Overcoming Toxicities Associated with Novel Checkpoint Inhibitor Immunotherapy

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Overcoming toxicity

• A new context for evaluating toxicity
  – Several new active immune checkpoint therapies
  – How have new active therapies impacted our goals of care?
Goals of care, melanoma

• Prior to 2011
  – Maintain quality of life
  – Palliate symptoms
  – Minimize treatment related toxicity
Advances in immune therapy

- 2011: Ipilimumab approved for melanoma
- 2014: Pembrolizumab approved for melanoma
- 2014: Nivolumab approved for melanoma
- 2015: Nivolumab approved for melanoma, RCC
- 2015: Pembrolizumab approved for lung cancer
- 2015: 1st combo approved (Ipi/Nivo in melanoma)
- Many promising agents in clinical trials
Goals of care, melanoma

• Prior to 2011
  – Maintain quality of life
  – Palliate symptoms
  – Minimize treatment related toxicity

• 2016
  – *Improve survival in individual patients*
  – Maintain quality of life
  – Palliate symptoms
  – Minimize treatment related toxicity
New toxicity considerations in the context of active therapies

• New standard for evaluating benefit/risk ratio with the availability of more active drugs
  – Immediate toxicity considerations
  – Survivorship and long term QOL free of AEs/sequelae
New toxicity considerations in the context of active therapies

• New willingness to accept increased risk for improved outcomes IF
  – A cure rate/survival benefit has been established
  – There is no equally effective, less toxic alternative
  – Current example: Stem cell transplant for AML
Outline

• Clinical perspective on the challenges of immune toxicity management
  – Toxicity profiles of checkpoint blockade and dual checkpoint blockade
  – Monitoring and management of checkpoint blockade-associated toxicities

• Implications for drug development, clinical trial design
Toxicity profiles of ICI, management

• Review of approved agents
  – Pembrolizumab
  – Nivolumab
  – Ipilimumab
  – Nivolumab/Ipilimumab
Immune therapy mediated adverse events (AEs)

• Considered related to mechanism of action
• Wide range of incidence and severity among approved and investigational approaches
• Immune mediated toxicity should be considered in the differential of any new symptom, involving any organ system
Immune related adverse events

• The majority of patients do not experience severe (grade 3-4) adverse events
• Most common immune related events:
  – Diarrhea/colitis
  – Pruritis/Rash
  – Elevated AST/ALT
  – Hypophysitis
  – Arthralgias
• Uncommon events
  – episcleritis/uveitis, pancreatitis, neuropathies
• Patients should be evaluated before each dose
Managing immune therapy side effects

• Patient education
• Patients should be evaluated before each dose
  – Labs (TSH, LFTs), H&P
• General treatment approach
  – Mild irAE: Supportive care, increase monitoring
  – Moderate irAE: Hold treatment, consider steroids
  – Severe irAE: Permanently discontinue, start steroids
Rash and pruritus

• Patients should immediately report symptoms

• Treatment
  – Mild: Supportive care, increase monitoring
    • Antihistamines, topical non-Rx strength steroids
  – Moderate: Hold treatment, consider steroids
  – Severe: Permanently discontinue, start steroids
Diarrhea and colitis

• Patients should immediately report BM changes
• Rule out infectious/alternative causes (C diff)
• Evaluate for high risk signs requiring urgent care
  – abdominal pain, mucus/blood in stool
  – Peritoneal signs, bowel perforation, ileus
Diarrhea and colitis

• Treatment
  – Mild: Supportive care, increase monitoring
  – Moderate: Hold treatment, consider steroids
  – Severe: Permanently discontinue, start steroids
    • Consider infliximab, GI consultation
    • Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis
Endocrinopathies and Hypophysitis

- Can present with severe HA
- Differential of HA includes CNS mets, bleed, hypophysitis
- MRI with pituitary thin cuts
- Monitor TSH before each dose
- Treat with high dose steroids if HA, hormone replacement as indicated
- Consultation with endocrinology
- Pituitary dysfunction may be reversible or permanent

Weber JCO 2012
Adrenal insufficiency

• Due to hypophysitis
• Rare, but risk of adrenal crisis if undetected
• Low threshold to consider AI EARLY
  – Non-specific complaints
  – New severe fatigue, fevers, nausea, vomiting, low BP
• Check cortisol, ACTH, consider other pituitary labs
  – Physiologic dose hydrocortisone 20mg daily adequate to reverse symptoms due to AI quickly once confirmed with low cortisol/ACTH
• Patient education after diagnosis
  – Need/timing for stress dosing, communication to providers
  – Endocrinology colleagues can help
Liver toxicity

• Monitor liver function tests before each dose
• Rule out viral hepatitis, disease progression
• Treatment of mild elevation
  – Increase frequency of monitoring
• AST/ALT > 2.5-5x ULN or Bilirubin > 1.5-3x ULN
  – Hold treatment, increase monitoring
• ASLT/ALT > 5x ULN or Bilirubin > 3x ULN
  – Permanently discontinue, start steroids
Pneumonitis

Image from Mike Postow
Pneumonitis

- Rare but potentially life threatening AE
- Radiographic only, isolated, asymptomatic
  - Can continue treatment, close observation
- Symptomatic
  - Hold treatment, initiate high dose steroids
- Severe symptoms or hypoxia
  - Hospitalize, steroids, consider bronch, pulmonary
  - Taper steroids slowly over at least several weeks
  - Consider opportunistic infectious prophylaxis
Dual checkpoint blockade

- Ipilimumab and nivolumab approved in 2015 for melanoma
- Ongoing studies in other tumor types
- Significant increase in severe toxicity
### Table 3. Adverse Events. *

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=313)</th>
<th>Nivolumab plus Ipilimumab (N=313)</th>
<th>Ipilimumab (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>311 (99.4)</td>
<td>312 (99.7)</td>
<td>308 (99.0)</td>
</tr>
<tr>
<td>Any adverse event grade 3 or 4</td>
<td>136 (43.5)</td>
<td>215 (68.7)</td>
<td>173 (55.6)</td>
</tr>
<tr>
<td>Treatment-related adverse event</td>
<td>257 (82.1)</td>
<td>299 (95.5)</td>
<td>268 (86.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (19.2)</td>
<td>138 (44.1)</td>
<td>103 (33.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>107 (34.2)</td>
<td>110 (35.1)</td>
<td>87 (28.0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>59 (18.8)</td>
<td>104 (33.2)</td>
<td>110 (35.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>81 (25.9)</td>
<td>126 (40.3)</td>
<td>102 (32.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (13.1)</td>
<td>81 (25.9)</td>
<td>50 (16.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (5.8)</td>
<td>58 (18.5)</td>
<td>21 (6.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34 (10.9)</td>
<td>56 (17.9)</td>
<td>39 (12.5)</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase level</td>
<td>12 (3.8)</td>
<td>55 (17.6)</td>
<td>12 (3.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (6.4)</td>
<td>48 (15.3)</td>
<td>23 (7.4)</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase level</td>
<td>12 (3.8)</td>
<td>48 (15.3)</td>
<td>11 (3.5)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>27 (8.6)</td>
<td>47 (15.0)</td>
<td>13 (4.2)</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (1.3)</td>
<td>37 (11.8)</td>
<td>36 (11.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24 (7.7)</td>
<td>33 (10.5)</td>
<td>19 (6.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (7.3)</td>
<td>32 (10.2)</td>
<td>24 (7.7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (4.5)</td>
<td>32 (10.2)</td>
<td>13 (4.2)</td>
</tr>
<tr>
<td>Treatment-related adverse event leading to discontinuation</td>
<td>24 (7.7)</td>
<td>114 (36.4)</td>
<td>46 (14.8)</td>
</tr>
</tbody>
</table>

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.
Combination has more severe AEs than either drug alone

<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></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Treatment-related adverse event (AE)</td>
<td>95.5</td>
<td>55.0</td>
<td>82.1</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>36.4</td>
<td>29.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).
PFS benefit of Ipi/Nivo vs. Ipi

- **Nivo + Ipi (N=314)**
  - Median PFS, months (95% CI): 11.5 (8.9–16.7)
  - HR (99.5% CI) vs. Ipi: 0.42 (0.31–0.57)*
  - HR (95% CI) vs. Nivo: 0.74 (0.60–0.92)**
  - Stratified log-rank P<0.00001 vs. Ipi

- **Nivo (N=316)**
  - Median PFS, months (95% CI): 6.9 (4.3–9.5)
  - HR (99.5% CI) vs. Ipi: 0.57 (0.43–0.76)*
  - Exploratory endpoint

- **Ipi (N=315)**
  - Median PFS, months (95% CI): 2.9 (2.8–3.4)
  - HR (99.5% CI) vs. Nivo: --
  - No exploratory endpoint

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*Stratified log-rank P<0.00001 vs. Ipi
**Exploratory endpoint

**Wolchok ASCO 2015**
What are the clinical applications?

• Dual checkpoint blockade with ipi/nivo has a high ORR, high risk of severe toxicity, unclear benefit versus single agent PD-1 blockade
  – Need OS data, randomized comparison to PD-1
  – Need biomarker driven patient selection

• 67.5% who discontinued Nivo/Ipi due AEs developed a response
  – Okay/preferable to stop therapy for severe AEs
    • Durable responses after stopping, unclear benefit, *risks*
    • Appears to be true for single agent therapy also
Additional consequences of AEs

• Severe liver toxicity, rash, colitis, pneumonitis may require slow long high dose steroid taper
  – Several steroid related side effects
  – Risk of compression fractures
  – Risk of atypical infections of immune suppression
    • PCP prophylaxis with tmp/smx
  – Need for biomarker driven patient selection and improved toxicity profiles of novel combination immune therapies while maintaining/increasing efficacy
Ongoing combination trials

• Ipi/nivo is a good proof of the concept of combination immune therapy trial feasibility, several others are in progress

• Need for less toxic novel combination immune therapies while maintaining/increasing efficacy
Ongoing combination trials

- PD1/L1+CTLA4 (alternate dosing regimens)
- PD1+Oncolytic viral therapy (TVEC)
- PD1+IDO inhibition
- PD1+CD137
- PD1+BRAF; PD1+BRAF/MEK
- PDL1 combination studies
- Checkpoint blockade with ACT/TIL therapy, SBRT, chemotherapy, TKIs, IFN, anti-VEGF
PD-1 blockade + TVEC

- TVEC (talimogene laherparepvec) is a 1st in class oncolytic viral therapy
- Phase I combination study completed
  - Pembrolizumab is safe, tolerable with TVEC
    - No grade 4 toxicity or deaths among 21 patients treated
    - 33% of patients with grade 3 AEs
  - Preliminary efficacy data in melanoma (38% stage III) – ORR 56%
- Randomized phase III study planned
PD-1 blockade + IDO1 inhibitor

• Epacadostat (INCB024360) is a potent, selective, oral IDO1 inhibitor

• Phase I combination study completed
  – Pembrolizumab is safe, tolerable with epacadostat
    • No grade 4 toxicity or deaths among 60 patients treated
    • 15% of patients with grade 3 AEs, primarily rash
  – Preliminary efficacy data in melanoma – ORR 53%

• Randomized phase III study planned
Toxicity: Implications for trial design
Toxicity: Implications for trial design

• Novel ICI therapies approved for melanoma, lung cancer, RCC

• Broad efficacy emerging in several tumors
  – Trials in GU, GI, Breast, Head/Neck, HCC, Merkel cell, mesothelioma, SCLC, other solid/heme tumors

• **Essential to understand all elements of clinical care for patients receiving immune therapy**
  – Patient selection, response, toxicity, follow up
Toxicity: Implications for trial design

• ICI Patient selection
  – Approved indications in mel, lung ca, RCC
  – Trials can still be considered among 1st line options
  – Consideration of clinical trials (including ICI) in 1st line and subsequent therapy for all patients with advanced cancer in which there is no curative intent option
Toxicity: Implications for trial design

• Standards for weighing risk and benefit shift with the availability of more active drugs
• Rational/individualized biomarker driven combination therapies
  – Enrich treatment population for likely responders to shift the benefit/risk ratio to more favorable
  – Limit dual checkpoint blockade to pts that benefit
    • Specific tumor types or subsets of patients
Toxicity: Implications for trial design

• Considerations for stopping therapy
  – Immediate toxicity considerations
  – Survivorship and long term QOL free of AEs/sequelae – short follow up to date
  – Durable responses after stopping for CR or toxicity

• Pre-clinical evaluation of synergy in both efficacy and toxicity

• Consideration of sequencing of therapies, alternate dosing regimens
Toxicity: Implications for trial design

- Differences in AE assessment/management during phase I trials versus phase II/III/clinical
  - Implications for assessing drug tolerability
  - Examples of mild-moderate rash, LFT elevation
  - Wide variability in management during late phase
    - Continuing vs. holding vs. stopping therapy
    - Variability in initiation of steroids for less severe AEs
    - Theoretical implications of unnecessary treatment interruption/steroid therapy on efficacy
  - Consideration of toxicity due to prior RT, prior ICI
Summary

• There are several new active immune therapies for advanced cancer
• Ongoing clinical trials will likely lead to more approved indications for immune therapies including combination therapy regimens with improved toxicity profiles
Summary

• Clinical trials of immune therapy combinations can be considered among 1st line options for all patients with advanced cancer

• Clinical trial design should aim to improve the benefit/risk ratio in individual patients

• Optimizing patient selection through biomarker development is essential to improving efficacy and reducing toxicity from combination immune therapy
Thank you