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Positive Quality Intervention: Loncastuximab tesirine-lply (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-lply (Zynlonta®) to optimize the outcomes for patients with relapsed/refractory large B-cell lymphoma.

Background: Loncastuximab tesirine-lply 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-lply 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-lply 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-lply 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/m^2 then use adjusted body weight
    - Pregnancy testing is recommended in women of childbearing potential
- Ensure appropriate supportive care accompanies orders for loncastuximab tesirine-lply
    - 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-lply, 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-lply 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[1]

Toxicity	Severity	Action
Hematologic Toxicities		
Neutropenia[a]	≥ Grade 3 Absolute Neutrophil Count (ANC) < 1000	Withhold loncastuximab tesirine-lply until ANC ≥ 1000
Thombocytopenia	≥ Grade 3 Platelet Count < 50,000	Withhold loncastuximab tesirine-lply until Platelet Count ≥ 50,000
Non-Hematologic Toxicities		
Edema / Effusion[b]	≥ Grade 2	Withhold loncastuximab tesirine-lply until toxicity resolves to ≤ Grade 1
Cutaneous Reactions / Rash[c]	≥ Grade 3	Withhold loncastuximab tesirine-lply until resolved
Infection	≥ Grade 3	
Other Adverse Reactions	≥ Grade 3	Withhold loncastuximab tesirine-lply until toxicity resolves to ≤ Grade 1

[a] Use of granulocyte colony stimulating factors (as management and/or as prevention) can be considered for neutropenia
[b] Consider diagnostic imaging and medical management
[c] Consider dermatology consult

Dose Modifications[1]

- 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-lply

- 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:

1. Zynlonta (loncastuximab tesirine-lply) [package insert]. Murray Hill, NJ: ADC Therapeutics America; 2021.
2. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, Kahl BS, Radford J, Solh M, Stathis A, Zinzani PL, Havenith K, Feingold J, He S, Qin Y, Ungar D, Zhang X, Carlo-Stella C. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790-800. doi: 10.1016/S1470-2045(21)00139-X. PubMed PMID: 33989558.