CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

YONDELIS (TRABECTEDIN)

Section: Nursing
Compliance: ACHC Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
TJC Standards: N/A
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I. POLICY

Yondelis (Trabectedin) 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 and protocol for coordination of 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 determine 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 / 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. 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. Insertion of PICC line, implanted port, or other central line access
2. Baseline labs including CBC with differential, LFTs, BUN/Cr, CPK
3. Verify pregnancy status of females of reproductive potential prior to initiating therapy
4. Left ventricular ejection fraction (ECHO or MUGA)

III. PHARMACOLOGY OVERVIEW

A. Indications and Dosing

1. Soft tissue sarcoma, unresectable/metastatic
    a. 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
2. Ovarian cancer, relapsed, platinum sensitive (off-label use)
    a. 1.1mg/m^2 IV over 3 hours every three weeks until disease progression, unacceptable toxicity, or for 2 cycles after assessment of a complete response
3. Dose adjustments
    a. Avoid in patients with severe hepatic impairment (bilirubin levels above 3 times the upper limit of normal, and any AST and ALT)
    b. The pharmacokinetics of Trabectedin has not been evaluated in patients with severe renal impairment (CLcr< 30 mL/min) or end stage renal disease
    c. The recommended dose modifications for Trabectedin based on abnormal labs or organ dysfunction are listed in the following tables:

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 Reductions

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.

B. Contraindications

1. Patients with known severe hypersensitivity, including anaphylaxis, to Trabectedin.

C. Precautions

1. Neutropenic Sepsis
    a. Ten patients (2.6%) experienced neutropenic sepsis, 5 of whom had febrile neutropenia, which was fatal in 4 patients (1.1%).
    b. 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
    a. In clinical trials, rhabdomyolysis leading to death occurred in 3 of the 378 patients receiving Trabectedin.
    b. Elevations in creatine phosphokinase (CPK) occurred in 122 of the 378 patients receiving Trabectedin (Grade 3 or 4 CPK elevation in 24 patients)
        i. Renal failure occurred in 11 of these patients
    c. Assess CPK levels prior to each administration of Trabectedin
        i. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction
3. Hepatotoxicity
    a. 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
    b. Assess LFTs prior to each administration of Trabectedin and as clinically indicated based on underlying severity of pre-existing hepatic impairment
    c. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality
4. Cardiomyopathy and decreased ejection fraction
    a. Patients with LVEF < lower limit of normal, prior cumulative anthracycline dose of ≥300 mg/m2, age ≥65 years, or a history of cardiovascular disease may be at increased risk of cardiac dysfunction
    b. 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
    c. Discontinue treatment with Trabectedin based on severity of adverse reaction
5. Capillary Leak Syndrome

a. Capillary leak syndrome (CLS) characterized by hypotension, edema, and hypoalbuminemia
b. Monitor for signs and symptoms of CLS
i. 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
a. Extravasation of Trabectedin, resulting in tissue necrosis requiring debridement, can occur
b. No antidote for extravasation of Trabectedin therefore, administer Trabectedin through a central venous line
7. Embryo-Fetal Toxicity
a. Advise male patients of reproductive potential to use adequate form of contraception during therapy and 5 months after discontinuation
b. Advise female patients of reproductive age to use adequate forms of contraception during and two months after therapy
c. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment
d. Advise lactating patients to not breastfeed while receiving therapy.
8. 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/m2 for patients with normal hepatic function or at 0.3 mg/m2 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 (AEs) indicative of cardiomyopathy or for subjects with an LVEF that decreases below the lower limit of normal

D. Adverse Reactions

1. ≥20%
a. Nausea
b. Fatigue
c. Vomiting
d. Constipation
e. Decreased appetite
f. Diarrhea
g. Peripheral edema
h. Dyspnea
i. Headache
2. The most common (≥5%) grades 3-4 laboratory abnormalities are:
a. Neutropenia
b. Increased ALT
c. Thrombocytopenia
d. Anemia
e. Increased AST
f. Increased creatinine phosphokinase

E. 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.

F. Pharmacokinetics

1. Binding of Trabectedin to human plasma proteins is approximately 97%, and steady state volume of distribution exceeds 5000 L. The terminal elimination half-life is approximately 175 hours. Approximately 58% of the drug is eliminated in feces and 6% in urine.

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. Ovarian cancer patients also receive dexamethasone as a pre-medication and pegylated Doxorubicin prior to Trabectedin administration.

C. Trabectedin is a NIOSH group 1 hazardous agent.

D. Infusion solution is compatible with the following: 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.

E. Administer via ambulatory infusion pump with volumes and continuous rate indicated on label as appropriate. Bags will contain a small amount of overfill (10-15 mL). Pharmacists are to use clinical judgement when rounding overfill to prevent waste.

F. Administer though central venous line over 24 hours using a 0.2-micron polyethersulfone (PES) in-line filter.

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.

G. Duration

1. Patients may continue therapy every 3 weeks until disease progression or unacceptable toxicity

V. NURSING PROCEDURE

A. Supplies

1. Alcohol swabs
2. Chemo spill kit
3. Ambulatory infusion pump
4. 9 Volt Duracell battery for Prizm or 4 Double A batteries for Solis or external battery pack for Sapphire
5. Chemotherapy precautions teaching sheet
6. CADD Prizm/Solis battery change procedure teaching sheet
7. Sapphire/CADD Prizm/Solis continuous delivery mode teaching sheet
8. Pump return box
9. Pouch for pump and bag

B. Preparation

1. Trabectedin is a cytotoxic drug - follow applicable special handling and disposal procedures
2. Using aseptic technique, inject 20 mL of Sterile Water for Injection, USP into the vial. Shake the vial until complete dissolution. The reconstituted solution is clear, colorless to pale brownish-yellow, and contains 0.05 mg/mL of Trabectedin
3. Inspect for particulate matter and discoloration prior to further dilution. Discard vial if particles or discoloration are observed.
4. Immediately following reconstitution, withdraw the calculated volume of Trabectedin (dose including overfill amount) and further dilute with 500 mL of 0.9% Sodium Chloride in an empty 500 mL Intravia bag.
    a. Calculate overfill to be ~ 10-12 mL (or best judgement accounting for tubing volume without using an extra vial)
5. Compounded product expires 30 hours after mixing – be mindful of appointment time and drive time to ensure compounded product will not expire prior to PC office hookup time
    a. Dispensing technician to write date and time on label that infusion will expire
6. Administer though central venous line over 24 hours using a 0.2-micron polyethersulfone (PES) in-line filter.

C. Storage and How Supplied

1. 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)

VI. ASSESSMENT AND CLINICAL MONITORING

A. Counseling points

1. Counsel patients to report any new onset of signs of infection as Trabectedin has caused neutropenic sepsis.
2. Inform patients of the risks of myelosuppression. Instruct patients to immediately contact their healthcare provider for fever or unusual bruising, bleeding, tiredness, or paleness.

B. Lab Monitoring

1. CPK levels
2. LFTs

C. Monitor patients for any signs/symptoms related to cardiac issues, rhabdomyolysis, liver toxicity, or capillary leak syndrome (hypotension, edema, or hypoalbuminemia)

D. 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

E. 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

VII. 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.

APPENDICES

A. Supplements to the policy that are numbered and assigned accordingly