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Positive Quality Intervention: Siltuximab (Sylvant®) in Patients with Idiopathic Multicentric Castleman Disease

Description:
The purpose of this PQI is to discuss the use of siltuximab (Sylvant®) in idiopathic multicentric Castleman disease (MCD).

Background: Siltuximab, a monoclonal antibody that targets inhibiting interleukin-6 (IL-6), has emerged as a significant therapeutic option in the management of idiopathic MCD, a rare and complex disorder primarily affecting the lymph nodes. The drug exerts its therapeutic effect by selectively inhibiting IL-6, a crucial cytokine implicated in the pathogenesis of Castleman disease.[1] The United States Food and Drug Administration (FDA) granted approval for siltuximab in 2014, marking a pivotal development in the treatment landscape for this challenging condition. The approval was based on compelling evidence derived from a multicenter, randomized, double-blind clinical trial (NCT01400503).[2] This trial compared siltuximab plus best supportive care to placebo plus best supportive care. Durable tumor and symptomatic responses occurred in 34% of patients randomized to siltuximab compared to 0% in the placebo arm.[2] This trial played a crucial role in establishing the efficacy of siltuximab in reducing the symptoms associated with Castleman disease. In a post-hoc analysis, siltuximab demonstrated improved progression-free survival (PFS) compared to placebo with a median PFS of 14.5 months in the placebo arm while median PFS was not reached for patients receiving siltuximab.[3] Siltuximab is listed as the National Comprehensive Cancer Network (NCCN) preferred first-line treatment option for idiopathic MCD that is HIV and HHV8 negative.[4]

PQI Process: Upon ordering Siltuximab[1,5]
Indication: Treatment of MCD in patients who are human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8) negative

Dosing

- FDA approved: 11 mg/kg IV over 1 hour every 3 weeks until treatment failure
- Off-label (severe disease in critically ill patients): 11 mg/kg IV once weekly x 4 then every 3 weeks until treatment failure
- Dosing Considerations

Prior to First Infusion	Absolute neutrophil count ≥1000 cells/mL Platelet count ≥75 cells/mL and 50 cells/mL for retreatment Hemoglobin ≤17 g/dL Severe impairment (Child-Turcotte-Pugh class C): No dosage adjustments provided in the manufacturer's labeling (has not been studied)
Initial Disease Control	Adjunctive corticosteroids may be also administered for 4 to 8 weeks, followed by a corticosteroid taper; patients who are more symptomatic may require higher initial dose corticosteroids and a more gradual taper
Altered Kidney Function	CrCl < 15 mL/min/End stage renal disease: No dosage adjustments provided in the manufacturer's labeling (has not been studied)
Cytokine Release Syndrome	Permanently discontinue
Hematologic Toxicity	Consider delaying treatment until ANC ≥1,000 cells/mL, platelets ≥50,000 cells/mL, and hemoglobin <17 g/dL
Severe Infection	Withhold siltuximab until infection resolves

Infusion Related Reactions	Immediately interrupt infusion for reaction of any severity and manage symptoms as clinically appropriate • *Grade 1 or 2 (mild to moderate) infusion reactions:* Once symptoms resolve, resume infusion at a lower infusion rate; consider antihistamines, acetaminophen, and corticosteroids; if patient does not tolerate infusion following intervention, permanently discontinue • *Grade 3 (severe) or Grade 4 (anaphylactic reaction or life-threatening) infusion reactions:* Permanently discontinue

Monitoring

- Complete blood count (CBC) with differential should be reviewed prior to each dose for the first 12 months and every 3 dosing cycles thereafter

Warnings and precautions

- Do not administer with concurrent active severe infections; hold until resolution
- Avoid administration of live vaccinations to patients or infants born to patients receiving siltuximab
- Administer in setting able to provide resuscitation in event of infusion related reaction
- Increased risk of gastrointestinal perforation; promptly evaluate at first signs/symptoms

Admixture

- Available in 100 mg and 400 mg single dose vials
- Prepare using a 21-gauge, 1.5" needle; infusion bag 250 mL D5W, polyvinyl chloride (PVC), polyurethane (PU), or polyethylene (PE) set which contains a 0.2-micron inline polyethersulfone (PES) filter
    - **Note: only stable with D5W**
- Allow vial to come to room temperature (approximately 30 min), reconstitute using sterile water for injection (SWFI), and gently swirl (do not shake)(approximately 60 min to fully dissolve)
    - 100 mg vial – 5.2 mL SWFI (reconstituted concentration 20 mg/mL)
    - 400 mg vial – 20 mL SWFI (reconstituted concentration 20 mg/mL)
- Inject calculated volume for final concentration into 250 mL D5W and invert bag gently

Administration

- Administer IV over 1 hour
- Do not infuse in the same line as other medications
- Complete the infusion within 4 hours of dilution of the reconstituted solution to the infusion container
- Administer in a setting to provide resuscitation equipment in case of an infusion related reaction; bronchodilators, antihistamines, and corticosteroids should be readily available

Patient-Centered Activities:

- Educate patients on siltuximab therapy and recommend appropriate interventions
    - Counsel on most common side effects: skin disorders (rash, pruritis), respiratory tract infection, edema, weight gain, hyperuricemia, fatigue, diarrhea
    - Avoid live vaccinations
    - Report signs of infection (fever, chills, cough, or sore throat) to your care team immediately
    - Increased risk of fetal harm; discuss risk/benefits; patients who could become pregnant should use effective contraception during treatment and for 3 months after the last dose of siltuximab
- Patient Assistance: NCODA Financial Assistance Tool, Recordati Patient Liaison

References:

1. Sylvant (siltuximab) [prescribing information].
2. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. The Lancet Oncology. 2014;15(9):966-974.
3. van Rhee F, Rosenthal A, Kanhai K, et al. Siltuximab is associated with improved progression-free survival in idiopathic multicentric Castleman disease. Blood Advances. 2022;6(16):4773-4781.
4. National Comprehensive Cancer Network. (2024) Castleman Disease.

5. Siltuximab. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed Jan 16th, 2024. http://online.lexi.com.