National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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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 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 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 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 therapy-related AML (t-AML) or AML with myelodysplasia-related changes (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 induction[3]
- Premedications[1]
  - Follow institutional practice for moderate emetic risk IV chemotherapy

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PQI Process Continued:

- Preparation[1]
  - Calculate the volume of reconstituted Liposomal daunorubicin-cytarabine required based on daunorubicin dose:
    [volume required (mL) = daunorubicin dose (mg/m^2) X BSA (m^2) ÷ 2.2 (mg/mL)]
  - Review PI for complete admixture details which must be followed to increase homogeneity of final product
  - Compatible with NS or D5W
  - Resulting product will be a deep 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 >3 mg/dL
  - Induction:
    - 44mg/m^2 daunorubicin + 100mg/m^2 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):
    - 44mg/m^2 daunorubicin + 100mg/m^2 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/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
  - May be administered as outpatient in an infusion center if patient is clinically stable[4,5]
  - Due to risk for tissue necrosis from extravasation, only administer through central line[1]
  - Review the PI regarding specifics surrounding infusion filtration[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]

PQI Process Continued:

- Copper Overload Risk[1]
  - When reconstituted for infusion, contains 5 mg/mL copper gluconate, of which 14% is elemental copper
  - 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[1]
  - 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:

1. Daunorubicin and cytarabine liposome for injection (Vyxeos®) [Package insert]. Jazz Pharmaceuticals, Inc, Palo Alto, CA; July 2019.
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 (Version 3.2020). https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed April 21, 2020.
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.