides started
PD-1/PD-L1 Associated Thyroiditis

• Transient, typically minimally symptomatic hyperthyroid phase with rapid progression to hypothyroidism
• TPO Antibodies typically positive

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• Rare case reports of Graves’
• Unclear if hypothyroidism occurs without thyroiditis

Levothyroxine
PD-1/PD-L1 Associated Thyroiditis

11/2016

3/14/2017

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<td>TSH</td>
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Take Away Points

• Immunotherapy can induce a variety of endocrine disorders
  • Most of them permanent, not clearly responsive to steroids
• Diabetes appears to have a prodrome of mild hyperglycemia
• Associations with genetic predispositions
• Rapid onset with high risk of DKA, little recovery of β-cell function
• Hypophysitis associated with CTLA-4 therapy
  • Steroids not clearly beneficial. ACTH least likely to recover
• Thyroiditis common with PD-1/PD-L1
  • Minimally symptomatic hyperthyroid phase followed by hypothyroidism
Case 2

• 53 y/o woman from the Middle East, travels to Houston intermittently for treatment.
• Diagnosed with uterine sarcoma, resected in 2014 presented for further monitoring.
• 2015 CT abdomen/pelvis shows new bilateral iliac adenopathy consistent with recurrent disease.
• Offered observation vs therapy with sunitinib (Sutent)
  • Multi-kinase inhibitor: VEGFRs, c-KIT, RET, others
PMH

- Uterine sarcoma
- Mild enlargement of the thyroid with possible cystic nodule noted
- Referred for ultrasound with biopsy of 1.9 x 1.4 x 1.4 cm nodule - benign
- TSH 3.27 uIU/mL
(Tyrosine) Kinase Inhibitors

• Broad class of small molecule “targeted therapy” in cancer
• Act as analogues of ATP, inhibit downstream phosphorylation
• Grouped together, but actual targets (and side effects) vary widely
• One inhibitor can affect multiple targets
• Targeted against growth factors, mutated proteins:
  • BCR-ABL: imatinib, multiple others
  • EGFR, VEGF, etc: suntinib, erlontinib, cabozantinib
  • BRAF: vemurafemib
• Adverse effects can be due to direct effect or off target effect
Case 2

• 4 months on therapy follow-up:
  • TSH: 31.89 uIU/mL
  • Free T4: 0.95 ng/dL (0.93 – 1.7)
  • Started on 25 mcg of levothyroxine

• 3 months later:
  • TSH: 0.53 uIU/mL
  • Total T4: 9.9 mcg/dL

• At home discontinued levothyroxine, continued sunitinib

• Returned to clinic 4 months later with no complaints
Guess the TSH!

• A. 5 uIU/mL
• B. 30 uIU/mL
• C. 100 uIU/mL
• D. 250 uIU/mL
Case 2

• TSH 250.1 uIU/mL
• Total T4: 2.9 mcg/dL (2.5-11.7)
• Started on levothyroxine 100 mcg with normalization of levels.
• Cancer progressed and switched to immunotherapy with Tremelimumab (CTLA-4) and Durvalumab (PD-L1)
• Will her hypothyroidism improve?
• Is there any effect on her nodule?
• Is this autoimmune? Is she at risk of more endocrine IRAEs on immunotherapy?
Vascular effects on the thyroid

Pani F, et al. “Thyroid Dysfunction in Patients with Metastatic Carcinoma Treated with Sunitinib” Is Thyroid Autoimmunity Involved?” *Thyroid* 25;11 (2015): 1255-1261
TKI Induced Hypothyroidism

• Mechanism thought to be decreased gland vascularity leading to cell death, but may be more complicated
• Autoimmunity with + TPO antibodies detected in some patients

TKI Induced Hypothyroidism

- Changes in hepatic deiodinase activity also reported
  - Patients already on levothyroxine often have increased dose requirement
- Some evidence for impaired thyroperoxidase activity

Kappers, MHW, et al. “Sunitinib-Induced Hypothyroidism is due to Induction of Type 3 Deiodinase Activity and Thyroidal Capillary Regression” *JCEM* 96: 3087–3094, 2011
TKI Induced Hypothyroidism

- Other agents show similar effects
  - Imatinib, sorafenib
- Destructive effect on the thyroid usually permanent
- Changes in T4 metabolism resolve if medication is discontinued
- Other drugs still classified as TKIs have no effect on the thyroid
- Unclear if autoimmune, unclear if she will be at higher risk of IRAEs
Take Away Points

• Multiple new form of chemotherapy can affect thyroid function
  • Sometimes dramatically and rapidly
• These effects can be permanent
• Treatment can also alter thyroid hormone metabolism and cause a higher requirement for levothyroxine than typically seen
• Review if treatment can affect thyroid function
• Monitor thyroid function tests monthly and adjust treatment if needed
Case 3

• 67 y/o woman with history of metastatic renal cell carcinoma
• Diagnosed 10 years ago – incidentally noted on imaging when she broke a rib waterskiing. Metastatic disease to pancreas and liver.
• Enrolled in a clinical trial of first line bevacizumab (Avastin) with advancement to everolimus (Afinitor) for progression or intolerance
• Gradually developed progressive proteinuria and disease progressed
• Switched to everolimus 10 mg daily
Past Medical History

• Type 2 diabetes for past 4 years
• Previously prescribed metformin, but developed diarrhea and discontinued
• Controlled with diet for years, believes A1c values 5-6%
• Told high triglycerides in the past (~200s) did not need treatment
• On atorvastatin 20mg daily one OTC omega 3 gummy daily
• Longstanding hypothyroidism on 88 mcg levothyroxine
• How aggressive should her lipid/diabetes care be?
Case 3

• Follow-up 2 months later
• Fasting BG 387 mg/dL
• Triglycerides 964 mg/dL
• Progressive renal decline to Cr 2.35 mg/dL
• Urgent referral due to risk she could be excluded from study
• Phase 1 trials intend to find maximum tolerated dose
  • Dose-limiting toxicity levels defined which can lead to dose reductions or medication discontinuation
• Phase 2-3 trials will dose reduce for adverse effects
Cancer adverse effect grading - Hyperglycemia

- Common Terminology Criteria for Adverse Effects
  - Published by US Health & Human Services, NIH, NCI
  - Grades adverse effects on a 1-5 scale

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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<td>Fasting glucose 251-500 mg/dL</td>
<td>Fasting glucose &gt; 500 mg/dL</td>
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Symptomatic Grade 4 or asymptomatic grade 3-4 which do not respond to treatment within 1 week considered dose-limiting toxicity

CTCAE v4.0
Cancer adverse effect grading - Hyperlipidemia

**• Total Cholesterol**

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**• Triglycerides**

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Grades 3-4 not improving despite 4 weeks treatment considered dose-limiting toxicity
Targeted Therapy and Hyperglycemia

**IGF receptor Ab**
Multiple in studies with hyperglycemia rates ranging from 10-100%

**PI3K/AKT Kinase inhibitors**
Multiple in studies with hyperglycemia rates ranging from 2-93%

**EGFR**
- Gefitinib – 5%
- Rociletinib – 46%

**BRAF**
- Vemurafenib – none
- Dabrafenib – 49-50%

**MEK**
- Selumetinib - none
- Trametinib - none

**mTOR**
- Everolimus – 7-93%
- Temsiroliimus – 7-76%

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Targeted Therapies

• Multiple in studies, some taken off market/research stopped
• Effect can be highly variable even if drugs have the same target
• Hyperglycemia is usually mild and manageable with medication – should not stop therapy if possible
• Other adverse effects are more severe/dose limiting
  • Hypertension
  • Rashes/ Hand foot syndrome
  • Vascular damage/hemorrhage
  • Diarrhea
• One study of a combination an IGF-1 antibody and temsirolimus showed best outcomes in patients who developed hyperglycemia

Recent Approval

- Copanlisib (Aliqopa) approved on 9/14/17 for treatment of Follicular lymphoma
  - Phase 2 data showed:
    - Hyperglycemia in 57.1%
    - Grade 3 or 4 (fasting BG 251-500 mg/dl or >500 mg/dl) 23.8%
    - No patients discontinued due to hyperglycemia
    - 17 patients (of 84 in the trial) required insulin

Mechanism - Hyperglycemia

- "Lipotoxicity"
  - ↓ insulin secretion
  - ↑ glucose production
  - ↓ glucose disposal

Free fatty acids

Insulin
  - signaling
  - secretion
  - ↓ beta cell mass

Adipose

Muscle glucose uptake

↑ glycogenolysis
↑ gluconeogenesis

↑ glucose

Mechanism - Hyperlipidemia

Management

• What are our goals managing hyperglycemia/hyperlipidemia in cancer patients?
• Depends on prognosis, comorbidities, risk
• Short term risks
  • Hyperglycemia: dehydration, infection, DKA (rare)
  • Hypertriglycerideridemia: pancreatitis
  • Hypercholesteroleemia: risk of MI in patients with known disease
Management

• Longer term risks
  • Idea of cancer becoming a “manageable” disease
  • Adverse effects of treatment could be compounded by metabolic issues
    • Renal dysfunction
    • Cardiovascular disease/cardiomyopathy
  • Could limit available treatment options in the future
Management - Hyperglycemia

• Transient grade 1-2 no treatment

• Grade 1 (fasting BG 125-160)
  • Daily BG and dietary counseling

• Grade 2 (160-250)
  • BID BG monitoring. Lifestyle intervention with addition of therapy if uncontrolled

• Grade 3 (250-500)
  • Therapy (straight to insulin if symptomatic), consider holding treatment, hydration

• Grade 4 (>500)
  • Endocrine referral, insulin therapy, consider holding treatment, hydration

Which Agents?

• Metformin considered first line
  • Reduces hepatic gluconeogenesis and glycogenolysis

• Sulfonylureas

• Basal insulin

• Basal/bolus insulin

• Other agents at prescribers discretion, particularly with renal insufficiency

• SGLT-2 inhibitors theoretically could be very effective, but potential risk of DKA
A

- Triglycerides = 150-289 mg/dL
  - TLC*
  - Treat LDL cholesterol to target†
  - If present, treat hyperglycemia

- Triglycerides = 300-499 mg/dL
  - TLC*
  - Treat LDL cholesterol to target†
  - Consider drug therapy, especially if high CV risk†

- Triglycerides ≥ 500 mg/dL
  - TLC1* + drug therapy§

B

Step 1: CV disease risk assessment

- No CV disease or CV disease risk equivalent*
  - Goal LDL: < 190 mg/dL

- CV disease risk equivalents (highest risk)
  - Goal LDL: < 100 mg/dL

All patients with LDL > 190

- TLC (if feasible) x 3 months†

- If LDL > goal:
  - If receiving no medications, consider starting statin drug
  - If already taking LDL-lowering agent, increase dose
  - versus add another class of LDL-lowering agent

Management - Hyperlipidemia

• Treat lower grade hyperlipidemias only if expected survival is > 6 months (earliest seen benefit from statins) or if known coronary disease or risk equivalent:
  • Known atherosclerosis, diabetes, multiple risk factors (FHx, smoking, HTN)
• Statins first line for hypercholesterolemia
• Fibrates, omega-3-fatty acids, extended release niacin all options
• Consider CYP metabolism of fibrates/statin and the chemotherapeutic agent before prescribing
Case 3

• Started on linagliptin with glipizide as needed for hyperglycemia and reduced dose fenofibrate
• Reduced carbohydrate intake
• Repeat labs
  • Blood glucose: 118 mg/dL
  • Triglycerides: 336 mg/dL
• Able to continue same dose of everolimus
Other causes of hyperglycemia - Steroids

- Multiple indications
- Antiemetic doses of dexamethasone with chemotherapy and radiation
- Treatment doses of dexamethasone and prednisone in hematologic malignancies
- Adjunct therapy for fatigue
- Reduction of CNS edema with metastatic disease/radiation
- Treatment of adverse effects (immunotherapy induced colitis, graft vs host disease)
Common Steroid Doses

• Dose for nausea depends on how emetogenic the chemotherapy is
  • Dexamethasone 20 mg IV for highly emetogenic (can reduce to 12 mg if aprepitant is added)
  • Dexamethasone 8-10 mg IV for low/moderately emetogenic
  • Additional oral dexamethasone sometimes given 2-3 days around treatment
• 4 mg dexamethasone po/iv for high/moderate emetogenic radiation
  • Total body/total nodal, upper abdomen, upper body, half-body
• Multiple Myeloma
  • Dexamethasone typically 20 or 40 mg, ranging from daily for 4 days to weekly
• Lymphoma/leukemia
  • Prednisone – variable dose, typically weight based or 100 mg daily x 5 days

Take Away Points

• Changes in cancer therapy can cause sudden and dramatic changes in glycemic control
• Multiple agents that can affect glycemic and lipid control being researched – too many to keep track of
• If a patient presents on oral chemo, research the drug and its effects
• Standard therapies for type 2 diabetes and hyperlipidemia apply
• Consider prognosis and risk factors
• Caution with newer, unstudied diabetes treatments
• If patient is in clinical trail – priority is to keep them on trial
Summary

• New, evolving endocrine effects of cancer therapy
• Endocrinologists can be valuable in co-managing these patients
  • Patient safety
  • Quality of life
  • Keeping on therapy
• Immunotherapy offers a new insight into autoimmune endocrine disorders
• An understanding of the agents used in modern cancer therapy is critical to appropriate treatment