Managing Multiple Complications in Multiple Myeloma

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Nov 19th, 2016
Presenter Disclosure

• Faculty / Speaker’s name: Isanne Schacter

• Relationships with commercial interests:
  – Grants/Research Support: None
  – Speakers Bureau/Honoraria: Astra-Zeneca
  – Consulting Fees: None
  – Other: None
Mitigating Potential Bias

• Not applicable
Learning Objectives

• Describe the mechanism of hypothyroidism in the context of immunomodulatory drug use, and how to treat appropriately

• Describe the mechanism of hyperglycemia and diabetes mellitus in a patient treated with high dose glucocorticoids, and how to treat accordingly
Learning Objectives (Cont.)

• Describe the mechanism of hypercalcemia in the setting of multiple myeloma

• List treatment options for acute hypercalcemia
Case 1

- 67 year old female with multiple myeloma
- Treated with lenalidomide and Dexamethasone
- Mild symptoms of ~2.5 lb weight gain, constipation, cold intolerance and dry skin
- “Routine bloodwork” by family MD reveals:
  - TSH of 10.2 mU/L (N )
  - Free T3 of 1.8 pmol/L (N )
  - Free T4 of 6.7 pmol/L

- What is the diagnosis?
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What Is the Differential Diagnosis?

- Primary hypothyroidism
  - Autoimmune (Hashimoto’s)
  - Iatrogenic
    - Thyroidectomy
    - Radioiodine therapy
    - External irradiation
  - Iodine deficiency OR excess
  - Infiltrative disease
  - Drugs
    - Thionamides
    - Lithium
    - Amiodarone
    - Tyrosine kinase inhibitors
    - Chemotherapy agents (i.e. thalidomide, lenalidomide)
Mechanism of Action

• Uncertain
  — Inhibition of thyroid hormone secretion
  — Reduction of iodide uptake into follicular cells
  — antiangiogenic function: decreased blood flow to thyroid
  — Autoimmune thyroiditis
    • Deregulation of cytokines
    • Direct effect on T lymphocytes
  — Direct toxic effects
How Commonly Does this Occur?

• AZ Badros et al, Am J Med 2002:
  – In pts receiving thalidomide:
    • 20% had a TSH > 5 mU/L
    • 7% had a TSH > 10 mU/L
  – In pts receiving lenalidomide
    • 5-10% rate of hypothyroidism
Management

• Treat just like any other case of hypothyroidism!
  ─ Starting dose levothyroxine ~1.6 mcg/kg/day
  ─ Adjust according to repeats TFTs, with the aim of bringing TSH into the euthyroid range

• Monitoring
  ─ A Giagounidis et al., Ann Hematol 2008
    • Recommend baseline TSH before starting treatment
    • Q 2-3 months checks while receiving treatment
Case 2

• 67 yo previously healthy female with multiple myeloma
• Treated with Lenalidomide and Dexamethasone
• After one month, she complains of increasing polyuria and polydipsia as well as blurry vision
• RBG on blood work found to be 15.7 mmol/L
• Subsequent HbA1c = 9.4%

• What is the diagnosis?
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What Is the Differential Diagnosis?

• Likely underlying Type 2 diabetes not previously diagnosed
  — HbA1c is fairly high, likely reflects insidious process
  — All patients > 40 years old should be screened for DM2 before initiation of steroids

• “Unmasking of type 2 diabetes”
  — i.e. NOT de novo
  — Dose-dependent, usually mild increase in FBG and greater increase in post-prandial values

Mechanism

• Multifactorial
  – Increased hepatic gluconeogenesis
  – Decreased glucose uptake in adipose tissue
  – Alteration of receptor and post-receptor functions

  – Relative risk of new-onset diabetes rose progressively with GC dose from 1.8 (equivalent of < 10 mg/day prednisone) to 10.3 (equivalent of > 30 mg/day prednisone)
  – Same risk factors as other patients with DM2

How Would You Treat?
Treatment

• **Step 1**
  – Initiate counseling re: diet and lifestyle choices to promote weight loss and normoglycemia
  – Provide/arrange diabetes education, including SMBG (minimum BID; target FBG 4-7 mmol/L, 2 hour post prandial glucose < 10 mmol/L)
  – If not already taking, start on **metformin** 250 mg PO BID, with the aim of titrating up to a maximum dose of 1000 mg PO BID if tolerated/necessary
  – Monitor HbA1c q 3 months
CDA Clinical Practice Guidelines

At diagnosis of type 2 diabetes
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

<table>
<thead>
<tr>
<th>A1C &lt; 8.5%</th>
<th>A1C ≥ 8.5%</th>
<th>Symptomatic hyperglycemia with metabolic decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>If not at target (2-3 mos)</td>
<td>Start metformin immediately</td>
<td>Initiate insulin +/- metformin</td>
</tr>
<tr>
<td>Start/Increase metformin</td>
<td>Consider initial combination with another antihyperglycemic agent</td>
<td></td>
</tr>
</tbody>
</table>

Add an agent best suited to the individual:

**Patient Characteristics**
- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obese
- Comorbidities (renal, cardiac, hepatic)
- Preferences and access to treatment
- Other

**Agent Characteristics**
- BG lowering efficacy and durability
- Risk of inducing hypoglycemia
- Effect on weight
- Contraindications and side effects
- Cost and coverage
- Other
Treatment (Cont.)

- Targets:
  - FBG (and pre-prandial BG) 4-7 mmol/L
  - 2 hour post-prandial BG < 10 mmol/L

- Shorter timeframe with steroids associated with chemotherapy

- If not yet at target, what would you do?

- Step 2:
  - If not within target at two weeks
    - Add additional OHA
    - Or proceed to insulin...
Treatment (Cont.)

• Step 3
  – If fasting blood glucose elevated (> 7 mmol/L) ONLY:
    – Initiate basal insulin
      • Start long-acting insulin (NPH/levemir/lantus) 10 units subcut at hs
      • Increase dose by 1 unit q 1 night until FBG 4-7 mmol/L
    – Maintain metformin +/- other OHAs
  – If daytime hypoglycemia, reduce dose of metformin/OHAs
• **Step 4**

  — If pre/post-prandial blood glucose values become **elevated** (>7 mmol/L pre-prandial, or > 10 mmol/L 2 hours post-prandial):
    
    • Add **bolus** insulin
      
      — Add 10% of basal dose as bolus insulin pre meals (i.e. if 50 units NPH at hs, add 5 units rapid ac meals

  — **Stop secretagogues**

  — Maintain basal dose and metformin
Treatment (Cont.)

• **Step 5**
  
  ─ If blood glucoses elevated all day long (i.e. pre-prandial BG values > 7 mmol/L and/or 2 hour post-prandial values > 10 mmol/L):
    
    • Initiate *basal/bolus insulin*
      
      ─ Calculate Total Daily Dose (TDD) insulin as 0.3-0.5 units/kg x total body weight (kg)
        
        » Administer 50% of TDD as basal insulin at hs
        » Administer 50% of TDD distributed in split bolus doses (Novorapid/Humalog/Apidra) before each meal

  
  ─ Stop secretagogues
  
  ─ Maintain metformin
Treatment (Cont.)

• For all patients receiving insulin:
  – Adjust basal insulin to target FBG of 4-7 mmol/L
    • If fasting blood glucose $< 7$ mmol/L $\rightarrow$ reduce dose by 10%
  – Adjust bolus insulin to target pre-prandial BG of 4-7 mmol/L of subsequent meal OR post-prandial BG of 5-10 mmol/L
    • Give rapid acting insulin 0-10 minutes prior to eating meal

  – Patients should be counseled about the prevention, recognition, and treatment of hypoglycemia

  – ***Continue to monitor HbA1c q 3 months***
Screening

• Patients will require screening for microvascular complications as per other patients with DM2
  – Annual dilated eye examination to rule out diabetic retinopathy
  – Annual urinary albumin:creatinine ration to rule out diabetic nephropathy
  – Annual foot exam (with either monofilament or tuning fork) to rule out peripheral diabetic neuropathy
Screening (Cont.)

• If cessation of steroids
  – Hyperglycemia improves with reduction in dose of GC, and usually reverses when medication stopped
  – However, some patients develop persistent diabetes
  – Increased risk of development of diabetes in future
    • Should be screened annually

Case 3

- 67 yo female with multiple myeloma
- Treated with Lenalidomide and Dexamethasone
- Increasingly lethargic, constipated, polyuria and polydipsia
- Unrousable by family
- Taken to local ER
- Routine blood work reveals a corrected calcium of 3.54 mmol/L
  - PTH within normal limits

- What is the diagnosis?
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Hypercalcemia of Malignancy

- 3 major mechanisms
  - Tumor secretion of parathyroid hormone-related protein (PTHrP)
  - Tumor production of 1,25-dihydroxyvitamin D (calcitriol)
  - Osteolytic metastases with local release of cytokines (including osteoclast activating factors)

- Osteoclast-induced bone resorption in discrete focal areas (lytic lesions) or throughout the skeleton
What Are the Typical Symptoms of Hypercalcemia?
Symptoms of Hypercalcemia

- **Renal**
  - Polyuria
  - Polydipsia
  - Nephrolithiasis
  - Nephrogenic DI
  - Acute and/or chronic KI

- **GI**
  - Anorexia, nausea, vomiting
  - Constipation
  - Pancreatitis

- **MSK**
  - Muscle weakness
  - Bone pain
  - Osteopenia/osteoporosis

- **Neurologic**
  - Decreased concentration
  - Confusion
  - Fatigue
  - Stupor
  - Coma

- **Cardiac**
  - QT interval shortening
  - Bradycardia
  - Hypertension

“Bones, stones, groans, moans and psychic overtones”
How Should this Be Managed?
Management

• **Mild** (Ca < 3 mmol/L and asymptomatic or mildly symptomatic)
  — Avoid aggravating factors
    • HCTZ, lithium
    • Volume depletion
    • Prolonged bed rest or inactivity
    • High calcium diet (> 1000 mg/day)
  — Adequate hydration (6-8 glasses water/day)
    • Minimizes risk of nephrolithiasis
Management (Cont.)

• **Moderate/severe** hypercalcemia (Ca > 3 mmol/L and or symptomatic)
  - Require immediate attention
  - Volume expansion- IV NS at 200-300 cc/hr initially
  - Only once “juicy”, may use loop diuretic to increase calcium excretion
Other Agents

• Bisphosphonates
  — Pamidronate 30-90 mg IV x 1 (over 2 hours)
  — Zolendronate 4 mg IV x 1 (over 15 minutes)
  — Takes on average 2-4 days to reach full effect
  — Do not use if eGFR < ~30

• IV calcitonin
  — Tachyphylaxis

• Denosumab 60 mg subcut
  — No adjustment in CKD

• If refractory, hemodialysis
Other Agents (Cont.)

• Unfortunately, hypercalcemia unlikely to resolve until underlying mechanism resolves

• Therefore, many patients require ongoing and intermittent treatment with calcium-lowering agents
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Take Home Messages

• Treat hypothyroidism as per usual
• Treat diabetes as per usual
  – Tighter timeframe
  – Lower threshold to use insulin
• Treat acute hypercalcemia with fluids, fluids, fluids, then some lasix, and maybe a bisphosphonate
  – Remember alternatives in A/CKD
• Thank you!

• Any questions?
My Complication
Had a Little Complication

Bad Things that Happen to Good People with Multiple Myeloma

Dr. Mark Kristjanson
Presenter Disclosure

• Faculty / Speaker’s name: Mark Kristjanson

• Relationships with commercial interests:
  – Grants/Research Support: None
  – Speakers Bureau/Honoraria: Speaker’s bureau for Casey Hein & Associates
  – Consulting Fees: Casey Hein & Associates
  – Other: N/A
Mitigating Potential Bias

• Not Applicable
Learning Objectives

Describe the clinical presentation and management of each of these potential complications:

- VTE
- Herpes zoster (shingles)
- Heartburn (esp. from steroids)
Questions? – Any time
VTE – Risk Factors

- Increase in risk of VTE with MM highest in first year after diagnosis (HR 7.5)
- Immobilization e.g. pathologic #
- Renal disease
- Diabetes due to glucocorticoid use
VTE – Risk Factors (cont.)

- Acute infection due to immunosuppression,
- Erythropoietin
- CVAD
- Lenalidomide *plus* (e.g. len/dex; induction chemo)
VTE – Risk Factors (cont.)

- Brain
- Lung
- Prostate
- Kidney
- Ovary
- Adenocarcinoma of: pancreas; colon; stomach

Journal of Thrombosis and Thrombolysis, 30, 286-293
VTE - Management

• CLOT* - randomized trial of 672 cancer patients with acute VTE
• 6 months of dalteparin vs. warfarin
• Significant reduction in the rate of recurrent VTE at six months (9 versus 17 %)

VTE – Management (Cont.)

- 200 international units/kg SQ once per day for the first month

- 150 international units/kg for the remaining five months

VTE – Dalteparin vs Warfarin

- No significant differences in:
  - Major bleeding (6 versus 4 %)
  - Any bleeding (14 versus 19 %)
  - Overall mortality (39 versus 41 %)

- However, a post-hoc analysis mortality benefit with dalteparin in patients *without* metastatic disease (20 versus 36 percent)

VTE – How Long to Treat?

• Controversial

• Provoked - 3 months of blood thinner

• Catheter associated- as long as the catheter is in place or a minimum of 3 months.
VTE – How Long to Treat? (Cont.)

• Unprovoked (i.e. due to the myeloma):
  • at least 3 mo but more commonly 6 mo
  • then *either* continue LMWH *or* switch to an oral blood thinner for:
    • As long as cancer is considered "active"
    • or until prevention of clot is no longer meaningful goal.
VTE – Recurrence on treatment

• If on DOAC or warfarin – switch to LMWH

• If on therapeutic dose of LMWH – increase dose to 120 – 130% of therapeutic.

• Recurrence vs. post-phlebitic syndrome? Check D-dimer

Herpes Zoster

• For patients on bortezomib – prophylaxis with valacyclovir 500 mg od (or acyclovir 400 mg BID)

• Treatment:
  – Valacyclovir 1000 mg TID x 7 days;
  – Famcylovir 500 mg TID x 7 days; or
  – Acyclovir 800 mg 5x/day x 7 days
Disseminated Shingles

• Hospitalize for IV acyclovir

• 5 to 10 mg/kg/dose every 8 hours for 2 to 7 days, follow with oral therapy to complete at least 10 days of therapy

• ID consult
Steroids & Tummy Aches
Steroid Gastropathy

- Do steroids cause ulcers? - not by themselves

- Combining a glucocorticoid with an NSAID (this includes ASA) raises x 4 the risk of upper GI injury (symptomatic or complicated ulcers)

Bonus content!

No extra charge

Estimating Fracture Risk with Bone Lesions
## Mirels’ Fracture Risk Calculator

<table>
<thead>
<tr>
<th>Score</th>
<th>Site of lesion</th>
<th>Size of lesion</th>
<th>Nature of lesion</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Upper limb</td>
<td>&lt; 1/3 of cortex</td>
<td>Blastic</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Lower limb</td>
<td>1/3 – 2/3</td>
<td>Mixed</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Trochanteric region</td>
<td>&gt; 2/3 of cortex</td>
<td>Lytic</td>
<td>Functional</td>
</tr>
</tbody>
</table>
Mirels’ Score

• 9 or greater: Fixation indicated
• 7 or less: manage using radiotherapy & drugs.
• 8: probability of fracture = 15%; use clinical judgement
Take Home Messages

• Myeloma patients are at risk for VTE
• Dalteparin is first line tx
• Treat for 3 months (provoked)
• or for as long as disease active (unprovoked)
Take Home Messages

• Prophylax for shingles if on bortezomib
• Valacyclovir 1 g TID x 7d if one dermatome
• Cytoprotection if ASA + steroids
• Prophylactic fixation for Mirels’ score 8 or more