Integrating Immuno-Oncology Into Therapy for Lung Cancer

INTERACTIVE CASES • INTERACTIVE PRESENTATIONS • EXPERT PANELS

SYMPOSIUM CO-CHAIRS

Roy S. Herbst, MD, PhD
Yale Comprehensive Cancer Center
New Haven, CT
USA

Frances A. Shepherd, MD, FRCPC
Princess Margaret Hospital
Toronto, Ontario
CANADA

MAY 31, 2015
SHERATON CHICAGO HOTEL & TOWERS
CHICAGO, IL

BMLI
BIOMEDICAL LEARNING INSTITUTE
Treatment-related Toxicity with Immune Checkpoint Inhibitor Therapy

Suresh S. Ramalingam, MD
Professor
Director of Medical Oncology
Emory University
Atlanta, USA
Question: Your Opinion

- Patients with lung cancer tolerate therapy with PD-1/PDL-1 inhibitors very well.

A. Yes
B. No
Question: Your Opinion

- PD-1/PDL-1 inhibitors will replace chemotherapy in the first-line setting for metastatic NSCLC.

A. Yes
B. No
Treatment Algorithm For Advanced NSCLC

Lung Adenocarcinoma

- Known Oncogenic Driver
  - Targetable (EGFR, ALK, ROS)
  - Targeted Therapy
    - First-line, Maintenance or Salvage
- Absence of Driver Mutations / Unknown Molecular Status
  - No Proven Targeted Therapy (KRAS, HER2, RAF, MET, PIK3CA)
  - Clinical Trial or Chemotherapy
- Chemotherapy

Immuno Therapy?
Tolerability of Oncology Therapies

**Chemotherapy**
- **Target**: Rapidly dividing tumour and normal cells
- **Adverse events**: Diverse due to non-specific nature of therapy

**I-O therapies**
- **Target**: Immune system
- **Adverse events**: Unique events can occur as a result of immune-system activity

**Targeted therapies**
- **Target**: Specific molecules involved in tumour growth and progression
- **Adverse events**: Reflect targeted nature

Different spectrum of AEs with each modality

Some AEs with I-O may present like those with other therapies

**BUT** – AEs may have different etiologies
- *e.g.* diarrhoea/colitis, fatigue, rash/pruritus, endocrinopathies

Require different management strategies

---

Case Study

61/M
Newly Diagnosed stage IV Squamous NSCLC
Bone metastasis
PS=1

Treatment:
1. Palliative RT to rib lesion for pain control
2. Enrolled to a clinical trial with an immune check point inhibitor
Case Study

Patient presents with:
- Dyspnea
- Non-productive cough
- Fever
- X 2 weeks

Feb 17, 2014
Management Question

What would you recommend?

A. Continue PD-1 inhibitor and start steroids
B. Hold PD-1 inhibitor and start steroids
C. Hold PD-1 inhibitor and start patient on antibiotics
D. Consider hospitalization
The patient was hospitalized. Work up for infectious pneumonia was negative.

What do you recommend?

1. Start high dose steroids and continue PD-1 inhibitor
2. Obtain an open lung biopsy
3. Start steroid therapy and hold PD-1 inhibitor
Case Study

- The patient was given high dose steroids and PD-1 inhibitor therapy was withheld.
Management Question

What do you think was the course of the patient?

A. PD-1 inhibitor therapy was re-introduced
B. PD-1 inhibitor therapy was permanently discontinued
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Any grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>87 (74%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (33%)</td>
<td>5 (4%)*</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (10%)</td>
<td>3 (3%)*</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13 (11%)</td>
<td>1 (1%)*</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (6%)</td>
<td>1 (1%)*</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (5%)</td>
<td>1 (1%)*</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (5%)</td>
<td>4 (3%)*</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>7 (6%)</td>
<td>1 (1%)*</td>
</tr>
</tbody>
</table>

Rizvi et al, Lancet Oncol, 2015
Pembrolizumab in NSCLC

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Grade 3–5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>96 (19.4)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>53 (10.7)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>52 (10.5)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>48 (9.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>45 (9.1)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40 (8.1)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (7.5)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>34 (6.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>24 (4.8)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>21 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21 (4.2)</td>
<td>19 (3.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 (4.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>19 (3.8)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>18 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis†</td>
<td>18 (3.6)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Elevation in aspartate aminotransferase</td>
<td>15 (3.0)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (2.8)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Dermatitis acniform</td>
<td>13 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Elevation in alanine aminotransferase</td>
<td>11 (2.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Chills</td>
<td>10 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (2.0)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>15 (3.0)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Algorithms for managing immune-related AEs: Nivolumab example (Pneumonitis)

**Grade 1**
Radiographic changes only
- Consider delay of I-O therapy
- Monitor symptoms every 2–3 days
- Consider pulmonary and infectious disease consults

**Grade 2**
Mild to moderate new symptoms
- Delay I-O therapy per protocol
- Pulmonary and ID consults
- Monitor symptoms and consider hospitalisation
- 1mg/kg/day methylprednisolone
- Bronchoscopy? Biopsy?

**Grade 3–4**
Severe new symptoms: new/worsening hypoxia, life threatening
- Discontinue I-O therapy
- Hospitalise
- Pulmonary and ID consults
- 2–4mg/kg/day methylprednisolone
- Antibiotics?
- Bronchoscopy? Biopsy?

**Re-image at least every 3 weeks**
- If worsens: treat as Grade 2–4

**Re-image every 1–3 days**
- If improves: when symptoms near baseline taper steroids over >1 month and resume I-O therapy
- Antibiotics?
- If worsens: treat as Grade 3–4

**If improves to baseline: taper steroids over > 6 weeks**
- If not improving after 48 hours or worsening: add additional immunosuppression
Patient on Combination Therapy

- 68 yr. male
- Stage IV lung adenocarcinoma
- PS=1
- On treatment with ipilimumab in combination with nivolumab as first line therapy (clinical trial)
- Presents with 1 weeks history of abdominal cramping, intermittent diarrhea and hematochezia (Grade 2)
You recommend..

A. Symptomatic care
B. Refer to Gastroenterologist
C. Hold therapy and provide symptomatic care
D. Remove patient from study protocol
Ipilimumab: Immune-related AEs

- Mechanism-based adverse events (G 3/4)
  - Colitis (8-23%)
  - Hypophysitis (1-4%)
  - Hepatitis (3-7%)
  - Skin eruptions (0-4%)
  - Pneumonitis

- Cytokine release by activated T-cells are thought to be responsible
Common immune-related AEs

### Pneumonitis (anti-PD-1)
- **Bowel edema and ulceration in the descending colon**

### Rash (anti-CTLA-4)\(^1\)
- **Reticular erythematous rash**
- **Perivascular lymphocyte infiltrate extending into epidermis**

### Gastrointestinal AEs (anti-CTLA-4)\(^2\)
- **Colonoscopy**
- **Histopathology**
  - **Focal active colitis (left) with crypt destruction, loss of goblet cells, and neutrophilic infiltrates in the crypt epithelium (right)**

---

GI Adverse Event Management Algorithm

### Grade of Diarrhea/Colitis
(NCI CTCAE v4)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| **Grade 1** | Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic | • Continue I-O therapy per protocol  
• Symptomatic treatment | • Close monitoring for worsening symptoms.  
• Educate patient to report worsening immediately  
If worsens:  
• Treat as Grade (G) 2 or 3/4 |
| **Grade 2** | Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL; Colitis: abdominal pain; blood in stool | • Delay I-O therapy per protocol  
• Symptomatic treatment | If improves to grade 1:  
• Resume I-O therapy per protocol  
If persists > 5-7 days or recur:  
• 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent  
When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol.  
If worsens or persists > 3-5 days with oral steroids:  
• Treat as grade 3/4 |
| **Grade 3-4** | Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL); Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs; G4: life-threatening, perforation | • Discontinue I-O therapy per protocol  
• 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent  
• Add prophylactic antibiotics for opportunistic infections  
• Consider lower endoscopy | If improves:  
• Continue steroids until grade 1, then taper over at least 1 month  
If persists > 3-5 days, or recurs after improvement:  
• Add Infliximab 5 mg/kg (if no contraindication).  
Note: Infliximab should not be used in cases of perforation or sepsis |

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
General Approach to Manage Immune-related AE

Immune-related adverse events

Result from increased or excessive immune activity

Systemic high-dose corticosteroids* may be required for severe events

Can be severe or life-threatening, may involve various organs

Early diagnosis and appropriate management essential to minimise life-threatening complications

Patient education for early recognition

Unless an alternate aetiology has been identified, consider all signs and symptoms

*with or without additional immunosuppressive therapy

Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at https://www.yervoy.co.uk/
Early Diagnosis and Management are essential for I-O therapies

- Frequent monitoring and early recognition
- Patient education and assessment for appropriate signs/symptoms at baseline and before each dose\(^1,2\)
- Most AEs grade 1–2, in rare cases serious or life-threatening\(^3-11\)
- Immune-related AEs are well-characterized, medically manageable, and typically reversible by using established algorithms\(^12\)
  - Include use of corticosteroids and dose interruption/delays
  - Some cases of grade 3–4 AEs managed by immunomodulators or discontinuation

1. Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at www.yervoy.co.uk/;
Thank You
Integrating Immuno-Oncology Into Therapy for Lung Cancer

INTERACTIVE CASES • INTERACTIVE PRESENTATIONS • EXPERT PANELS

SYMPOSIUM CO-CHAIRS

Roy S. Herbst, MD, PhD
Yale Comprehensive Cancer Center
New Haven, CT
USA

Frances A. Shepherd, MD, FRCPC
Princess Margaret Hospital
Toronto, Ontario
CANADA

MAY 31, 2015
SHERATON CHICAGO HOTEL & TOWERS
CHICAGO, IL