Positive Quality Intervention: Loncastuximab tesirine-lpl (Zynlonta®) in Relapsed/Refractory Large B-Cell Lymphoma

Description: The purpose of this PQI is to discuss the clinical considerations around the use of loncastuximab tesirine-lpl (Zynlonta®) to optimize the outcomes for patients with relapsed/refractory large B-cell lymphoma.

Background: Loncastuximab tesirine-lpl is a CD19 directed antibody-drug conjugate with a pyrrolobenzodiazepine (PBD) dimer payload.1, 2 The PBD dimer acts as an alkylating agent and has a relatively short half-life, decreasing likelihood of accumulation and reducing overall systemic toxicity. On April 23, 2021, loncastuximab tesirine-lpl received FDA-approval for the management of relapsed/refractory large B-cell lymphoma (including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, or high-grade B-cell lymphoma) following 2 or more lines of prior systemic therapy. Approval was based on data from the phase 2, multicenter, single-arm LOTIS-2 study demonstrating an overall response rate of 48.3% in 145 treated patients, half of whom had a complete response.

Other key findings:
- Median time to response = 41 days; median duration of response = 10.3 months
- Median treatment cycles = 3 (range 1 – 15)
- Overall acceptable safety profile with a few notable considerations:
  - Hematologic toxicities: neutropenia (26%), thrombocytopenia (18%)
  - Effusions and edema related to the PBD dimer did occur in 31% of patients, but were generally low grade; see below for considerations around preventative corticosteroid use
  - Grade ≥3 elevations of gamma-glutamyltransferase (17%)
  - Infusion-related reactions were uncommon (5%)
- No signal indicating CD19-loss after loncastuximab tesirine-lpl was found in a small cohort of progressing patients who were able to proceed to CAR T-cell therapy

PQI Process: Use of loncastuximab tesirine-lpl should include the following safety considerations
- Verification of dosage, schedule, and concomitant conditions
  - Recommended dosage is 0.15 mg/kg IV over 30 minutes of Day 1 of cycles 1 and 2, then 0.075 mg/kg IV over 30 minutes on Day 1 of cycles 3 and onward; cycle length is 21 days
    - Use total body weight to determine dose, unless BMI ≥ 35 kg/m² then use adjusted body weight
  - Pregnancy testing is recommended in women of childbearing potential
- Ensure appropriate supportive care accompanies orders for loncastuximab tesirine-lpl
  - Dexamethasone 4 mg by mouth orally or intravenously twice daily x 3 days (day prior to infusion, day of infusion, and day after infusion) to reduce the risk of edema and effusions
    - If patient forgets to take doses the day prior to loncastuximab tesirine-lpl, then dexamethasone dose should be given at least 2 hours prior to infusion

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PQI Process Continued:

- Preparation and administration
  - Follow appropriate precautions for NIOSH Hazardous Agents with respect to handling and disposal and prepare in an environment that is USP 800 compliant
  - Add loncastuximab tesirine-lpl in a 50 mL infusion bag containing 5% Dextrose Injection, USP
    - Diluted product may be stored in the refrigerator (2°C to 8°C) for up to 24 hours or room temperature (20°C to 25°C) for up to 8 hours
  - Administer as a 30-minute intravenous infusion through a dedicated infusion line using a sterile, non-pyrogenic, low-protein binding in-line filter (0.2 – 0.22 micron pore size)
- Review patient’s medications for drug-drug interactions
  - The PBD dimer component is a substrate of P-glycoprotein (P-gp), but otherwise does not inhibit any key enzyme

Adverse Events and Management

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Severity</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>Hematologic Toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥ Grade 3</td>
<td>Withhold loncastuximab tesirine-lpl until ANC ≥ 1000</td>
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<tr>
<td>Absolute Neutrophil Count (ANC) &lt; 1000</td>
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<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>≥ Grade 3</td>
<td>Withhold loncastuximab tesirine-lpl until Platelet Count ≥ 50,000</td>
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<tr>
<td>Platelet Count &lt; 50,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hematologic Toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema / Effusion&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥ Grade 2</td>
<td>Withhold loncastuximab tesirine-lpl until toxicity resolves to ≤ Grade 1</td>
</tr>
<tr>
<td>Cutaneous Reactions / Rash&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≥ Grade 3</td>
<td>Withhold loncastuximab tesirine-lpl until resolved</td>
</tr>
<tr>
<td>Infection</td>
<td>≥ Grade 3</td>
<td>Withhold loncastuximab tesirine-lpl until toxicity resolves to ≤ Grade 1</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>≥ Grade 3</td>
<td>Withhold loncastuximab tesirine-lpl until toxicity resolves to ≤ Grade 1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Use of granulocyte colony stimulating factors (as management and/or as prevention) can be considered for neutropenia

<sup>b</sup> Consider diagnostic imaging and medical management

<sup>c</sup> Consider dermatology consult

Dose Modifications<sup>1</sup>

- Reduce dose by 50% if treatment is delayed 3 weeks or longer due to treatment-related toxicity
  - If toxicity requiring dose reduction occurs following 0.15 mg/kg (Cycle 2), proceed with planned dose of 0.075 mg/kg

Patient Centered Activities:

- Patient Education:
  - Provide written and verbal education
    - Consider providing treatment calendar and include dosing for dexamethasone for the day before, day of, and day after each infusion
  - Educate patients on the signs of fluid overload (edema and effusions) and to contact their healthcare provider for swelling, weight gain, and shortness of breath or labored breathing
  - Encourage patient to report and signs or symptoms of infection including fever, chills, and upper respiratory symptoms such as cough or difficulty breathing

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Patient Centered Activities Continued:

- Advise patient to minimize sun exposure, wear sun-protective clothing, and to use sunscreen
- Inform patients of reproductive risks and importance of appropriate contraception to avoid becoming pregnant or fathering a child while receiving loncastuximab tesirine-lpl

- ADC Advancing Patient Support program (https://www.advancingpatientsupport.com)
  - Benefits investigation
  - Financial support
    - Copay program for commercially insured, eligible patients
    - Patient assistance program for uninsured and underinsured patients
  - Nursing support
    - Free service offered Monday – Friday (8 am – 5 pm EST) staffed with nurses to answer questions and connect patients with available resources

References: