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Immune mediated toxicity from Immuno-oncology therapies

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Disclosure

Employee and shareholder of Bristol-Myers Squibb
Immuno-Oncology (I-O) Is an Emerging Therapeutic Modality

- Traditional therapies for advanced cancer include\textsuperscript{1,2}
  - Surgery, radiation, and cytotoxic/targeted therapy

- Immunotherapy harnesses the body’s own immune system to fight diseases\textsuperscript{3}

- I-O, use of immunotherapy to treat cancer, is an emerging treatment modality\textsuperscript{1,2}

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Activation of the Immune System May Lead to Immune-mediated Toxicity

- **Potential mechanisms:**
  - Systemic or local disruption in immune homeostasis/tolerance
  - New immune response to self antigens
  - Supraphysiologic response to commensal flora (eg, GI or skin)

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I-O Therapy May Induce Inflammation in Certain Organ Systems

I-O therapy–associated AEs target certain organ systems

<table>
<thead>
<tr>
<th>Skin</th>
<th>1-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine system</td>
<td>2,4,6,7-10</td>
</tr>
<tr>
<td>Liver</td>
<td>2,6,11-12</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>2,6,9,13</td>
</tr>
<tr>
<td>Nervous system</td>
<td>6,10,14,15</td>
</tr>
<tr>
<td>Eyes</td>
<td>1,4,16-18</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>1,5,6,10,15,19</td>
</tr>
<tr>
<td>Hematopoietic cells</td>
<td>6,9,12,20-22</td>
</tr>
</tbody>
</table>

Ipilimumab, anti–CTLA-4 monoclonal antibody, augments T-Cell Activation and Proliferation

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

Adapted from O'Day S, et al. Presented at: Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, IL.

Please see Full YERVOY Prescribing Information, including Boxed WARNING regarding immune-mediated adverse reactions.
Deletion of CTLA-4 in Mice Leads to Massive Lympho-proliferation

CTLA-4 deletion in mice:

- massive lympho-proliferation in multiple organs
- death by Week 3

Blockade of CTLA-4 in mice:

- no evidence of immune pathology
- exacerbate chemically (oxazolone , TNBS) induced colitis

Ipilimumab can Induce Immune-Mediated Adverse Events

| Severe to fatal immune-mediated side effects in the YERVOY (ipilimumab) pivotal phase 3 study | PERCENTAGE (%) OF PATIENTS |
|---|---|---|
| n=511 | YERVOY 3 mg/kg n=131 | YERVOY 3 mg/kg + gp100 n=380 |
| Any immune-mediated side effect | 15 | 12 |
| Enterocolitis\(^a\),\(^b\) | 7 | 7 |
| Hepatotoxicity\(^a\) | 1 | 2 |
| Dermatitis\(^a\) | 2 | 3 |
| Neuropathy\(^a\) | 1 | <1 |
| Endocrinopathy | 4 | 1 |
| Hypopituitarism | 4 | 1 |
| Adrenal insufficiency | 0 | 1 |
| Other | | |
| Pneumonitis | 0 | <1 |
| Meningitis | 0 | <1 |
| Nephritis | 1 | 0 |
| Eosinophilia\(^c\) | 1 | 0 |
| Pericarditis\(^a\),\(^c\) | 0 | <1 |

\(^a\)Including fatal outcome. \(^b\)Including intestinal perforation. \(^c\)Underlying etiology not established.

Key Questions in Early Clinical Development

Management algorithm

Is it possible to prevent toxicity?
- Focus on GI (most frequently severe)

Mechanism of toxicity?
- Characterize histology
- Differentiation from auto-immunity: Crohn’s Disease (CD), ulcerative colitis (UC) and Graft-vs-Host Disease (GVHD)
Generic Management Algorithm for Immune-mediated AEs

Immune mediated AEs can be severe or fatal

Management requires close monitoring

- May require corticosteroids and drug interruption or discontinuation
- Majority respond with complete resolution

Rescue medication for corticosteroid-refractory toxicity

- Infliximab (enterocolitis)
- Mycophenolic acid (hepatitis)
Prophylactic budesonide did not reduce immune-mediated diarrhea (CA184-007)

Hypothesis: Prophylactic oral budesonide could reduce GI toxicity

Conducted large, randomized phase 2 study in melanoma
- Primary endpoint: incidence of Grade ≥2 diarrhea
- Design: randomized (1:1) placebo vs oral budesonide
- All patients received ipilimumab

Results:
- Prophylactic budesonide did not reduce incidence of diarrhea

<table>
<thead>
<tr>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipi + budesonide (N=58)</td>
</tr>
<tr>
<td>Grade ≥ 2 diarrhea rate</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
<tr>
<td>Difference in rate (95% CI)</td>
</tr>
</tbody>
</table>
Pathology of Immune mediated colitis overlaps but distinct from IBD and GVHD

Patients biopsied (week 1-2) to identify incipient changes

- Up to 23% had inflammation, mostly left colon
  - neutrophils, lymphocytes, cryptitis, excess plasma cells
- No significant association with subsequent Grade ≥ 2 enterocolitis

Histology overlaps with, but distinct from, IBD and GVHD

- Similar to UC; however left colon > rectum and no continuous, diffuse, and extensive ulceration
- Hallmarks of CD (granulomas, deep fissures, and transmural chronic inflammation) not consistently observed.
- Distinct from GVHD (sparse inflammation with epithelial apoptosis in the crypts)
Fecal calprotectin not specific for Grade ≥ 2 immune mediated enterocolitis

Neutrophil-derived biomarker of inflammatory bowel disease activity

- Ipilimumab induced an increase in fecal calprotectin
- Not specific for Grade ≥ 2 enterocolitis

Cancer Immunity 2010; 10: 11
No association between humoral response to enteric flora and Grade ≥ 2 enterocolitis

Antibodies to select enteric flora linked to inflammatory bowel disease

- CD associated with anti-ASCA, CBIR1, I2, OmpC
- UC associated with anti-pANCA
- Ipilimumab induces non-specific fluctuations in humoral responses

<table>
<thead>
<tr>
<th>Enterocolitis*</th>
<th>Anti-I2</th>
<th>Anti-ASCA IgA</th>
<th>Anti-ASCA IgG</th>
<th>Anti-CBir</th>
<th>Anti-pANCA</th>
<th>Anti-OmpC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade (N=115)</td>
<td>18</td>
<td>17</td>
<td>18</td>
<td>20</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>None (n=61)</td>
<td>13</td>
<td>11</td>
<td>13</td>
<td>15</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Grade ≥ 2 (n=42)</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>

*Enterocolitis defined as ‘immune related’ gastrointestinal adverse events. Twelve patients had worst Grade 1 (not included in table)
I2: fragment of bacterial DNA associated with *P. Fluorescens*; ASCA: anti-*S. cerevisiae* antibody; pANCA: perinuclear staining anti-neutrophil cytoplasmic antibody; Ompc: *E. coli* outer membrane porin; CBir: bacterial flagellin CBir


**Ipilimumab**: Cancer Immunity 2010; 10: 11
Ipilimumab induced Hepatitis

Case series of 5 patients with severe hepatitis

- Non-specific histological damage (portal and periportal inflammation, necrosis, plasma cells, eosinophils)
- Histology overlaps with acute viral hepatitis or autoimmune hepatitis
- Requires clinicopathologic correlation
Ipilimumab induced Dermatitis

NCl case series of 63 patients, 8 of whom developed dermatitis

- Predominantly T cell, occasional eosinophil
- Similar to maculopapular drug reaction
- Distinct from GVHD or autoimmune skin disease

Arch Dermatol 2006 Feb;142(2):166-72
Multiple Potential I-O Targets to Activate the Immune System

Immune activation is balance of inhibitory and stimulatory interactions between APC, T cell, and tumor

Multiple potential I-O targets

- T-cell co-stimulatory or checkpoint receptors
- Antigen Presenting Cell (APC)
- Microenvironment

Manipulation of targets in patients with cancer, but no pre-existing auto-immune disease, may inform biology of auto-immunity

- Does AE profile from ipilimumab shed light on role of CTLA4 in preventing autoimmunity?

Conclusion

Immuno-oncology is an emerging treatment modality

♦ May be associated with severe or fatal immune mediated toxicity

♦ Majority of toxicities resolve with close monitoring, corticosteroids and interruption or discontinuation

Ipilimumab induced, immune mediated toxicity appears to be distinct from classic auto-immunity or GVHD

♦ Overlapping histology and biomarkers

♦ In contrast to auto-immune disease, majority immune mediated AEs resolve with appropriate management

More study needed of mechanism of these novel toxicities

♦ Need biomarkers to predict which patients may be at risk of severe toxicity