Treatment Considerations for Patients With Unresectable or Metastatic Liposarcoma or Leiomyosarcoma After Prior Anthracycline Therapy—A Roundtable Discussion

Learning Objectives

- Review the epidemiology of soft tissue sarcoma, including liposarcoma and leiomyosarcoma
- Examine YONDELIS®, a recently available treatment option for patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen
- Understand the dosage and administration guidelines of YONDELIS®
- Identify appropriate candidates for treatment with YONDELIS®

Indications

- YONDELIS® is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen

Contraindications

- YONDELIS® is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin

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Yondelis® (trabectedin)

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Important Safety Information

CONTRAINDICATIONS - YONDELIS® is contraindicated in patients with known severe hypersensitivity, including anaphylaxis, to trabectedin.

WARNINGS AND PRECAUTIONS

Neutropenic sepsis, including fatal cases, can occur. In Trial 1, the incidence of Grade 3 or 4 neutropenia, based on laboratory values, was 43% (161/378). Median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range: 8 days to 9.7 months). Median time to complete resolution of neutropenia was 13 days (range: 3 days to 2.3 months). Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 18 patients (5%). 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 YONDELIS® and periodically throughout the treatment cycle. Withhold YONDELIS® for neutrophil counts of less than 1500 cells/microliter on the day of dosing. Permanently reduce the dose of YONDELIS® for life-threatening or prolonged, severe neutropenia in the preceding cycle.

Rhabdomyolysis - YONDELIS® can cause rhabdomyolysis and musculoskeletal toxicity. In Trial 1, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients. Elevations in creatine phosphokinase (CPK) occurred in 122 (32%) of the 378 patients receiving YONDELIS®, including Grade 3 or 4 CPK elevation in 24 patients (6%), compared to 15 (9%) of the 172 patients receiving dacarbazine with any CPK elevation, including 1 patient (0.6%) with Grade 3 CPK elevation. Among the 24 patients receiving YONDELIS® with Grade 3 or 4 CPK elevation, renal failure occurred in 11 patients (2.9%); rhabdomyolysis with the complication of renal failure occurred in 4 of these 11 patients (1.1%). Median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months). Median time to complete resolution was 14 days (range: 5 days to 1 month). Assess CPK levels prior to each administration of YONDELIS®. Withhold YONDELIS® for serum CPK levels more than 2.5 times the upper limit of normal. Permanently discontinue YONDELIS® for rhabdomyolysis.

Hepatotoxicity, including hepatic failure, can occur. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 x ULN were not enrolled in Trial 1. In Trial 1, the incidence of Grade 3-4 elevated liver function tests (defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378). Median time to development of Grade 3-4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3 to 4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months). In Trial 1, the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% (5/378). ALT or AST elevation greater than eight times the ULN occurred in 18% (67/378) of patients. Assess LFTs prior to each administration of YONDELIS®. Manage elevated LFTs with treatment interruption, dose reduction, or permanent discontinuation based on severity and duration of LFT abnormality.

Cardiomyopathy, including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction can occur. In Trial 1, patients with a history of New York Heart Association Class II to IV heart failure or abnormal left ventricular ejection fraction (LVEF) at baseline were ineligible. In Trial 1, cardiomyopathy occurred in 23 patients (6%) receiving YONDELIS® and in four patients (2.3%) receiving dacarbazine. Grade 3 or 4 cardiomyopathy occurred in 15 patients (4%) receiving YONDELIS® and 2 patients (1.2%) receiving dacarbazine; cardiomyopathy leading to death occurred in 1 patient (0.3%) receiving YONDELIS® and in none of the patients receiving dacarbazine. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving YONDELIS® was 5.3 months (range: 26 days to 15.3 months). Assess left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition (MUGA) scan before initiation of YONDELIS® and at 2- to 3-month intervals thereafter until YONDELIS® is discontinued. Withhold YONDELIS® for LVEF below lower limit of normal. Permanently discontinue YONDELIS® for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to lower limit of normal within 3 weeks.

Extravasation Resulting in Tissue Necrosis - Extravasation of YONDELIS®, resulting in tissue necrosis requiring debridement, can occur. Evidence of tissue necrosis can occur more than 1 week after the extravasation. There is no specific antidote for extravasation of YONDELIS®. Administer YONDELIS® through a central venous line.

Embryofetal Toxicity - Based on its mechanism of action, YONDELIS® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during therapy and for at least 2 months after the last dose of YONDELIS®. Advise males with female partners of reproductive potential to use effective contraception during therapy and for at least 5 months after the last dose of YONDELIS®.

Adverse Reactions - The most common (≥20%) adverse reactions are nausea (75%), fatigue (69%), vomiting (46%), constipation (37%), decreased appetite (37%), diarrhea (35%), peripheral edema (28%), dyspnea (25%), headache (25%).

The most common (≥5%) grades 3-4 laboratory abnormalities are: neutropenia (43%), increased ALT (31%), thrombocytopenia (21%), anemia (19%), increased AST (17%), and increased creatine phosphokinase (6.4%).

DRUG INTERACTIONS

Effect of Cytochrome CYP3A Inhibitors - Avoid use of strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS®. Avoid taking grapefruit or grapefruit juice. 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 YONDELIS® infusion, and discontinue it the day prior to the next YONDELIS® infusion.

Effect of Cytochrome CYP3A Inducers - Avoid administering strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) to patients who are taking YONDELIS®

Please see accompanying full Prescribing Information for YONDELIS®. 040598-150918

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Yondelis® (trabectedin)

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You are cordially invited to attend a live educational program.

Please find registration details below.

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Presented by

Bartosz Chmielowski, M.D.
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David Geffen School of Medicine at UCLA
Los Angeles, CA

Wednesday, February 22, 2017

6:00 PM Dinner and Presentation
Please RSVP by Wednesday, February 15, 2017

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If you have any questions about this program, call **1-888-735-7418**.
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by Wednesday, February 15, 2017

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