Evolution of Cancer Treatment: The Immune System Versus Cancer

Megan Hames Pollack, PharmD, BCOP, BCPS
Clinical Pharmacist, Outpatient Medical Oncology
Vanderbilt-Ingram Cancer Center, Nashville, TN
September 24, 2016

Disclosures
Nothing to disclose at this time.

Objectives
- Discuss the evolution of treatment in solid tumor oncology.
- Explain the data supporting the use of immunotherapy agents in solid tumor malignancies.
- Recognize appropriate dosing and monitoring for the FDA approved immunotherapy agents.
- List the toxicities that are common among the various immunotherapy agents available.

Patient Case: RF
- 56yo Caucasian male
- No significant PMH
- Diagnosed with T3N1M1c (stage IV) melanoma in June 1990

Cytotoxic Chemotherapy Timeline

- 1948: Antifolates
- 1951: Thiopurines
- 1957: 5FU
- 1959: Antitumor antibiotics
- 1963: Vinca alkaloids
- 1968: Adjuvant chemotherapy described
- 1976: Cure of testicular cancer

Immunotherapy Timeline

Description of immune infiltrates in tumors by Virchow

First study with BCG in bladder cancer
Interleukin-2 FDA approval
Interleukin-2 FDA approval
Interleukin-2 FDA approval
Interleukin-2 FDA approval
Interleukin-2 FDA approval
Interleukin-2 FDA approval

Patient Case: RF

- Treatment options for this patient in 1990
  - Cytotoxic chemotherapy
    - Dacarbazine
      - Response rates in melanoma: 15-25%
      - Median duration of response: 5-6 months
      - < 5% complete responses
      - Long-term follow-up of patients treated with dacarbazine shows < 2% of patients could survive for 6 years
    - Clinical trial

Evolution of Anticancer Agents

- Many types of malignancies have a lack of response to cytotoxic chemotherapy
  - Melanoma
  - Renal cell carcinoma
  - Hepatocellular carcinoma
- Malignancies noted to be responsive to chemotherapy can have and/or develop resistance
  - Primary/Innate resistance - occurs prior to drug exposure
  - Secondary/Acquired resistance - develops over time following exposure to the drug

Immune Checkpoint Inhibitors

Immune Checkpoint Inhibitors: Anti-CTLA-4

Ipilimumab (Yervoy®)

T-cell proliferation
Ipilimumab Indications and Dosage

- FDA approved indications
  - Unresectable or metastatic melanoma
    - 3mg/kg IV q 3 weeks x 4 doses
  - Adjuvant treatment of stage III or IV resected melanoma
    - 10mg/kg IV q 3 weeks x 4 doses then q 12 weeks up to 3 years

CTLA-4 Inhibitor Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>41</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31</td>
</tr>
<tr>
<td>Rash</td>
<td>29</td>
</tr>
<tr>
<td>Colitis</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterocolitis</td>
<td>7</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>4</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1</td>
</tr>
<tr>
<td>Neupathy</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Meningitis</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Patient Case: RF

- Presents to medical oncology clinic to discuss options to prevent recurrence
  - Interferon alfa-2b
  - Clinical trial
- Enrolled on MEL0823
  - Ipilimumab versus placebo

Patient Case: RF

- Diagnosed with T1a (stage I) melanoma February 2001
  - Surgical resection – 3/2001
- Remained disease free until March 2010
  - Nodal recurrence
  - T3N3 (stage III)
- Complete surgical resection and left axillary lymph node dissection March 2010
**Patient Case: RF**

- Patient presents to the ED on 7/14/2010
  - Bloody diarrhea with 8-12 bowel movements per day and febrile to 101.5°F

- Vital signs
  - Temp 100.6°F
  - HR 92
  - BP 130/72
  - RR 20
  - ANC = 2.85

**Colonoscopy report**
- Evidence of moderately severe colitis in the entire colon
  - The mucosa appeared edematous, erythematous, and friable with bleeding on contact

**Pathology report**
- There is a marked mononuclear infiltrate within the lamina propria that also focally involves glandular epithelium

---

**CTLA-4 Inhibition and Immune Toxicity**

![Kinetics of appearance of immune-related adverse event.](image)

- CTCAE Grade 3 diarrhea
- Prednisone 2mg/kg PO started
  - 80mg PO BID tapered over 6 weeks
  - No recurrence of symptoms
- Removed from clinical trial due to grade 3 toxicity

---

**Immune Checkpoint Inhibitors: Anti-PD-1**

- Pembrolizumab (Keytruda®)
- Nivolumab (Opdivo®)

---


*CTLA-4 Inhibition and Immune Toxicity.*

*Fig 1. Kinetics of appearance of immune-related adverse event.*


Pembrolizumab Indications & Dosing

- FDA approved indications
  - Unresectable or metastatic melanoma
    - 2mg/kg IV q 3 weeks
  - Metastatic NSCLC who have PD with platinum-based chemotherapy and tumor expresses PD-L1
    - 2 mg/kg IV q 3 weeks
  - Metastatic head and neck squamous cell carcinoma who have PD with platinum-based chemotherapy
    - 200mg IV q 3 weeks

*Approved with a companion diagnostic test, the PD-L1 IHC 22C3 pharmDx test to determine TPS.

Nivolumab Indications & Dosing

- FDA approved indications
  - Unresectable or metastatic melanoma
    - 240mg IV q 2 weeks
  - Advanced RCC who have received prior anti-angiogenic therapy
    - 240mg IV q 2 weeks
  - Metastatic NSCLC who have PD with platinum-based chemotherapy
    - 240mg IV q 2 weeks

Nivolumab - Melanoma

Nivolumab – Head and Neck Cancer
Nivolumab - RCC


Nivolumab - NSCLC


Anti-PD-1 Toxicities


Patient Case: RF

- Patient remains disease free until 4/23/13
  - Recurrence within para-aortic and mesenteric lymph nodes, brain, retroperitoneum (M1c – stage IV)
  - Molecular profiling – BRAF V600R positive
  - Started MEL1168 - 5/2013
    - Vemurafenib 960mg PO BID
  - Progressive disease noted 1/14/14
  - Started dabrafenib 150mg PO BID + trametinib 2mg PO daily – 2/2014

- July 2014 – PD on dabrafenib + trametinib
  - Started MK-3475 on EAP - 8/2014
    - Pembrolizumab 2mg/kg IV q 3 weeks
  - December 2015 – CR to pembrolizumab with plan to stop therapy and monitor for disease recurrence
    - Last dose of pembrolizumab = 12/8/15

<table>
<thead>
<tr>
<th>Percentage of Patients</th>
<th>Pembrolizumab 2mg/kg IV q 3 weeks</th>
<th>Nivolumab 3mg/kg IV q 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>19.1</td>
<td>19.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14.4</td>
<td>16</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14.1</td>
<td>17</td>
</tr>
<tr>
<td>Rash</td>
<td>13.4</td>
<td>15</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Colitis</td>
<td>3.6</td>
<td>2</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Myositis</td>
<td>0.7</td>
<td>NR</td>
</tr>
<tr>
<td>Nephritis</td>
<td>0.4</td>
<td>1</td>
</tr>
</tbody>
</table>

NR = not reported
Patient Case: RF

- 1/17/2016 - Brought in by EMS because he went out with the dogs at 6 AM and his family found him at 10 AM unable to vocalize and generally weak

- Patient's wife states he had a "cold sore breakout" within the past 4 weeks

- Vital signs
  - Temp 105.2°F
  - HR 87
  - BP 144/84
  - RR 22

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug therapy</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/17/16</td>
<td>Ceftriaxone</td>
<td>Bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td>1/18/16</td>
<td>Acyclovir</td>
<td>HSV meningitis</td>
</tr>
</tbody>
</table>

- No improvement in neurologic status after 7 days

- Brain MRI
  - Left temporal lesion has imaging findings that could be consistent with herpes vs. limbic encephalitis including the location and associated hemorrhage
  - Melanoma metastases are also known to be associated with hemorrhage
    - Known prior melanoma metastases

- CSF studies
  - EBV positive
  - HSV negative

- Blood cultures
  - Negative

- Encephalitis and Anti-PD-1

  - Two reported cases of limbic encephalitis
    - Nivolumab for NSCLC
      - Patient presented with fatigue, hallucinations, delirium and personality change
      - Treated with antidepressant
      - Died 4 weeks later from encephalitis (autopsy confirmed)
    - Pembrolizumab for metastatic melanoma
      - Patient presented with progressive cognitive decline
      - Treated with 2mg/kg methylprednisolone IV
      - Patient currently alive but still with cognitive dysfunction

- Patient Case: RF

  - Started on methylprednisolone 2mg/kg IV daily - 1/24/16

  - Patient had no further cognitive decline and was discharged on 2/12/16 with prednisone taper

  - Readmitted to VUH on 2/16/16 with progressive cognitive decline
    - Prednisone 60mg PO daily upon admission

  - IVIG 0.4 grams/kg IV x 5 days given 2/17/16 thru 2/21/16

  - No further functional decline and modest improvements after IVIG completed

  - Developed loss of motor function in BLEs and urinary retention on 2/28/16

  - Patient passed away on 2/29/16
Immune Checkpoint Inhibitors: Anti-PD-L1

Atezolizumab Indications & Dosing
- FDA approved indication
  - Locally advanced or metastatic urothelial carcinoma who have PD during or following platinum-based chemotherapy or have PD within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy
  - 1200mg IV q 3 weeks

Atezolizumab – Urothelial Carcinoma

Anti-PD-L1 Toxicities

Combination Immunotherapy
Anti-CTLA-4 + Anti-PD-1

- **Ipilimumab + Nivolumab**
  - Ipilimumab 3mg/kg IV + nivolumab 1mg/kg IV q 3 weeks x 4 doses \( \rightarrow \) nivolumab 240mg IV q 2 weeks until PD or toxicity

- FDA approved for the treatment of metastatic melanoma

- Intensive toxicity monitoring required

---

### Clinical Trials

- **Single agent**
  - Anti-CTLA-4
    - Tremelimumab
  - Anti-PD-1
    - Pidilizumab (CT-011)
  - AMP-224
  - AMP-514 (MEDI0680)
  - Anti-PD-L1
    - BMS-936559 (MDX1105)
    - Durvalumab (MEDI4736)
  - Avelumab (MSB0010718C)

- **Combination therapy**
  - Anti-CTLA-4 + Anti-PD-1
    - Durvalumab + Tremelimumab
  - Anti-PD-1/Anti-PD-L1 + chemotherapy
  - Anti-PD-1/Anti-PD-L1 + targeting therapy
  - Anti-PD-1/Anti-PD-L1 + radiation

---

### Immunotherapy agents are becoming a mainstay of treatment for many solid tumor malignancies

- Melanoma, NSCLC, RCC, Urothelial carcinoma

- Many of these agents have shown survival advantages over SOC drugs as well as improved tolerability

- Toxicity still a concern with these agents
  - Importance of patient education
  - Algorithms are available for the treatment of toxicities
  - Important to HOLD treatment for severe/life-threatening toxicities

---

### Intensive monitoring required

- Lab/vital signs prior to each treatment
  - CBC with diff, BMP, LFTs, TFTs
  - BP, O2 sats, RR, HR

- Reliable patient report of symptoms is vital
  - Diarrhea, SOB/cough, fatigue, pruritus/rash

- Combination therapy will likely be a mainstay of treatment in the near future

- Combination immunotherapy
- Immunotherapy + targeted therapy and/or chemotherapy
Question 1

- Ipilimumab is an anti-CTLA-4 monoclonal antibody and is the first drug to improve OS in metastatic melanoma.
  A. True
  B. False

Question 2

- Which agents are FDA approved for the first line treatment of metastatic melanoma?
  A. Nivolumab
  B. Pembrolizumab
  C. Atezolizumab
  D. All of the above
  E. A and B only

Question 3

- Patient AD presents to the ED complaining of SOB and new onset cough. She states that she has “lung cancer” and is being treated with “chemo” by Dr. Horn. She is currently febrile to 101F, otherwise her labs and vital signs are all within normal limits. What is the next step for treatment of this patient?
  A. Assume she is being treated with cytotoxic chemotherapy; draw cultures and start antibiotics immediately
  B. Determine what treatment she is actually getting as this will help with determining the cause of SOB/cough
  C. Do nothing – lung cancer patients often have this problem

Question 4

- Atezolizumab has data supporting its use in patients with urothelial carcinoma that have had a recurrence of disease within 6 months of platinum based chemotherapy.
  A. True
  B. False