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Positive Quality Intervention: Liposomal Daunorubicin-Cytarabine (Vyxeos®) Management

Description: The purpose of this PQI is to discuss the option of using liposomal daunorubicin-cytarabine for patients with newly diagnosed therapy-related Acute Myeloid Leukemia (AML) or AML with myelodysplasia-related changes (AML-MRC).[1]

Background: Liposomal daunorubicin-cytarabine is a combination of daunorubicin and cytarabine in a fixed molar ratio of 1:5 (44 mg daunorubicin and 100 mg cytarabine) encapsulated together in liposomes.[1] Daunorubicin and cytarabine are commonly used together in the "7+3" regimen for AML induction. However, in the "7+3" regimen, the drugs are mixed and administered separately. Daunorubicin is given as a bolus on days 1 through 3 and cytarabine is administered as a continuous infusion on days 1 through 7. Liposomal daunorubicin-cytarabine, in contrast, while including the same core medications, is administered as 90-minute infusion days 1, 3, and 5 or days 1 and 3 (depending on use for induction or consolidation). In a randomized clinical study in patients 60-75 years of age with newly-diagnosed therapy-related AML (t-AML) or AML-MRC observed all-cause day-30 mortality was 6% in the liposomal daunorubicin-cytarabine arm and 11% in the control arm utilizing standard 7+3 combination. During the first 60 days of the study, 14% (21/153) of patients died in the liposomal daunorubicin-cytarabine arm vs. 21% (32/151) of patients in the 7+3 treatment group.[1] Animal studies have shown that the pharmacokinetics are changed due to the liposomal formulation of daunorubicin/cytarabine:[1,2]

- Liposomes persist in the bone marrow
- Liposomes favor uptake into leukemia cells more than normal bone marrow cells
- Once intracellular, liposomes degrade and release daunorubicin-cytarabine to intracellular environment
- Half-life of daunorubicin-cytarabine is significantly longer in liposomal daunorubicin-cytarabine compared to non-liposomal formulations of each drug

PQI Process:

- Patient eligibility
  - Confirmation of t-AML or AML-MRC
  - Anthracycline eligibility[1]
    - If approaching or over recommended lifetime maximum, consider alternative therapy
    - Evaluate baseline echocardiogram; if patient exhibits significant cardiac dysfunction at baseline, discuss risks/benefits of continuing this therapy vs. choosing alternative
      - Re-evaluate echocardiogram prior to consolidation with liposomal daunorubicin-cytarabine and as clinically necessary
  - Consolidation with liposomal daunorubicin-cytarabine is only preferred if given in induction[3]
- Premedications:[1] Follow institutional practice for moderate emetic risk IV chemotherapy
- Preparation[1]
  - Calculate the volume of reconstituted liposomal daunorubicin-cytarabine required based on daunorubicin: **[volume required (mL) = daunorubicin dose (mg/m^2) X BSA (m^2) ÷ 2.2 (mg/mL)]**
  - Compatible with NS or D5W
  - Resulting product will be a purple, opaque, homogeneous dispersion with no visible particulates
- Dosing[1]
  - Dose adjustments:
    - Renal: not required (not studied in severe renal impairment or end-stage renal disease)
    - Hepatic: not required (not studied in patients with bilirubin >2.92 mg/dL)

    - Induction: 44 mg/m^2 daunorubicin + 100 mg/m^2 cytarabine IV infusion over 90 minutes on Days 1, 3, and 5
    - Second induction (2-5 weeks after first induction, if remission is not achieved with first induction): 44 mg/m^2 daunorubicin + 100 mg/m^2 cytarabine IV infusion over 90 minutes on Days 1 and 3
    - First consolidation cycle (5-8 weeks after start of last induction cycle) and second consolidation cycle (5- 8 weeks after start of first consolidation cycle): 29 mg/m^2 daunorubicin + 65mg/m^2 cytarabine IV infusion over 90 minutes on Days 1 and 3
        - Do not administer consolidation until neutrophils and platelets have recovered to >0.5 Gi/L and >50 Gi/L respectively[1]
- Administration: due to risk for tissue necrosis from extravasation, only administer through central line[1]
- Adverse events
    - Some common events include (>25%): hemorrhagic events, febrile neutropenia, rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, arrhythmia, pneumonia
    - Differences in adverse events compared to standard 7+3 regimen[1,2]
        - Prolonged high-grade cytopenias in absence of active leukemia (lasting past cycle day 42) were more frequent in liposomal daunorubicin-cytarabine than 7+3 regimen
        - Prolonged neutropenia in liposomal daunorubicin-cytarabine vs. 7+3 regimen (neutrophils < 0.5 Gi/L): 17% vs 3% (induction), 10% vs 3% (consolidation)
        - Prolonged thrombocytopenia (platelets < 50 Gi/L): 28% vs 12% (induction), 25% vs 16% (consolidation)
        - Hemorrhage: In an observed clinical study, fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in liposomal daunorubicin-cytarabine (2%) vs 7+3 (0.7%)
            - Grade 3 or higher hemorrhagic events from severe thrombocytopenia in liposomal daunorubicin-cytarabine (12%) vs 7+3 (8%)
        - Grade 5 infection related events: 7.2 % liposomal daunorubicin-cytarabine vs 2.6% 7+3; rates of febrile neutropenia: 68.0% vs 70.9%[2]
- Copper Overload Risk[1]
    - When reconstituted, contains 5 mg/mL copper gluconate, of which 14% is elemental copper
    - History of Wilson's disease or other copper-related metabolic disorder, evaluate risk/benefit
        - Monitor total serum copper, serum nonceruloplasmin bound copper, 24-hour urine copper levels and serial neuropsychological examinations in this patient population
    - If signs or symptoms of acute copper toxicity develop, discontinue

Patient-Centered Activities:

- Provide written and verbal patient education
- Monitor and educate patient for signs and symptoms for:
    - Heart failure
    - Infection
    - Bleeding
    - Rash
    - GI side effects: Nausea, Vomiting, Diarrhea, Abdominal pain, Colitis
- Patient Assistance: NCODA Financial Assistance Tool

Supplemental Information

- Billing Information
    - Permanent, product specific HCPCS J-code: J9153
    - Dosage: Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine
    - Billing unit per dose: 1
    - Billing unit per vial: 44 units
    - See manufacturer website for further billing information including NTAP designation

References:

1. Daunorubicin and cytarabine liposome for injection (Vyxeos®) [Package insert].
2. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. JCO 2018;36(26):2684-2692.
3. National Comprehensive Cancer Network. Acute Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.
4. Kubal TE, Salamanca C, Komrokji RS, et al. Safety and feasibility of outpatient induction chemotherapy with CPX-351 in selected older patients with newly diagnosed AML. J Clin Oncol. 2018:36(15)(suppl):e19013.
5. Deutsch YE, Presutto JT, Brahim A, et al. 3559 Safety and feasibility of outpatient liposomal daunorubicin and cytarabine (Vyxeos®) induction and management in patients with secondary AML. Paper presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.