The Immune Toxicity Program (ITOX) at DFCI/BWH, A Novel Approach to Mitigate Immune Related Adverse Events

Osama Rahma, MD
Co-Director, Immune Toxicity Program
Assistant Professor of Medicine, Harvard Medical School
Center for Immuno-Oncology, Gastrointestinal Cancer Dana-Farber Cancer Institute

Houry Leblebjian Pharm.D, BCOP
Clinical Pharmacy Practice Administrator

Disclosure

- Dr. Osama Rahma
  - Research support from Merck
  - Speaker for activities supported by educational grants from BMS and Merck
  - Advisory Board/Consulting: Celgene, Five Prime, GSK, GPF, Defined Health INC, Roche/Genentech, Puretech,
    Leerink and PRMA Consulting

- Dr. Houry Leblebjian has no relevant affiliations or financial relationships with a commercial interest to disclose

Objectives

- To understand the mechanism of immune related toxicities
- To review specific immune related toxicities
- To describe the ITOX program and how its utilized to tackle immune toxicities
- To review the pharmacist role in ITOX program

Question 1

Mr. AB is a 65-yr-old male receiving pembrolizumab for metastatic melanoma

12 weeks after starting on the treatment he developed diarrhea 4 times per day

No nausea, vomiting or fever

In addition to stopping pembrolizumab, you will:

1. Give IVF only
2. Start methylprednisolone at 2 mg/kg/day
3. Start infliximab 5 mg/kg/day
4. Start methylprednisolone and infliximab

Question 2

Mr. AB is 56 yo receiving nivolumab for NSCLC

He presents with cough, dyspnea, and decrease O2 sat (85%)

His CT scan showed diffuse ground glass opacities/infiltrations

No fever and no leukocytosis on blood work
Question 2

How would you treat this patient

1. Strat Steroids inhaler
2. Give one dose of methylprednisolone at 2 mg/kg
3. Start infliximab 5 mg/kg/day
4. Admit to the hospital and start methylprednisolone 2 mg/kg

Question 3

How would you treat this patient

1. Hold nivolumab until LFTs return to normal
2. Start methylprednisolone at 2 mg/kg
3. Start infliximab 5 mg/kg/day
4. Admit to the hospital and start methylprednisolone 2 mg/kg

Tumor Immunology: Overview


General Approaches for Cancer Immunotherapy

Focus on 2 Actionable Immune Synapses

CTLA-4 Pathway

PD-1 Pathway

Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Name</th>
<th>Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab</td>
<td>10 mg/kg IV over 60 min</td>
<td>Melanoma, NSCLC, RCC, classical Hodgkin lymphoma, unHBBR CA, HCC, HNSCC, skin cancer (dendritic cell)</td>
</tr>
<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>240 mg IV over 30 min</td>
<td>Melanoma, NSCLC, RCC, checkpoint inhibitors (ipilimumab or nivolumab), classical Hodgkin lymphoma, unHBBR CA, HCC</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Atezolizumab</td>
<td>1200 mg IV over 60 min</td>
<td>Melanoma, NSCLC, RCC, classical Hodgkin lymphoma, unHBBR CA, HCC, HNSCC</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Durvalumab</td>
<td>10 mg/kg IV over 40 min</td>
<td>Melanoma, NSCLC, RCC, classical Hodgkin lymphoma, unHBBR CA, HCC</td>
</tr>
</tbody>
</table>

immune checkpoint inhibitors

Key Milestones

1970s
- Antibodies, vaccines, cytokines

1980s
- Adoptive T-cell therapy

1990s
- Checkpoint inhibition (CTLA-4)

2011
- First CTLA-4 (ipilimumab) approved for melanoma

2014
- Nivolumab approved for melanoma

2015
- Pembrolizumab approved for melanoma

2016
- Pembrolizumab & nivolumab approved for NSCLC

2017
- Pembrolizumab & nivolumab approved for MSI CRC

2018
- Pembrolizumab & nivolumab approved for HCC

History of Cancer Immunotherapy: Key Milestones

Priming Phase

CTLA-4 Pathway

Effector Phase

PD-1 Pathway

irAEs With Immunotherapy

If not vigilant, may result in more serious immune-related AE

Immune-Related AEs (irAEs): Mechanism of Action

- "Achilles heel" of checkpoint inhibitors: autoimmunity via irAEs
- Unique toxicities of immunomodulators caused by dysregulation of the host immune system, similar to autoimmune disease

IrAE, % All Grades Grade 3 Grade 4

<table>
<thead>
<tr>
<th>IAE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>41.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.6</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2.3</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased in ALT</td>
<td>1.5</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0.8</td>
</tr>
</tbody>
</table>


Kinetics of Appearance of Immune-Related AEs With Ipilimumab

- Rash, pruritus (3%)
- Liver toxicity (7%)
- Diarrhea, colitis (12%)
- Endocrine (3%)

Combined analysis of 325 participants with 10 mg/kg IV Q3W x 4

Nivolumab (Anti–PD-1): Suspected irAEs in Pts with Melanoma

- n = 206 pts with malignant melanoma and wild-type BRAF

<table>
<thead>
<tr>
<th>Suspected irAE, % All Grades</th>
<th>Suspected irAE, % Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>37.4</td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>16</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>15</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>15</td>
</tr>
</tbody>
</table>

Time to Onset of First Treatment-Related Select AE With Nivolumab (Any Grade)

- Majority of treatment-related AEs occurred within first 3 mos of treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Pts (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>85</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>51</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>25</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
</tr>
<tr>
<td>Endocrine</td>
<td>22</td>
</tr>
<tr>
<td>Renal</td>
<td>5</td>
</tr>
</tbody>
</table>

Distribution of Immune-Related AEs With CTLA-4, PD-1, and PD-L1 Inhibition

- Distribution of Grade 1/2 Immune-Related AEs
- Distribution of Grade 3-5 Immune-Related AEs

Combination Immunotherapy: irAEs

<table>
<thead>
<tr>
<th>Treatment-Related AEs, %</th>
<th>Ipilimumab + Nivolumab (n = 46)</th>
<th>Ipilimumab + Placebo (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any tx-related AE</td>
<td>91</td>
<td>54</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>93</td>
<td>24</td>
</tr>
<tr>
<td>Immune-related AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>71.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>51.0</td>
<td>21.3</td>
</tr>
<tr>
<td>Hepatic</td>
<td>34.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Endocrine</td>
<td>27.7</td>
<td>14.9</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Renal</td>
<td>3.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Dermatologic irAEs: Incidence, Features

- Clinical features:
  - Rashes may be asymptomatic or accompanied by pruritus
  - Often develops on trunk and extremities
  - Severe/life threatening manifestations have been reported
  - Stevens–Johnson syndrome
  - Toxic epidermal necrosis

- Incidence: 47% to 68%
  - Rash, pruritus, vitiligo
  - Typically occur earlier in treatment than other types of irAEs
Gastrointestinal irAEs: Incidence and Presentation

- CTLA-4 blockade results in dysregulation of GI mucosal immunity
- Incidence: ~ 30%
  - Diarrhea
  - Colitis
- Presenting signs/symptoms
  - Frequent stooling
  - Abdominal pain
  - Bloody stools
  - Nausea/vomiting
  - Constipation
- Fatal immune-related GI complications (intestinal perforation, complications of enterocolitis) have been reported

Endocrine irAEs: Thyroid Disease and Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Endocrine irAE</th>
<th>Presentation</th>
<th>Signs/Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Thyroid Disease</td>
<td>Primary hypothyroidism or hyperthyroidism</td>
<td>Largely nonspecific (eg, fatigue)</td>
<td>High-dose corticosteroids (1 mg/kg prednisone daily) for acute thyroiditis</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism more common</td>
<td>Increased TSH, Decreased T4</td>
<td>Thyroid replacement therapy (levothyroxine)</td>
</tr>
<tr>
<td>Adrenal Insufficiency</td>
<td>Acute swelling or chronic destruction of adrenal glands</td>
<td>Fatigue, Headache, Satiety, Hypotension, Electrolyte disturbances, Low ACTH/cortisol</td>
<td>Hold therapy, High-dose corticosteroids (1 mg/kg prednisone daily)</td>
</tr>
<tr>
<td>Most Urgent Endocrine irAE</td>
<td>May present as life-threatening adrenal crisis</td>
<td></td>
<td>Chronic corticosteroid replacement therapy may be necessary (5-10 mg/day)</td>
</tr>
</tbody>
</table>

Endocrine irAEs: Hypophysitis

- Hypophysitis
  - A pituitary autoimmune disease characterized by diffuse enlargement of the pituitary gland
  - Incidence reported in up to 17%
  - Signs/symptoms
    - Headache (often presenting symptom)
    - Visual disturbances
    - Fatigue
  - Results in pituitary dysfunction
    - Decreased ACTH (adrenal insufficiency)
    - Decreased gonadotropins (sexual dysfunction)
    - Decreased TSH/free T4 (thyroid dysfunction)

Pneumonitis

- Occur mainly with PD-1 and PD-L1 inhibitors
- Symptoms: SOB, cough
- R/o infection, bronchoscopy
- Respond to high dose steroids with slow taper
- Could be life-threatening and may require intubation

Neurologic Toxicities

- Peripheral neuropathy (sensory and motor) has been reported in < 1% of pts treated with ipilimumab; similarly enigmatic with anti-PD-1 therapy
  - May resolve spontaneously
  - Encourage pt to report muscle weakness or sensory alterations
  - Pt may present with muscle weakness or sensory neuropathies lasting > 5 days or milder neuropathies confirmed by physical exam
  - Rule out noninflammatory causes: disease progression, infections (eg, Lyme disease), metabolic syndromes, and medications (eg, taxanes or platinum salts)
  - including cases of Guillain-Barre syndrome

Additional irAEs

- Hepatic
- Acute renal failure
- Autoimmune diabetes
- Ocular inflammation
- Hematologic (neutropenia, thrombocytopenia, hemophilia A)
Management of Immune Related Adverse Events (irAE)

IrAE Management

- Vast majority of irAE can be managed effectively if recognized and addressed early
  - Trained teams of oncologists, nurses and pharmacists
  - Education of oncology providers
  - Laboratory testing in all patients to ascertain structured assessment
  - Early involvement of multidisciplinary teams with disease specialists

General Management

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contine ICPi</td>
<td>Suspend ICPi</td>
<td>Suspend ICPi</td>
<td>Discontinue therapy</td>
</tr>
<tr>
<td>Monitor for symptoms every 2-3 days</td>
<td>Start high-dose corticosteroids (Pred or MethylPred 0.5 mg/kg)</td>
<td>Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks)</td>
<td>Hospitalize</td>
</tr>
<tr>
<td>Monitor for symptoms every 2-3 days</td>
<td>Start high-dose corticosteroids (Pred or MethylPred 0.5 mg/kg)</td>
<td>Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks)</td>
<td>Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks)</td>
</tr>
</tbody>
</table>

IrAE Management Guidelines

Published at jco.org on February 24, 2018
Published at NCCN.org on February 14, 2018

Management of Dermatologic irAEs

Management of Gastrointestinal irAEs

Management of Endocrine irAEs: Hypophysitis

- Hypophysitis management
  - Unlike other irAEs, hypophysitis responds poorly to high-dose corticosteroids
  - Primarily managed with hormone replacement therapy (often chronic)

- Adrenal insufficiency
  - Low-dose corticosteroids
- Hypothyroidism
  - Levothyroxine (T4)
- Decreased gonadotropins
  - Sex hormone replacement if necessary


How Does It Work?

- EPIC RED FLAG for Admitted Patients Received IO
- PA Review List and Triage Patients to IO TOX Service
- Attending Round
- Consult Specialists Based on Toxicity

Studies Looking at Factors that Determine Immune Toxicities

- Retrospective Cohort
- Prospective Cohort

Dana-Farber/BWH Immunotherapy Toxicity Workgroup

- Immunology Subgroups
  - Management Algorithms
  - Implementation
  - Research TOX Subgroup
  - IT Data Collecting Reporting
  - Education
Patient and Family Education

- Different AE profile than chemotherapy
  - Most common ones to educate about are: skin reactions, flu-like symptoms, muscle aches, shortness of breath (trouble breathing), swelling of legs (edema), sinus congestion, headaches, weight gain from retaining fluid, diarrhea, hormone changes including hypothyroidism, cough
- Early recognition of irAEs is essential to effective treatment
- Patients must notify their care provider if symptoms develop or they are admitted to local facility
- irAEs are related to the mechanism of action of immunotherapies
- irAEs are treatable and respond well to steroids

Patient and Family Education

- Resources for patients
  - ONS website: https://www.ons.org/practice-resources/cancer-therapies/immunotherapy-resources

Education Survey

![Education Survey Table]

- Overall completion rate: 93.0%
- Initial group of 542 RNs and NPs assigned. 186 completed the live version. 316 completed the online version. Total completed 504 RNs and NPs.
- As of 4/16/19, 38 of the original assigned group had not completed either version.

Pharmacist Role

- Monitoring Guidelines for Immune Checkpoint Inhibitors
  - [Guideline Link]
  - [Guideline Link]
Pharmacist Role

Question 1

- Mr. AB is a 65-yr-old male receiving pembrolizumab for metastatic melanoma
- 12 weeks after starting on the treatment he developed diarrhea 4 times per day
- No nausea, vomiting or fever

In addition to stopping pembrolizumab, you will:
1. Give IVF only
2. Start methylprednisolone at 2 mg/kg/day
3. Start infliximab 5 mg/kg/day
4. Start methylprednisolone and infliximab

Question 2

- Mr. AB is 56 yo receiving nivolumab for NSCLC
- He presents with cough, dyspnea, and decrease O2 sat (85%)
- His CT scan showed diffuse ground glass opacities/infiltrations
- No fever and no leukocytosis on blood work

How would you treat this patient
1. Strat Steroids inhaler
2. Give one dose of methylprednisolone at 2 mg/kg
3. Start infliximab 5 mg/kg/day
4. Admit to the hospital and start methylprednisolone 2 mg/kg
Question 3

- Mr. AB is 56 yo receiving nivolumab for HCC
- He was noted to have elevated LFTs on routine blood work (5 times the ULN)
- He is completely asymptomatic

Question 3

How would you treat this patient
1. Hold nivolumab until LFTs return to normal
2. Start methylprednisolone at 2 mg/kg
3. Start infliximab 5 mg/kg/day
4. Admit to the hospital and start methylprednisolone 2 mg/kg

Conclusions

- Immune checkpoint inhibitors toxicities can occur any time during treatment
- Types of toxicities could vary based on targets
- Combination of PD-1+CTLA-4 high rate of toxicity
- Ongoing efforts to determine factors for toxicities
- Guidelines are published and patients should be managed in multidisciplinary fashion
- Patient and family education plays a major role in identifying these toxicities early on for better reversal

Questions?