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Doxorubicin, Etoposide, and Vincristine (as a part of DA-EPOCH-R regimen) Clinical Guideline for Home Intravenous Therapy

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I. BACKGROUND

Etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin ± rituximab is a five-day chemotherapy regimen used to treat aggressive or high-risk lymphomas. The dose adjusted (DA)-EPOCH-R regimen is traditionally administered in an inpatient setting but can be administered safely as an ambulatory regimen. It includes a continuous infusion of doxorubicin, etoposide and vincristine, which can be safely provided for home infusion, and clinic-administered oral prednisone and cyclophosphamide bolus. Doxorubicin is an anthracycline topoisomerase II inhibitor. Etoposide is an antineoplastic agent that inhibits DNA-topoisomerase II or free radical formation. Vincristine is an oncolytic vinca alkaloid that arrests replicating cells of the metaphase stage through prevention of microtubule formation in the mitotic spindle.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon the dispensing pharmacy's admission criteria.

B. Patients will be eligible for outpatient DA-EPOCH-R after completion of the first cycle inpatient.

C. Physician orders for doxorubicin, etoposide and vincristine must include:

1. Patient weight and body surface area (BSA)
2. Drugs
3. Doses (total dose and BSA-based dose)
4. Route of administration
5. Frequency of administration
6. Emergency medications per protocol
7. Orders for pre-medications
8. Line care protocol
9. Routine lab monitoring, if applicable

D. Central venous access is required for administration.

E. Recommended baseline labs include CBC with differential and platelet count, complete metabolic, hepatitis B screening and assessment of left ventricular function but will be ordered at the discretion of the prescriber/referring facility protocol.

III. PHARMACOLOGY OVERVIEW

Refer to manufacturers' full Prescribing Information for most up to date information

A. Indication: as a part of DA-EPOCH-R chemotherapy regimen for non-Hodkin's lymphoma or other susceptible malignancies.

B. Dosing and dose adjustments:

Drug	Dose Level									
	-3	-2	-1	**1**	2	3	4	5	6	7
Etoposide (mg/m^2/day)	50	50	50	**50**	60	72	86.4	103.7	124.4	149.3
Doxorubicin (mg/m^2/day)	10	10	10	**10**	12	14.4	17.3	20.7	24.8	29.8
Vincristine (mg/m^2/day)	0.4	0.4	0.4	**0.4**	0.4	0.4	0.4	0.4	0.4	0.4

*Dosing is based off BSA calculated from actual body weight. DA-EPOCH-R has not been studied in extremes of body weights

Patients will initiate cycle 1 at Dose Level 1. Dose modifications and management of toxicity will be determined by the prescribing oncology team.

C. Duration: six cycles, unless otherwise specified by ordering provider.

D. Contraindications:

1. Doxorubicin is contraindicated in patients with a baseline neutrophil count of <1500 cells/mm^3, severe hepatic impairment, recent myocardial infarction, severe myocardial insufficiency, severe arrhythmias, previous treatment with complete cumulative doses of anthracyclines or hypersensitivity to doxorubicin, any of its excipients or other anthracyclines.
2. Etoposide is contraindicated in patients with a hypersensitivity to etoposide or any of its excipients.
3. Vincristine is contraindicated in patients with the demyelinating form of Charcot-Marie-Tooth syndrome.

E. Warnings and Precautions:

1. Myelosuppression: doxorubicin, etoposide and vincristine may all independently cause severe bone marrow suppression, including infection or bleeding. Myelosuppression is dose dependent and dose limiting. Doxorubicin-related nadirs usually occur between days 10 and 14. Etoposide-related nadirs usually occur between days seven and 16.

2. Cardiac function: doxorubicin can cause dose-dependent myocardial damage which usually presents as decreased left ventricular ejection fraction. The risk of cardiotoxicity is increased in patients with prior radiation treatment to the mediastinum or concurrent treatment with other cardiotoxic drugs, including cyclophosphamide (also a part of the DA-EPOCH-R regimen). Treatment with doxorubicin may also result in arrhythmias or EKG changes during or after administration. The total lifetime cumulative doxorubicin dose should be taken into account prior to each treatment with doxorubicin or any anthracycline.

3. Hepatotoxicity: doxorubicin clearance is decreased in patients with elevated serum bilirubin and is contraindicated in patients with severe hepatic impairment.

4. Tumor lysis syndrome: doxorubicin may induce tumor lysis syndrome in patients with rapid-growing tumors.

5. Neurotoxicity: attention should be given to patients receiving vincristine that have preexisting neuromuscular disease or are prescribed other drugs with neurotoxic potential.

6. Hypersensitivity, including anaphylaxis: doxorubicin, etoposide and vincristine may all independently illicit hypersensitivity reactions. Symptoms can include chills, fever, tachycardia, dyspnea, facial/tongue swelling and hypotension.

7. Extravasation: IV doxorubicin, etoposide and vincristine are venous irritants and tissue inflammation may occur after extravasation. If extravasation occurs, discontinue infusion and initiate proper treatment.

8. Pregnancy and lactation: treatment with doxorubicin, etoposide or vincristine may all independently cause fetal harm. Advise patients of reproductive potential to use adequate form of contraception during therapy and 6 months after discontinuation. Lactating patients should not breastfeed during treatment. Etoposide has potential to induce premature menopause, infertility, and amenorrhea in females and loss of fertility in males. Vincristine may cause azoospermia in males.

F. Pharmacokinetics: (ADME section in PI)

1. Doxorubicin:

   a. V_d: 809 to 1214 L/m^2
   b. Metabolism: hepatic to active metabolite (doxorubicinol), then inactive metabolites
   c. Half-life elimination: 20 to 48 hours
   d. Excretion: feces (~40% as unchanged drug), urine (5 to 12% as unchanged drug and metabolites)

2. Etoposide:

   a. V_d: 10 to 17 L/m^2
   b. Metabolism: hepatic, via CYP3A4 and 3A5
   c. Half-life elimination: 4 to 11 hours
   d. Excretion: urine (56%, 45% as unchanged drug), feces (44%)

3. Vincristine:

   a. Metabolism: hepatic via CYP3A4
   b. Half-life elimination: 85 hours
   c. Excretion: feces (~80%), urine (10-20%; <1% as unchanged drug)

G. Adverse Reactions:

1. Cardiovascular: cardiomyopathy, hypertension, hypotension
2. Dermatologic: alopecia

3. Endocrine and metabolic: dehydration, hyperuricemia, weight loss
4. Gastrointestinal: cramps, anorexia, constipation, intestinal necrosis, intestinal perforation, nausea, oral mucosa ulcers, diarrhea, vomiting
5. Genitourinary: bladder dysfunction, dysuria
6. Hematologic and oncologic: leukopenia, bone marrow depression
7. Hepatic: hepatotoxicity
8. Hypersensitivity: anaphylaxis
9. Nervous system: peripheral neuropathy, abnormal gait, abnormal sensory symptoms, cranial nerve disorder
10. Neuromuscular and skeletal: amyotrophy
11. Renal: polyuria

H. Drug Interactions: concurrent use of strong CYP3A4, CYP2D6 or P-glycoprotein inducers or inhibitors should be avoided. Additional drug-drug interactions may exist. Live vaccines should not be administered to patients receiving immunosuppressive therapy. Consult interaction database for patient specific assessment.

IV. ADMINISTRATIVE GUIDELINES

A. Bag hook ups, changes and disconnects will typically occur in outpatient clinic. Requests for bag changes (days 2 through 4) at home will be reviewed as needed.

B. Administer through 0.2-micron filter.

C. Do not co-administer with other products in the same IV line.

D. Hazardous handling: doxorubicin, etoposide and vincristine are all neoplastic agents and require handling, administering and disposing of with hazardous precautions. **It is the responsibility of the dispensing pharmacy to ensure medication handling is in compliance with organizational policies and procedures.**

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:

1. Alcohol Swabs
2. Gloves
3. Tape
4. IV access supplies as applicable
5. Pump pouch (750-1000 mL size)
6. Chemotherapy spill kit
7. Chemotherapy gloves, as needed
8. Chemotherapy gown, as needed
9. Chemotherapy prep mat, as needed
10. Chemotherapy precautions teaching sheet
11. Supplies for ambulatory infusion pump:

    a. Batteries for ambulatory pump (Ex: 9 Volt Duracell battery or 4 Double A batteries)
    b. Battery change procedure teaching sheet
    c. Continuous delivery mode teaching sheet

d. Pump return box

B. Prescription items:

1. Doxorubicin, etoposide, vincristine in 0.9% NaCl 1000 mL bag with 0.2-micron tubing.
2. Standard flushes per protocol.

C. How Supplied:

1. Doxorubicin, etoposide and vincristine will be provided as a 3-in-1 daily compounded bag with a total infusion volume of 1000 mL/day. The following concentrations of each have been studied:

   a. Doxorubicin 0.025 mg/mL-0.040 mg/mL
   b. Etoposide 0.125 mg/mL-0.20 mg/mL
   c. Vincristine 1 mcg/mL-1.6 mcg/mL

   All drugs should not exceed the upper limit of studied concentration, if possible. Etoposide is of particular concern for precipitation and should not exceed 250 mcg/mL in any case.

2. Compounded product will include the following:

   a. Doxorubicin daily dose + 5% overfill
   b. Etoposide daily dose + 5% overfill
   c. Vincristine daily dose + 5% overfill
   d. 0.9% NaCl diluent, QS to daily infusion volume of 1000 mL + 5% overfill
   e. DEHP-/PVC plastic-free 1000 mL bag
   f. Ambulatory pump tubing with 0.2-micron filter
   g. Closed system transfer device

D. Storage and Handling: the compounded bag should be stored at room temperature (59 to 77° F) for up to 72 hours, protected from light. Hazardous precautions are required.

E. Procedure for bag change, if not completed in clinic:

1. Explain the reasoning for visit and use of doxorubicin, etoposide and vincristine.
2. Don chemo gloves and gown. Prepare a chemotherapy prep mat.
3. Assess line for signs and symptoms of infection and complete line dressing change when indicated. Notify the ordering physician and pharmacist if line infection suspected. Educate patient on IV-line complications, line access procedures, and what to do if any complications arise.
4. Counsel patient on warnings, precautions, and potential side effects including but not limited to nausea, vomiting, diarrhea, alopecia, and myelosuppression.
5. Obtain labs, if ordered.
6. Perform bag change and educate patients against stopping the infusion at any point unless instructed to do so by a healthcare professional. Do not flush before or after bag change.

VI. CLINICAL MONITORING

A. Prior to therapy: baseline CBC with differential and platelet count, liver function tests, serum creatinine, blood urea nitrogen, hepatitis screening and assessment of left ventricular function is recommended.

B. During therapy:

1. Prior to the new cycle, telephone assessment will include:

    a. Tolerance of prior cycle, including of signs and symptoms of adverse effects including severe nausea and vomiting, infection, heart dysfunction, alopecia, mouth sores and hypersensitivity reactions.
    b. Reminder for patient to bring pump to cancer center on day 1 of cycle.

2. CBC with differential is recommended prior to each cycle. Patient should be monitored for severe myelosuppression.

3. Cumulative doxorubicin dose: **The recommended lifetime cumulative dose of doxorubicin is 450-550mg/m2. Obtain baseline dose from prescribing team at time of initial referral. Maintain documentation of cumulative dose on written Plan of Treatment.**

Please refer to the package inserts for the most up to date guidance on this medication.

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