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 eligibility¹
    - 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 induction³
- Premedications:¹ Follow institutional practice for moderate emetic risk IV chemotherapy
- Preparation¹
  - Calculate the volume of reconstituted liposomal daunorubicin-cytarabine required based on daunorubicin: [volume required (mL) = daunorubicin dose (mg/m²) X BSA (m²) ÷ 2.2 (mg/mL)]
  - Compatible with NS or D5W
  - Resulting product will be a purple, opaque, homogeneous dispersion with no visible particulates
- Dosing¹
  - 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)

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o Induction: 44 mg/m² daunorubicin + 100 mg/m² cytarabine IV infusion over 90 minutes on Days 1, 3, and 5
o Second induction (2-5 weeks after first induction, if remission is not achieved with first induction): 44 mg/m² daunorubicin + 100 mg/m² cytarabine IV infusion over 90 minutes on Days 1 and 3
o 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/m² daunorubicin + 65 mg/m² 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 respectively¹

• Administration: due to risk for tissue necrosis from extravasation, only administer through central line¹

• Adverse events
  o 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
  o Differences in adverse events compared to standard 7+3 regimen¹,²
    ▪ 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 Risk¹
  o When reconstituted, contains 5 mg/mL copper gluconate, of which 14% is elemental copper
  o 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
  o 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:
  o Heart failure
  o Infection
  o Bleeding
  o Rash
  o GI side effects: Nausea, Vomiting, Diarrhea, Abdominal pain, Colitis
• Patient Assistance: NCODA Financial Assistance Tool

Supplemental Information
• Billing Information
  o Permanent, product specific HCPCS J-code: J9153
  o Dosage: Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine
  o Billing unit per dose: 1
  o Billing unit per vial: 44 units
  o See manufacturer website for further billing information including NTAP designation
References:
1. Daunorubicin and cytarabine liposome for injection (Vyxeos®) [Package insert].