Activity Overview

This 30-minute audiocast discusses best practices in the management of treatment toxicities in patients with advanced classical Hodgkin lymphoma (cHL), along with strategies to educate and support patients throughout the continuum of care. Brief clinical case vignettes are included to illustrate strategies for monitoring for and managing adverse events.

Target Audience

This activity is intended for community-based hematologist/oncologists, hematology/oncology nurse practitioners, and hematology/oncology nurses.
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Consulting fees/advisory boards: AstraZeneca, Merck & Co., Inc.
Contracted research: Acerta Pharma, Incyte Corporation, Merck & Co., Inc.,
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To receive credit, read the introductory CME material, listen to the audiocast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.

Contact Information

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Learning Objectives

Upon completion, participants should be able to:

- Develop strategies for the prompt recognition and management of treatment-emergent adverse events
- Identify supportive and educational opportunities and/or resources that can help patients with cHL become active members of their care team
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Recent FDA Approvals in cHL: Brentuximab Vedotin (BV)

- August 2011: relapsed/refractory cHL failing ASCT (or after ≥ 2 Tx, and ASCT-ineligible)
- August 2015: cHL at high risk of progression after ASCT (maintenance)
- March 2018: first-line in combination with chemotherapy for cHL (BV+AVD)

BV: Mechanism

- Anti-CD30 antibody-drug conjugate with MMAE
  - MMAE: microtubule-destabilizing agent
    - Internalizes, binds to tubulin, inhibits microtubule polymerization → cell cycle arrest/apoptosis
  - Some bystander cytotoxic effect within tumor
    - Free, diffusible MMAE may result in systemic toxicity
BV Toxicities: Overview

- Neuropathy, nausea, fatigue, neutropenia
- Grade 3+: neutropenia, neuropathy, thrombocytopenia
- Neuropathy (sensory > motor)
  - Cumulative and dose-dependent
  - Age-related (60 or older fare worse)
  - Common cause of dose modifications in trials
- Neutropenia:
  - Most notable effect with BV+AVD combination
    ▪ 11% F+N with GCSF prophylaxis (21% without)

Single-Agent BV: Dose Delivery in Relapsed/Refractory HL

- Single-agent BV in relapsed HL: N = 102
  - Dose administered: median 9 cycles
    ▪ 18 pts received all 16 cycles
    ▪ 20% of pts discontinued treatment due to AEs (49% due to progression)
  - Modifications
    ▪ 47% of pts had dose delays
      » Due to neutropenia, neuropathy
    ▪ 11% reduced to 1.2 mg/kg
  - Deaths: No pts died within 30 days of a BV dose
## BV: Rates of Sensory Neuropathy in Large Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Median # Doses/ Doses Planned</th>
<th>Sensory Neuropathy*</th>
<th>Resolution/Stabilization Improvement of Neuropathy: % pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal trial, r/r HL¹</td>
<td>9/16</td>
<td>42%</td>
<td>80% improved, 50% resolved @ 13 wks</td>
</tr>
<tr>
<td>AETHERA (maintenance post-ASCT)²</td>
<td>15/16</td>
<td>66%</td>
<td>85%</td>
</tr>
<tr>
<td>Relapsed ALCL³</td>
<td>7/16</td>
<td>41%</td>
<td>91% (with 6-yr f/u)</td>
</tr>
<tr>
<td>ECHELON-1: First-line HL with A+AVD 1.2 mg/kg⁴</td>
<td>12/12</td>
<td>65%</td>
<td>≈10%</td>
</tr>
<tr>
<td>ALCANZA (CD30+ CTCL)⁵+</td>
<td>67%</td>
<td>9%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*Includes term “paresthesia” and peripheral sensory categories. MOTOR neuropathy also occurs in 10%-20%.


## BV—Dose Modifications From Package Insert

- New or worsening grade 2 or 3 neuropathy:
  - Hold BV until improvement to grade 1 or baseline, then resume at 1.2 mg/kg
  - (Not in current insert: if recurs, reduce to 0.9 mg/kg, lengthen Tx to q4-6 weeks)

- Grade 4 sensory neuropathy: discontinue

- Grade 3 motor neuropathy: consider discontinuing depending on the degree of interference with activities of daily living

BV—Neuropathy Supportive Care and Treatment

• Prevention: no strong data supporting supplements
  – Oral B group vitamin no better than placebo
    ▪ But B12-deficient patients should be identified and treated
  – Glutamic acid derivatives for prevention:
    ▪ Some support in reducing vincristine neurotoxicity in pediatric population
• Treatment
  – NCCN/ASCO consider gabapentin* /pregabalin* or tricyclics on a “trial” basis


Recent FDA Approvals in cHL: Checkpoint Inhibitors

• Nivolumab
  – May 2016: rel/ref cHL after ASCT and BV
• Pembrolizumab
  – March 2017: rel/ref cHL after ≥ 3 Tx

New drugs that enhance immune responses and have unique toxicity profiles

Checkpoint Inhibitor Toxicities: Consistent Findings

- Fatigue (usually mild)
- Rash
- Infusion reactions (about 10%, usually mild)
- Hepatitis (< 10%), pneumonitis (< 5%)
- Endocrinopathy: < 10%
  - Thyroid, adrenal, hypophysitis with pituitary/hypothalamic dysfunction

CheckMate 205 (Nivolumab in cHL): Toxicities

- N = 243 patients (all 3 cohorts)
- Median f/u 18 months
- All-cause AEs: % of patients (% grade 3-4)
  - Diarrhea 35% (< 1%)
  - Fatigue 35% (< 1%)
  - Cough 34% (0)
  - Fever 30% (< 1%)
  - Infusion-related reactions 14% (< 1%)
  - Lipase increased 9% (6%)
  - Neutropenia 8% (4%)
  - Hypothyroidism 12% (0)
  - Rash 9% (2%)
  - Pneumonitis 4% (0)
  - AST/ALT 7%-8% (2%-3%)

CheckMate 205 (Nivolumab in cHL): Mature Data

- No study-drug-related deaths
- 7% discontinued drug due to AEs
- Among those who received allo-HCT: comparable aGVHD/TRM to historical controls
  - No effect of nivolumab serum concentration on aGVHD
  - No effect of nivolumab timing pre- allo on aGVHD

Keynote-087 (Pembrolizumab in cHL): Toxicities

- N = 210 patients (all 3 cohorts)
- Median f/u 10.1 months
- All-cause AEs: % of patients (% grade 3-4)
  - Diarrhea 16% (3%)
  - Fatigue 19% (1%)
  - Cough 21% (0.5%)
  - Fever 23% (1%)
  - Infusion-related reactions 5% (0)
  - Neutropenia 3% (2%)
  - Hypothyroidism 13% (0.5%)
  - Rash 11% (0)
  - Pneumonitis 3% (0)
Management of Immune-Related Toxicities: Principles

• Early intervention with steroids is key
  – Steroids not shown to impact anti-tumor efficacy
• Taper steroids slowly (especially with lung/liver toxicity)
• Antimicrobials if on long-term steroids
  – TMP-SMX, antifungals

Management of Immune-Related Toxicities: ASCO Practice Guidelines

• Systematic review ➔ panel recommendations
• General principles:
  – Withhold treatment for grade-2+ symptoms
  – Administer corticosteroids (1 mg/kg/d prednisone equivalent) for persistent grade-2 symptoms, or immediately for select toxicities or any grade-3+
  – Urgent workup for grade-3+ (inpatient) symptoms
  – Permanently discontinue for all life-threatening toxicities
Balancing Efficacy and Safety

• Toxicity of treatment is balanced with goal of cure
• Late effects risk
• Second-line therapy: treatment resistance, therapeutic intensity

Shared Decision Making

• Goal: make treatment decisions with the patient
  – Choice of treatment relies on the application of evidence-based information, the healthcare professional’s knowledge and experience, and the patient’s values and preferences
  – Discuss all treatment options, goals, and side effects to make a decision that best fits the patient’s needs
  – Discuss patient concerns (eg, fertility, cardiovascular disease, financial issues)

Benefits of Shared Decision Making

• Healthcare professionals:
  – Higher quality of care
  – Patient satisfaction

• Patients:
  – Improved patient experience
  – Improved treatment adherence

Educational Resources for Patients

• Chemocare.com
• Lymphoma Research Foundation
• Leukemia Lymphoma Society
• National Comprehensive Cancer Network: https://www.nccn.org/patients/guidelines/hodgkin/index.html
Case 1

• A 46-year-old man with a 15 pack-year smoking history presents with weight loss, night sweats, and hip pain. He is found to have HL with extensive bone involvement.
  – Hgb 10.3
  – WBC 16,000
  – ALC 400/µL
Case 1: Summary of Presentation

• Classical HL
• IPS score 6 (42% FFP at 5 years)
• Ongoing tobacco use as a risk factor for bleomycin toxicity
• No neuropathy


Case 1: Treatment

• Starts BV+AVD with GCSF support
• Cycle 2: tingling in fingertips, PET scan Deauville 3
• At cycle 4: progressive neuropathy, now involving feet; can no longer tie shoelaces, type as well as before at work

Case 1: Management of BV Neuropathy

Which of the following should be done?
A) No modification, add vitamin B complex
B) Hold this BV dose, continue chemotherapy, then restart at 0.9 mg/kg
C) Hold all therapy for 1 month then reevaluate
D) Permanently discontinue BV, finish 6 cycles AVD

Case 1: Discussion

• Patient education and counseling
• Monitor for adverse events
• Manage adverse events
Case 2

A 68-year-old woman with a history of CKD and CHF has relapsed HL after receiving ABVD in 2016 and a brief course of BV in 2017. She is treated with pembrolizumab 200 mg IV q 3 weeks, but at cycle 5 develops loose stools progressing to 6 times per day with mucous and abdominal pain.

Case 2: Management of Checkpoint-Inhibitor–Associated Colitis

What is the best course of action?
A) Continue therapy with loperamide, hydration, and close monitoring
B) Hold therapy; treat colitis with infliximab*, budesonide*, and hospitalization
C) Hold therapy, consult GI for C-scope, and administer steroids 1 mg/kg/day
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