Managing Immunotherapy Toxicity: The Good, the Bad, and the Ugly

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DISCLOSURE

Relevant Financial Relationship(s)
Consultant- Bristol Myers Squibb Advisory Board (money paid to institution)
Consultant- Novartis Nurse Advisory Board
Consultant-Merck – Internal Training Program (money paid to institution)
Objectives

Participants should be able to:

● Describe the mechanism of action of anti-CTLA-4 and anti PD-1 antibodies in cancer.

● List the frequency of the most common immune related adverse events (irAE’s) experienced by patients undergoing cancer therapy with checkpoint blockade.

● Describe immunologic immune related adverse event (irAE) management and nursing’s role in the management of patients on immunotherapy.
FDA approval timelines

- **Ipilimumab (Yervoy™)**
  - 10/28/2015 - Resected HR melanoma

- **Pembrolizumab (Keytruda™)**
  - 9/4/2014 - Advanced melanoma
  - 10/2/2015 - Advanced NSCLC

- **Nivolumab (Opdivo™)**
  - 12/22/2014 - Advanced melanoma
  - 3/4/2015 - Advanced NSCLC
  - 11/23/2015 - Advanced RCC
  - 5/17/2016 - Hodgkin’s Lymphoma

- **Ipi/Nivo**
  - 10/1/2015 - Advanced melanoma

- **Atezolizumab (Tecentriq™)**
  - 5/18/2016 – Advanced urothelial carcinoma
Blocking CTLA-4 and PD-1

Tumor Microenvironment

Activation (cytokines, lysis, proliferation, migration to tumor)

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)
Safety Summary

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

<table>
<thead>
<tr>
<th>Patients reporting event, %</th>
<th>NIVO+IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related adverse event (AE)</td>
<td>95.8</td>
<td>56.5</td>
<td>84.0</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>38.7</td>
<td>30.7</td>
<td>10.5</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)
### Most Common Treatment-related Select AEs

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Skin AEs, %</td>
<td>60.4</td>
<td>5.8</td>
<td>43.8</td>
</tr>
<tr>
<td>Rash</td>
<td>28.4</td>
<td>2.9</td>
<td>22.7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35.1</td>
<td>1.9</td>
<td>20.4</td>
</tr>
<tr>
<td>Gastrointestinal AEs, %</td>
<td>47.6</td>
<td>15.3</td>
<td>21.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45.4</td>
<td>9.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Colitis</td>
<td>11.5</td>
<td>8.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Endocrine AEs, %</td>
<td>32.3</td>
<td>5.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16.0</td>
<td>0.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10.2</td>
<td>1.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Hepatic AEs, %</td>
<td>31.6</td>
<td>19.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>17.9</td>
<td>8.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>15.7</td>
<td>6.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Pulmonary AEs, %</td>
<td>7.3</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6.7</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Renal AEs, %</td>
<td>6.4</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>4.2</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients.

Database lock Nov 2015
Gastrointestinal

- Diarrhea/Colitis
  - Most commonly seen with Ipi-30%(10% grade 3/4), combo therapy-50% (20% grade 3/4)
  - Less common with anti-PD-1/anti-PD-L1 therapy alone- 18-20% (1-3% grade 3/4)
  - 1%- fatal bowel perforation (Ipi)
  - Median onset is 7.4 wks (1.6-13.4)
Dermatologic

- Rash/Pruritus
  - Most common reported irAE (40-50% monotherapy-up to 60% combo therapy)
  - Pruritus in absence of rash occurs approximately 10-30% of cases.
  - Reported cases of Stevens-Johnsons Syndrome or Toxic Epidermal Necrolysis (TENS)

- Vitiligo
  - 3% grade 1-2
  - 0% grade 3-5
Hepatotoxicity

- Immune mediated hepatitis/elevated LFT’s
  - 30% any grade in combo therapy (15% grade 3-4)
  - <10% in monotherapy
  - 0.2% hepatic failure
  - Can manifest as transaminitis, hyperbilirubinemia or both
Endocrinopathies

- Hypothyroidism/hyperthyroidism common
- Incidence around 4-10% (mono) up to 20% (combo)
  - Usually presents in two phases:
    - Acute/inflammatory/painless thyroiditis associated thyrotoxicosis (↓TSH, ↑FT4 and/or T3)
    - Resolution to euthyroid or progress to overt hypothyroidism (TSH >10)
  - May present as lab abnormalities only (asymptomatic)
  - May be early indicator of other endocrinopathies (i.e hypophysitis)
Endocrinopathies cont.

- PGA incidence
  - Likely underreported, and/or lumped in with other irAE’s

- Hypophysitis
  - Clinically present with fatigue (the “run over by the truck” phenomenon) abrupt onset headache, possible visual changes/nausea/vomiting
  - Low or undetectable ACTH & AM cortisol levels
  - Enlarged pituitary on MRI (75%)

- Panhypopituitarism

- Adrenal Insufficiency
  - Primary-rare
  - Secondary- almost universal after hypophysitis
Neuropathy

- Several cases of Guillain-Barre type syndrome have been reported
- Severe motor/sensory neuropathy
  - Unilateral or bilateral
- Incidence around 1%
- Can present late
Hematologic

- Anemia (including hemolytic anemia)
- ITP/TTP
- Thrombocytopenia
- HUS
- DIC
- Exact incidence not known
Additional irAE’s

- Incidence rate of around 1-2%
- Most common with anti-PD-1 therapy
  - Pneumonitis (up to 6% in combo therapy)
  - Pancreatitis
  - Nephritis
  - Myocarditis
  - Pericarditis
  - Uveitis/Iritis
  - Diabetes
Pneumonitis

- May present asymptotically (only seen on scans)
- DOE, SOB at rest, orthopnea
- Dry nagging cough (deep in chest)
- Chest pain
Pancreatitis/diabetes

- Often present with vague abdominal pain (postprandial)
- Extreme fatigue
- Nausea and vomiting
- Sudden unexplained weight loss
- Steatorrhea (oily, smelly stools)
- Polydipsia, polyuria
Uveitis/iritis

- “Dry eyes”
- Pain, visual changes
- Floaters
- Field vision deficit
Pretreatment Nursing Evaluation and Pertinent Education
Gastrointestinal-Nursing Assessment

- # of baseline stools
- Stool consistency
- History of GI problems (i.e. IBS, chronic constipation)
Dermatologic- Nursing Assessment

- Skin integrity
- History of dermatitis, chronic rash
- Complete skin assessment for existing rash
Neurologic-Baseline Nursing Assessment

- Has patient had prior neurotoxic chemotherapy?
- Pre-existing diabetes or diabetic neuropathy?
- Other history of neuropathy or neurologic condition?
- Existing brain mets?
Endocrinopathies- Baseline Nursing Assessment

- History of thyroid disease (i.e. primary hypothyroidism, Hashimoto's)
- Baseline history of headaches
- Baseline fatigue level
Hematologic-Baseline Nursing Assessment

- Assess pre-treatment CBC
- Any history of hematologic disorder?
- Is patient a lymphoma patient?
Additional Baseline Nursing Assessments

- Any pulmonary conditions (i.e. asthma, COPD)?
- Any pre-existing cardiac conditions? Received any other cardiotoxic drugs?
- History of dry eyes, cataracts, other ocular issues?
- History of pancreatitis?
- History or predisposition for diabetes?
Additional Pretreatment Labs/Evaluation

- PE, CBC w/differential, CMP, LFT’s, TSH (FT4 if abnormal)
- Assess for any history of autoimmune disorder or history of/risk for diabetes
- Assess medications for current steroid use, or thyroid replacement
- Assure provider has given patient prescription for steroids
  - Patients should have this filled
  - Instruct not to use unless under direction of provider.

Assure patient has emergency phone numbers
Ongoing Assessments (prior to subsequent cycles)

- PE, repeat baseline labs
- Skin assessment (rash, pruritus, vitiligo)
- Bowel assessments (quantity, quality, hematochezia)
- Fatigue (assess 0-10)
- Abdominal pain (cramping, bloating)
- Respiratory status (DOE, orthopnea, dry nagging cough in absence of fever)
- Neurologic status (numbness, tingling, weakness)
- Eye discomfort (dryness, pain in the eye)
- Headache (sudden onset, unrelenting)
Principles of irAE Management
STEROIDS-STEROIDS-STEROIDS
MANAGEMENT OF DIARRHEA/COLITIS
Management of diarrhea/colitis

- Assess the following:
  - # of stools over baseline

- Red flags:
  - Abdominal pain
  - Blood or mucus in stool
  - Fever
  - If any of the above- pt needs to be ruled out for bowel perforation

- Rule out any infectious etiology
  - Don’t hold steroids while awaiting results
Management of diarrhea/colicis cont.

- Grade 1 (<4 stools above baseline)
  - BRAT diet
  - Avoid anti-diarrheals
  - Increase fluid intake
  - Instruct patients to report any of the following:
    - Increase in #
    - Bloody stools
    - Abdominal pain

- Contact patient weekly between treatments
Management of diarrhea/colitis cont.

- Grade 2 (4-6 stools over baseline)
- Grade 3 and above (>7 stools over baseline)
  - Everything from grade 1
  - Steroids
  - Patients need to be called twice weekly until resolved to ≤ grade 1
  - Patients at risk for dehydration (may need hospitalization).
Management of diarrhea/colitis cont.

- Once patients have improvement of symptoms to grade 0 or 1-taper of steroids should occur over at least 1 month
  - Beware of rebound diarrhea!
- If patients have been started on budesonide in addition to systemic steroids, start tapering the prednisone **FIRST**.
- **Do NOT** administer antidiarrheals in patients with ≥ Grade 2 diarrhea as this may cause toxic megacolon and/or perforation.
MANAGEMENT OF RASH/PRURITUS
Management of Rash/Pruritis

- Assess the following:
  - Percentage BSA of rash/pruritis
  - Any blistering/skin peeling?
  - Any fever?
  - Any lesions in oral mucosa/anogenital area?

- Instruct patient to report:
  - Any of the above
  - Worsening of rash/pruritis
• Management of Rash/Pruritis cont.

- Contact patients 1-2 times weekly between treatments
- Assess compliance with topical medications/oral steroids/antihistamines
- Have patients avoid hot showers, excessive drying, etc.
- Encourage photoprotection in those with vitiligo
Algorithm for Dermatologic (rash and/or pruritus) irAE’s from checkpoint inhibitor therapy

Kottschade, L et. al- Melanoma Research 2016
MANAGEMENT OF ENDOCRINOPATHIES
Thyroid disorders (hypo/hyperthyroidism)

- Assess for the following
  - Fatigue (both)
  - Hair loss (hypo)
  - Weight gain (hypo) - Weight loss (hyper)
  - Palpitations (hyper)
  - Sweating (hyper)
  - Nervousness/irritability/tremor (hyper)
  - Cold intolerance (hypo) heat intolerance (hyper)
  - Tightness of clothing around neck (both)
Thyroid Disorders cont.

- Monitor patient compliance with medication
- Continue to reassess symptoms (may fluctuate with continued treatment)
- Instruct patients in proper method for taking thyroid replacement
  - Assess for concomitant medications
    - Iron, Antacids, calcium supplements
  - Take in am 1 hour prior to food or other medications
Pituitary/Adrenal dysfunction

- Assess for the following:
  - Fatigue
  - Nausea/vomiting
  - Unrelenting headache
  - Weakness
  - Dizziness
  - Visual changes
  - Electrolytes (low NA- High K, low glucose-
    primary- may be normal in secondary)
Pituitary/Adrenal Dysfunction cont.

- Primary Adrenal Insufficiency - medical emergency
- Secondary adrenal insufficiency (pituitary failure)
  - Instruct patients on the following:
    - Taking steroids as directed
    - Need for lifelong steroid replacement
    - “sick day” steroids
    - Stress dose steroids (prior to surgery, etc)
    - Medic alert bracelet
    - Long term sequelae of steroid use
PNEUMONONITIS
Management of Pneumonitis

- Assess the following:
  - DOE, orthopnea, any SOB at rest
  - Dry nagging cough (especially in absence of infectious symptoms)
  - Chest pain
  - Pulse ox prior to treatments (random spot checks)
  - Respiratory rate
  - Compliance with prior COPD/Asthma medications
Management of Pneumonitis cont.

- Instruct patients on the following:
  - The need to report any difficulty breathing, cough, chest pain
  - Compliance with steroids (oral and inhaled)
Principles of steroid management

● DO NOT use Medrol Dose paks
● Once irAE is resolved to grade 1 or baseline, taper steroids over at least one month.
● Closely monitor diabetics (or those at risk) for changes in glucose levels
● Be mindful of patients on long term steroid therapy and possibility of secondary infections, difficulty wound healing, GERD, etc.
Important take home points

- Up front education - empower pts
- Frequent assessments
- Don’t be afraid to use steroids
- Beware of rebound symptoms (GI, rash) - need to taper steroids slowly.
Case Study #1

- 39 yo. Female-
- Receiving Ipilimumab/Nivolumab for metastatic melanoma
- After cycle #3 she calls with diarrhea-3 stools in 24 hours. Watery, no fever, no hematochezia

What would you do?
1. Tell her she “likely picked up a bug” and it will go away in a few days
2. Tell her to take Imodium and call if it gets worse
3. Discuss the BRAT diet, keeping well hydrated, get stool studies, check in with her weekly, and instruct to call if worse
4. Tell her to go to the ER
Patient calls back 4 days later and now has 12 stools in a 24 hour period, is lightheaded and dizzy and has noticed some blood in her stool, with abdominal pain.

What would you do?
1. Tell her to start taking 60 mg of prednisone (1 mg/kg).
2. Have her come to the clinic for fluids
3. Instruct her to report to the nearest ER.
4. Get stool studies and you’ll call her once those results are available, but for now to keep hydrated and use a liquid diet.
Case Study #2

- 60 y.o male on adjuvant ipilimumab for high risk resected melanoma.
- Patient has had 3 cycles of induction therapy and present to clinic for his 4th induction cycle with the following symptoms:
  - Moderate fatigue and a pruritic rash that covers 30-40% of his body.
  - Labs show moderately elevated LFT’s (approximately 3x ULN)

What would you do?
1. Have him use OTC hydrocortisone cream, rest and call you if the rash gets worse. Proceed with next dose of therapy.

2. Hold therapy and start prednisone at 1 mg/kg daily-recheck LFT’s in 1 week.

3. Tell patient to take zyrtec 10 daily & Benadryl 25 mg every 6 hr prn and avoid hot showers. Manage fatigue symptomatically. Give next dose of Ipi.
Questions?
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THANK-YOU!