Brentuximab
A New Treatment Approach for Hodgkin Lymphoma
POGO Satellite Education Day
May 15, 2017
Objectives

- To review the mechanism of action of brentuximab vedotin

- To review the rationale for the use of brentuximab vedotin for the treatment of Hodgkin lymphoma (HL)
  - Phase I/II studies
  - Phase III studies

- To review the most common toxicities associated with brentuximab vedotin
Hodgkin Lymphoma

- Lymphoid neoplasm

- 6% of childhood cancers\(^1\)

- Incidence of HL is age related
  - Highest among adolescents aged 15 to 19 years\(^1\)

- Pathology is characterized by malignant cells known as *Reed–Sternberg cells* or large mononuclear cell variants (lymphocytic and histiocytic cells) with a background of inflammatory cells\(^1\)
Reed–Sternberg Cell

- Binucleated or multinucleated giant cell with a bilobed nucleus

- Two large nucleoli that give a characteristic *owl’s eye* appearance\(^1\)

- 1% of the abundant reactive cellular infiltrate\(^1\)

- Among other phenotypic markers, CD30 is highly expressed on the surface\(^1\)

- A potential target!
Hodgkin Lymphoma Treatment

- Multi-modal
  - Multi agent chemotherapy
  - Radiation

- Contemporary protocols are *risk-based* and *response-adapted*
Hodgkin Lymphoma

- 5-year survival >90%\(^6\)

- 10–20% pediatric HL patients\(^4\)
  - Refractory
  - Relapse

- Late effects
  - Secondary malignancy (skin, thyroid, breast, hematologic)
  - Cardiac toxicity
  - Pulmonary toxicity
  - Fertility and premature menopause
Hodgkin Lymphoma: New Therapies

- Antibody drug conjugates (ADC’s)
  - Targeted therapies

- Brentuximab vedotin (Bv)
  - ADC

  - *Anti–CD30* chimeric monoclonal antibody linked to monomethyl auristatin E (MMAE)
Brentuximab vedotin: Mechanism of Action

- CD30 binds to Anti-CD30
- SGN35 internalized through endocytosis
- MMAE is cleaved from SGN35
- MMAE potently disrupts microtubule polymerization
- Diffusible MMAE responsible for bystander cell killing
- Microtubule polymerization
- MTOC

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Brentuximab vedotin: The Evidence

- **Phase I trials**

- A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies (2012)³

- Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study (2013)⁸
Brentuximab vedotin: The Evidence

- **Phase II trial**
  - Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma (2012)\(^9\)
  - Post auto-HSCT
  - Brentuximab vedotin every 3 weeks
  - Objective response rate in 75% of patients
  - Durable CR's approaching 2 years
Brentuximab vedotin: The Evidence

- Phase III trials

  - *Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial (2015)*\(^7\)

  - *A Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma (2013)*\(^8\)

(ClinicalTrials.gov Identifier:NCT01712490)
What about pediatrics?

- **Phase II**
  - **HLHR13**: *Pharmacokinetics, immunogenicity, and safety of weekly dosing of brentuximab vedotin in pediatric patients with Hodgkin lymphoma (2016)*
    - OEPA/COPDac (traditional backbone)
    - AEPA/CAPDac (replace vincristine with brentuximab vedotin)
  - Determine efficacy after 2 cycles of AEPA in high patients with HL
  - Compare EFS in high risk HL patients with AEPA/CAPDac with historical control
Brentuximab vedotin for the treatment of newly diagnosed HL

Upfront randomization to assess the event free survival (EFS) of a novel regimen including brentuximab vedotin

Evaluate and establish the efficacy of brentuximab vedotin

Reduce the number of patients who require radiotherapy as part of their treatment

Compare the rate of neuropathy in both arms
EXPERIMENTAL DESIGN SCHEMA

(Experimental Arm)
2 cycles of Bv-AVEPC

PET for SRL or RRL determination by nodal site

3 cycles of Bv-AVEPC

Response Adapted Targeted ISRT to any SRL and any LMA

Follow-up

(Standard Arm)
2 cycles of ABVE-PC

PET for SRL or RRL determination by nodal site

3 cycles of ABVE-PC

Response Adapted Targeted ISRT to any SRL and any LMA

Follow-up

Randomize to Bv-AVEPC or ABVE-PC

OFF PROTOCOL THERAPY

Follow-up
Brentuximab vedotin: Administration

- Brentuximab vedotin 1.8mg/kg every 3 weeks (MTD)
- Intravenous medication
Brentuximab vedotin: Toxicities

- **Pulmonary Toxicity**
  - Previous studies in adults have shown associated lung toxicity when brentuximab vedotin is given with bleomycin (also known to have lung toxicity)

- **AHOD1331**
  - Elimination of bleomycin in the backbone of the experimental arm

- **Pneumonitis, interstitial lung disease, ARDS**
  - Treated with corticosteroid, supportive measures (antibiotics, oxygen, etc.)
Brentuximab vedotin: Toxicities

- Peripheral Neuropathy (sensory* and motor)
  - The incidence of Grade 3+ neuropathy in 3 previous trials (POG and COG) is less than 3%.

- Given that brentuximab vedotin acts similarly to vincristine, there could be additive neurotoxicity.

- Dose modifications
  - Vincristine
  - Brentuximab vedotin

- Neuropathy is cumulative, dose dependent and reversible.
Brentuximab vedotin: Toxicities

- Allergic reactions/infusion related reactions/cytokine release syndrome
- Anaphylaxis
- Pancreatitis
- Progressive multifocal leukoencephalopathy (PML)
- Myelosuppression
**Table 2** Grade 3 or 4 adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>GPOH-HD-2002 data for OEPA, % (n = 561)</th>
<th>HLHR13 data for AEPA % (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>11.9 (67)</td>
<td>6.3 (1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>70.5 (396)</td>
<td>75 (12)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>81.5 (457)</td>
<td>81.3 (13)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.8 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8.7 (49)</td>
<td>6.3 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7.3 (41)</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxicity, sensory</td>
<td>1.3 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxicity, motor</td>
<td>1.4 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

**HLHR13: Pharmacokinetics, immunogenicity, and safety of weekly dosing of brentuximab vedotin in pediatric patients with Hodgkin lymphoma (2016)**
Summary

- Despite the overall good prognosis of HL, there remains a subgroup of patients where novel therapy is required.

- Antibody drug conjugates are being used more commonly.

- HL expresses CD30, which can be used to more specifically treat the disease using brentuximab vedotin, not only in relapse/refractory disease, but in newly diagnosed patients as well.

- Brentuximab vedotin has been shown to be efficacious, safe and tolerable, but we must consider pulmonary toxicity and neurotoxicity.

- We are optimistic that we can strengthen the current evidence, in terms of efficacy and safety, to minimize treatment related complications in the long term.
QUESTIONS?
References

1. Childhood Hodgkin Lymphoma Treatment PDQ, National Cancer Institute