These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

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Trabectedin (Yondelis) Clinical Guideline for Home Intravenous Therapy

Section: Clinical Guideline
Compliance: ACHC Infusion Pharmacy
Policy ID: CG034
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Approved by: Kathleen Patrick, President, 7/15/22, 7/7/25

I. BACKGROUND

Trabectedin (Yondelis) is a chemotherapy agent used in the treatment of unresectable or metastatic leiomyosarcoma and liposarcoma after failure on an anthracycline-containing regimen. Trabectedin also has a non-FDA approved use for the treatment of ovarian cancer in combination with pegylated liposomal doxorubicin following the failed treatment of 1 or 2 platinum-based regimens. Trabectedin is an alkylating agent which causes a disruption in the tumor cell cycle. The drug also causes cell death by initiating a cascade of events triggered by the binding of guanine resides in the minor groove of DNA that results in bending the DNA helix. Home infusion allows for the 24-hour continuous trabectedin infusion regimen utilized for leiomyosarcoma and liposarcoma. The following outlines the procedures for servicing patients in need of a continuous 24-hour infusion trabectedin therapy.

II. PATIENT ACCEPTANCE CRITERIA

A. All patients referred for outpatient trabectedin therapy must meet clinical admission criteria. Patients who may be eligible for outpatient administration will be identified by the oncologist, physician extender and/or pharmacist. The decision to initiate the first cycle in the home following clinic observation will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. Candidates for outpatient administration will demonstrate:

1. Patient is willing to receive treatment as an outpatient
2. Acceptable performance status at diagnosis
3. Availability of at least one caregiver
4. No perceived difficulty with instructions and no deficits in memory or cognition
5. No current substance abuse. Patients with remote history of substance abuse will be evaluated on a case-by-case basis.
6. Residence that is a reasonable distance to Cancer Center
7. Residence that is a reasonable distance to hospital facility in case of emergency such as extravasation
8. Reliable transportation
9. Insurance approval for outpatient administration of chemotherapy

B. Physician orders for must include:

1. Patient's height and weight
2. Drug
3. Dose (including body surface area dosing)

4. Route of administration
5. Frequency of administration
6. Emergency medications per protocol
7. Orders for pre-medications
8. Line care per protocol
9. Routine lab monitoring, if applicable

C. Venous access must be adequate for administration. Trabectedin must be administered through a central venous line. An inserted PICC line, implanted port, or other central line access will need to be confirmed prior to starting therapy.

D. Lab work will be completed per protocol or at the discretion of outpatient oncology team or provider. In addition, the following must be completed prior to the receipt of outpatient trabectedin:

1. Baseline labs including CBC with differential, LFTs, BUN/Cr, CPK
2. Verify pregnancy status of females of reproductive potential prior to initiating therapy
3. Left ventricular ejection fraction. Assess with echocardiogram (ECHO) or multigated acquisition scan (MUGA).

III. PHARMACOLOGIC REVIEW

Refer to manufacturer's full Prescribing Information for most up to date information

A. Indications: Soft tissue sarcoma, unresectable/metastatic

1. Leiomyosarcoma
2. Liposarcoma

B. Dosing: Dose is 1.5mg/m^2 IV infusion continuously over 24 hours through a central venous line every 21 days until disease progression or unacceptable toxicity.

C. Dose adjustments:

1. Hepatic:
   a. Reduce the initial dose to 0.9 mg/m^2 over 24 hours every 21 days for moderate hepatic impairment (defined as bilirubin levels greater than 1.5 time to 3 times the upper limit of normal, and AST/ALT less than 8 times the upper limit of normal).
   b. Avoid in patients with severe hepatic impairment (bilirubin levels above 3 times the upper limit of normal, and any AST and ALT).
2. Renal: The pharmacokinetics of trabectedin has not been evaluated in patients with severe renal impairment (CLcr< 30 mL/min) or end stage renal disease.
3. The recommended dose modifications for trabectedin based on abnormal labs or organ dysfunction are listed in the following table:

Table 1: Recommended Dose Modification

Laboratory Result or Adverse Reaction	DELAY next dose of YONDELIS for up to 3 weeks	REDUCE next dose of YONDELIS by one dose level for adverse reaction(s) during prior cycle
Platelets	Less than 100,000 platelets/microliter	Less than 25,000 platelets/microliter
Absolute neutrophil count	Less than 1,500 neutrophils/microliter	• Less than 1,000 neutrophils/microliter with fever/infection • Less than 500 neutrophils/microliter lasting more than 5 days
Total bilirubin	Greater than the upper limit of normal	Greater than the upper limit of normal
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	More than 2.5 times the upper limit of normal	More than 5 times the upper limit of normal
Alkaline phosphatase (ALP)	More than 2.5 times the upper limit of normal	More than 2.5 times the upper limit of normal
Creatine phosphokinase	More than 2.5 times the upper limit of normal	More than 5 times the upper limit of normal
Other non-hematologic adverse reactions	Grade 3 or 4	Grade 3 or 4

4. Dose Reduction

    a. The recommended starting dose reductions mentioned in the table above are found in the table below:

Table 2: Recommended Starting Doses and Dose Reductions

Starting Dose and Dose Reduction	For patients with normal hepatic function or mild hepatic impairment* prior to initiation of YONDELIS treatment	For patients with moderate hepatic impairment** prior to initiation of YONDELIS treatment
Starting Dose	1.5 mg/m^2	0.9 mg/m^2
Dose Reduction		
First dose reduction	1.2 mg/m^2	0.6 mg/m^2
Second dose reduction	1.0 mg/m^2	0.3 mg/m^2

* Including patients with bilirubin greater than 1 to 1.5 times the upper limit of normal, and any AST or ALT.
** Including patients with bilirubin levels greater than 1.5 times to 3 times the upper limit of normal, and AST and ALT less than 8 times the upper limit of normal.

5. Permanently discontinue trabectedin for:

    a. Persistent adverse reactions requiring a delay in dosing of more than 3 weeks
    b. Adverse reactions requiring dose reduction following trabectedin administered at 1.0 mg/m^2 for patients with normal hepatic function or at 0.3 mg/m^2 for patients with pre-existing moderate hepatic impairment.
    c. Severe liver dysfunction: bilirubin two times the upper limit of normal, and AST or ALT three times the upper limit of normal, and alkaline phosphatase less than two times the upper limit of normal in the prior treatment cycle for patients with normal liver function at baseline.
    d. Exacerbation of liver dysfunction in patients with pre-existing moderate hepatic impairment.
    e. Capillary leak syndrome
    f. Rhabdomyolysis

g. Grade 3 or 4 cardiac adverse events indicative of cardiomyopathy or for subjects with a left ventricular ejection fraction (LVEF) that decreases below the lower limit of normal.

D. Duration: Patients may continue therapy every 3 weeks until disease progression or unacceptable toxicity.

E. Contraindications: Patients with known severe hypersensitivity to trabectedin.

F. Warnings and Precautions

1. **Neutropenic sepsis:** Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%). Assess neutrophil count prior to administration of each dose of trabectedin and periodically throughout the treatment cycle. Withhold or reduce dose of trabectedin based on severity of adverse reaction.
2. **Rhabdomyolysis:** In clinical trials, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients receiving trabectedin. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving trabectedin (Grade 3 or 4 CPK elevation in 24 patients)**.** Renal failure occurred in 11 of these patients**.** Assess CPK levels prior to each administration of trabectedin**.** Withhold, reduce dose, or permanently discontinue based on severity of adverse reactions.
3. **Hepatotoxicity:** In clinical trials, the incidence of Grade 3-4 elevated liver function tests (LFTs; defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% in patients receiving trabectedin**.** Assess LFTs prior to each administration of trabectedin and as clinically indicated based on underlying severity of pre-existing hepatic impairment**.** Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality
4. **Cardiomyopathy:** Patients with a left ventricular ejection fraction (LVEF) < lower limit of normal, prior cumulative anthracycline dose of $\geq$300 mg/m^2 , age $\geq$65 years, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction. Assess LVEF by echocardiogram (ECHO) or multigated acquisition (MUGA) scan before initiation of trabectedin and at 2- to 3-month intervals thereafter until trabectedin is discontinued**.** Discontinue trabectedin based on severity of adverse reactions.
5. **Capillary Leak Syndrome (CLS):** CLS is characterized by hypotension, edema, and hypoalbuminemia. Monitor for signs and symptoms of CLS**.** If confirmed, discontinue trabectedin and promptly initiate standard management for patients with CLS, which may include a need for intensive care.
6. **Extravasation Resulting in Tissue Necrosis:** Extravasation of trabectedin, resulting in tissue necrosis requiring debridement, can occur more than 1 week after extravasation. There is no antidote for extravasation of trabectedin therefore, trabectedin must be administered through a central venous line.
7. **Embryo-Fetal Toxicity:** Trabectedin can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive age to use adequate forms of contraception during and two months after therapy. Advise male patients of reproductive potential to use adequate form of contraception during therapy and 5 months after discontinuation.

    a. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment.
    b. Advise lactating patients to not breastfeed while receiving therapy.

G. Pharmacokinetics

1. Distribution: Trabectedin is ~97% bound to plasma proteins and steady state volume of distribution exceeds 5,000 L.

2. Metabolism Trabectedin is a substrate of and is metabolized by CYP3A4 in the liver
3. Excretion: 6% in the urine unchanged, 58% in the feces unchanged.
4. Elimination half-life: 175 hours.

H. Adverse Reactions: Most common (≥20%) adverse reactions

1. Endocrine/metabolic: hypoalbuminemia [63% all grades, 3.7% (grade 3 or 4)].
2. Gastrointestinal:
   a. Constipation [37% all grades, (0.8% grade 3 or 4)]
   b. Decreased appetite [37% all grades, 1.9% (grade 3 or 4)]
   c. Diarrhea [35% all grades, 1.6% (grade 3 or 4)]
   d. Nausea [75% all grades, 7% (grade 3 or 4)]
   e. Vomiting [46% all grades, 6% (grade 3 or 4)]

3. Hematologic:
   a. Anemia (96% all grades)
   b. Neutropenia (66% all grades)
   c. Thrombocytopenia (59% all grades)

4. Hepatic:
   a. Elevation in Alkaline phosphatase [70% all grades, 1.6% (grade
   b. 3 or 4)]
   c. Elevation in ALT [90% all grades, 31% (grade 3 or 4)]
   d. Elevation in AST [84% all grades, 17% (grade 3 or 4)]

5. Musculoskeletal:
   a. Elevation in creatinine kinase level [33% all grades, 6.4% (grade 3 or 4)]

6. Neurologic: Headache [25% all grades, 0.3% (grade 3 or 4)]

7. Renal: Elevation in serum creatinine [46% all grades, 4.2% (grade 3 or 4)]

8. Respiratory: Dyspnea [25% all grades, 4.2% (grade 3 or 4)]

9. Other: Fatigue [69% all grades, 8% (grade 3 or 4)]

I. Drug Interactions

1. Avoid using strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) and strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) in patients taking trabectedin.
2. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the trabectedin infusion, and discontinue it the day prior to the next trabectedin infusion.
3. Drug-drug interactions may exist. Consult interaction database for patient specific assessment.

J. Compatibility:

1. Compatible with 0.9% Sodium chloride and Dextrose 5% in water.
2. Infusion solution is compatible with the following containers: Type I colorless glass vials, PVC, and polyethylene (PE) bags and tubing, PE and polypropylene (PP) mixture bags, polyethersulfone (PES) in-line filters, titanium, platinum or plastic ports, silicone and

polyurethane catheters, and pumps with PVC, PE, or PE/PP surfaces.

K. How Supplied and storage:

1. The drug vial contains a sterile, lyophilized white to off-white powder/cake in a single-dose glass vial containing 1 mg of trabectedin.
2. Store trabectedin vials in a refrigerator at 2°C to 8°C (36°F to 46°F).
3. The final compounded sterile preparation (CSP) that is connected to the patient is supplied in a bag with tubing and 0.2-micron filter attached. The CSP has a BUD of 30 hours at room temperature or under refrigeration after compounding.

***Note: Compounded sterile preparation (CSP) should be dispensed in final form from the compounding pharmacy to facilitate optimal BUD assessment per USP 797.**

IV. ADMINISTRATIVE GUIDELINES

A. Patients receiving trabectedin for soft tissue sarcoma via home infusion will be connected to the trabectedin cassette at their oncology office and disconnected at the office the following day. In addition, the oncology office will administer dexamethasone 20 mg IV as a pre-medication 30 minutes prior to starting trabectedin administration.

B. Trabectedin is a NIOSH group 1 hazardous agent. **It is the responsibility of the dispensing pharmacy to ensure medication handling is in compliance with organizational policies and procedures. This medication meets the definitions of a hazardous drug as outlined by the National Institute for Occupational Safety and Health (NIOSH).**

C. Administer though central venous line over 24 hours using a **0.2 micron polyethersulfone (PES) in-line filter** and a closed system transfer device.

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

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:

1. Alcohol swabs
2. Gloves
3. Tape
4. Chemo spill kit
5. Chemotherapy gloves, as needed
6. Chemotherapy gown, as needed
7. Chemotherapy prep mat, as needed
8. Ambulatory infusion pump
9. Batteries for ambulatory pump (Ex: 9 Volt Duracell battery or 4 Double A batteries)
10. Battery change procedure teaching sheet
11. Continuous delivery mode teaching sheet
12. Chemotherapy precautions teaching sheet
13. Pump return box
14. Pouch for pump and bag

B. Prescription Items:

1. Compounded tradebectin bag with closed system transfer device
2. Standard flushes per protocol

C. Compatibility:

1. Compatible with 0.9% Sodium chloride and Dextrose 5% in water.
2. Infusion solution is compatible with the following containers: Type I colorless glass vials, PVC, and polyethylene (PE) bags and tubing, PE and polypropylene (PP) mixture bags, polyethersulfone (PES) in-line filters, titanium, platinum or plastic ports, silicone and polyurethane catheters, and pumps with PVC, PE, or PE/PP surfaces.

D. Infusion Rates: Administer though central venous line and via an ambulatory infusion pump continuously over 24 hours using a 0.2-micron polyethersulfone (PES) in-line filter.

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

1. Explain the reasoning for visit and use of tradebectin.

2. Don chemo gloves and gown. Prepare 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, headache, and myelosuppression.

5. Obtain labs, if ordered.

6. Perform bag disconnect, flush IV line per protocol, and deaccess port if applicable.

VI. CLINICAL MONITORING

A. Prior to therapy:

1. Baseline labs including CBC with differential, LFTs, BUN/Cr, CPK
2. Verify pregnancy status of females of reproductive potential prior to initiating therapy
3. Left ventricular ejection fraction. Assess with echocardiogram (ECHO) or multigated acquisition scan (MUGA).
4. Ensure patient has central venous access for administration.

B. During therapy:

1. Instruct patients to monitor for and contact their healthcare provider regarding catheter site reactions, including new or worsening catheter site infection, pain, redness, inflammation, or dislodgment. Refer patient to ER if extravasation or tissue necrosis occurs.
2. Counsel patients to report any new onset of signs of infection as trabectedin has caused neutropenic sepsis.

3. Inform patients of the risks of myelosuppression. Instruct patients to immediately contact their healthcare provider for fever or unusual bruising, bleeding, tiredness, or paleness.
4. Monitor patients for any signs/symptoms related to cardiac issues, rhabdomyolysis, liver toxicity, or capillary leak syndrome (hypotension, edema, or hypoalbuminemia).
5. Monitor for adverse effects including nausea, vomiting, anemia, headache, diarrhea, and fatigue.
6. Laboratory work monitoring to include: LFTs, CPK, CMP, and CBC with differential.

C. Follow up pharmacy assessment will include:

1. Assessment of signs and symptoms of adverse effects
2. Reminder for patient to bring infusion pump to cancer center

D. Patients receiving this outpatient regimen will have 24/7 access to nursing and/or pharmacy staff outside of clinic hours for any questions or pump troubleshooting.

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

REFERENCES

Jones RL, Maki RG, Patel SR, et al. Safety and Efficacy of Trabectedin When Administered in the Inpatient Versus Outpatient Setting: Clinical Considerations for Outpatient Administration of Trabectedin. *Cancer.* 2019 Dec 15; 125(24):4435-4441.

Yondelis [package insert]. Horsham, PA. Janssen Products, LP; 2017.