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

Background: Loncastuximab tesirine-lpyl 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-lpyl 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.[2]
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-lpyl 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-lpyl should include the following safety considerations

- Verification of dosage, schedule, and concomitant conditions
    - Recommended dosage is 0.15 mg/kg IV over 30 minutes on 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 or use adjusted body weight 35 kg/m^2 times (height in meters)
    - Pregnancy testing is recommended in women of childbearing potential
- Ensure appropriate supportive care accompanies orders for loncastuximab tesirine-lpyl
    - 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-lpyl, then dexamethasone dose should be given at least 2 hours prior to infusion
- Preparation and administration
    - Add loncastuximab tesirine-lpyl 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)

Adverse Events and Management[1]

Toxicity	Severity	Action
Hematologic Toxicities		
Neutropenia	≥ Grade 3 Absolute Neutrophil Count (ANC) < 1000	Withhold loncastuximab tesirine-lpyl until ANC ≥ 1000 Use of granulocyte colony stimulating factors as management and/or as prevention
Thombocytopenia	≥ Grade 3 Platelet Count < 50,000	Withhold loncastuximab tesirine-lpyl until Platelet Count ≥ 50,000
Non-Hematologic Toxicities		
Edema/Effusion	≥ Grade 2	Withhold loncastuximab tesirine-lpyl until toxicity resolves to ≤ Grade 1 Use of spironolactone with or without a loop diuretic can be considered for edema management Consider diagnostic imaging and medical management with symptoms of pleural effusion or pericardial effusion and/or ascites
Cutaneous Reactions/ Rash	≥ Grade 3	Withhold loncastuximab tesirine-lpyl until resolved Consider dermatology consult
Infection	≥ Grade 3	Withhold loncastuximab tesirine-lpyl until resolved
Other Adverse Reactions	≥ Grade 3	Withhold loncastuximab tesirine-lpyl until toxicity resolves to ≤ Grade 1

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 second dose of 0.15 mg/kg (Cycle 2), proceed with planned dose of 0.075 mg/kg with Cycle 3

Patient-Centered Activities:

- Provide Intravenous Cancer Treatment Education (IVE) Sheet
    - 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
    - Advise patient to minimize sun exposure, wear sun-protective clothing, and to use sunscreen as sunlight can make rash/itching worse
    - Inform patients of reproductive risks and importance of appropriate contraception to avoid becoming pregnant or fathering a child while receiving loncastuximab tesirine-lpyl
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Zynlonta (loncastuximab tesirine-lpyl) [package insert].
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.