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 (44mg daunorubicin and 100mg 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 whether used for induction or consolidation). In a randomized clinical study in patients 60 to 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/cytarabine¹,²

- 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 and cytarabine to intracellular environment
- Half-life of daunorubicin and 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
    - Calculate patient’s previous lifetime anthracycline dose. If approaching or over recommended lifetime maximum, consider alternative therapy. Liposomal daunorubicin-cytarabine is not recommended for patients who have reached maximum lifetime anthracycline dose
    - Evaluate baseline echocardiogram for signs of cardiac dysfunction. 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
- **Premedications¹**
  - Follow institutional practice for moderate emetic risk IV chemotherapy
- **Preparation¹**
  - Calculate the volume of reconstituted Liposomal daunorubicin-cytarabine required based on daunorubicin dose: [volume required (mL) = daunorubicin dose (mg/m²) X BSA (m²) ÷ 2.2 (mg/mL)]
  - Review PI for complete admixture details which must be followed to increase homogeneity of product

**Important notice:** NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.
PQI Process Continued:

- **Compatible with NS or D5W**
- **Resulting product will be a purple, opaque, homogeneous dispersion with no visible particulates**

- **Dosing**
  - **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/m² daunorubicin + 100 mg/m² cytarabine IV infusion over 90 minutes on Days 1, 3, and 5
  - **Second induction (administered 2 to 5 weeks after first induction, if remission is not achieved with first induction cycle):**
    - 44 mg/m² daunorubicin + 100 mg/m² cytarabine IV infusion over 90 minutes on Days 1 and 3
  - **First consolidation cycle (administered 5 to 8 weeks after start of last induction cycle) and second consolidation cycle (administered 5 to 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**
  - May be administered as outpatient in an infusion center if patient is clinically stable⁴,⁵
  - Due to risk for tissue necrosis from extravasation, only administer through central line¹
  - Review the PI regarding specifics surrounding infusion filtration¹

- **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 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 Risk**
  - When reconstituted for infusion, contains 5 mg/mL copper gluconate, of which 14% is elemental copper

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PQI Process Continued:

- If a patient has a 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:

- Patient monitoring
  - May cause severe neutropenia, anemia, and thrombocytopenia. Monitor blood counts during therapy
  - Monitor liver function
    - Daunorubicin is metabolized by the liver. No dose adjustments are recommended by manufacturer at this time but has not been studied in patients with total bilirubin greater than 3mg/dL
  - Monitor cardiac function due to daunorubicin
  - Monitor daunorubicin lifetime cumulative dose from liposomal daunorubicin-cytarabine and other therapies

- 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

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: