YONDELIS® (trabectedin)
YONDELIS – Hepatotoxicity

SUMMARY

- Hepatotoxicity, including hepatic failure, can occur with YONDELIS. In the phase 3 randomized study (SAR-3007)[1] in patients (N=550) with advanced liposarcoma (LPS) or leiomyosarcoma (LMS) previously treated with an anthracycline and ≥1 additional systemic therapy, patients with serum bilirubin levels above the upper limit of normal (ULN) or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >2.5 x ULN were not enrolled. The incidence of grade 3-4 elevated liver function tests (LFTs; defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378) in patients receiving YONDELIS. The median time to development of grade 3-4 elevation in ALT or AST was 29 days (range, 3 days-11.5 months). Of the 134 patients with grade 3-4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range, 4 days-4.4 months).[2]
- In the phase 3 randomized study (SAR-3007)[1], the incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST >3 x ULN, alkaline phosphatase <2 x ULN, and total bilirubin ≥2 x ULN) was 1.3% (5/378) in patients receiving YONDELIS. ALT or AST elevation >8 x ULN occurred in 18% (67/378) of patients receiving YONDELIS.[2]
- Assess LFTs prior to each administration of YONDELIS 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.[2] Please refer to the YONDELIS Prescribing Information for dose modification guidelines in patients who develop hepatotoxicity.
- In a hepatotoxicity analysis of patients treated with YONDELIS in the phase 3 randomized study (SAR-3007), median progression-free survival (PFS) in patients with grade 3-4 hepatotoxicity was similar to that seen in patients with grade 0-2 hepatotoxicity (4.63 months vs 3.55 months; hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.68-1.23).[3]
- Please refer to the DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, USE IN SPECIFIC POPULATIONS, and PATIENT INFORMATION sections of the full Prescribing Information.

CLINICAL DATA

To provide the most relevant information, the summary below is limited to a phase 3 study and a large, retrospective analysis of 19 phase 2 studies. Additional studies and case reports describing hepatotoxicity associated with YONDELIS, as well as studies evaluating use of prophylactic dexamethasone with YONDELIS, are included in the OTHER RELEVANT LITERATURE section.

Phase 3 Study in Patients with Advanced LPS or LMS (SAR-3007)

Demetri et al (2016)[1,2,4] evaluated the efficacy and safety of YONDELIS vs dacarbazine in patients (N=550) with locally advanced or metastatic LPS or LMS previously treated with an anthracycline and at least 1 additional systemic therapy. Patients were randomized 2:1 to YONDELIS (n=378; 1.5 mg/m^2 intravenously [IV] via central venous access over 24 hours every 21 days) or to dacarbazine (n=172; 1 g/m^2 IV over 20-120 minutes every 21 days). All patients treated with YONDELIS were required to receive dexamethasone 20 mg IV injection 30 minutes prior to the start of the YONDELIS infusion. Major prognostic factors were well balanced among patients and most patients received ≥2 prior lines of chemotherapy. The primary efficacy endpoint was overall survival, while secondary efficacy endpoints included PFS, objective response rate, duration of response, and time to progression. Patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 x ULN were not enrolled. Patients with significant chronic liver disease such

as cirrhosis or active hepatitis were excluded. The median duration of exposure to YONDELIS was 13 weeks (range, 1-127 weeks), with 30% of patients exposed to YONDELIS for >6 months and 7% of patients exposed to YONDELIS for >1 year.

The incidence of grade 3-4 elevated LFTs (defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% (134/378) in patients receiving YONDELIS. The median time to development of grade 3-4 elevation in ALT or AST was 29 days (range, 3 days-11.5 months). Of the 134 patients with grade 3-4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range, 4 days-4.4 months). The incidence of drug-induced liver injury (defined as concurrent elevation in ALT or AST >3 x ULN, alkaline phosphatase <2 x ULN, and total bilirubin ≥2 x ULN) was 1.3% (5/378) in patients receiving YONDELIS. ALT or AST elevation >8 x ULN occurred in 18% (67/378) of patients receiving YONDELIS.[2]

Relevant laboratory adverse events (AEs) of all grades are described in Table: Relevant Laboratory AEs.

Relevant Laboratory AEs[2]

	YONDELIS[a]		Dacarbazine[a]	
	All Grades	**Grades 3-4**	**All Grades**	**Grade 3-4**
Increased ALT	90%	31%	33%	0.6%
Increased AST	84%	17%	32%	1.2%
Increased alkaline phosphatase	70%	1.6%	60%	0.6%
Hyperbilirubinemia	13%	1.9%	5%	0.6%
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase. [a]YONDELIS group (range, 373-377 patients) and dacarbazine group (range, 166-168 patients).				

Post-Hoc Analysis

Calvo et al (2018)[3] conducted a hepatotoxicity analysis of patients treated with YONDELIS in a phase 3 randomized study (SAR-3007). The impact of LFT abnormalities on treatment outcomes was analyzed through a comparison of PFS in patients who experienced worst grade 3-4 hepatotoxicity (n=109) vs PFS in patients who experienced worst grade 0-2 hepatotoxicity (n=231). Transaminase elevations were common and were the most frequent reason for dose reductions. In addition, transaminase elevations were transient and noncumulative in all patients, including those with grade 3-4 elevations. Median PFS in patients who developed grade 3-4 hepatotoxicity was similar to that seen in patients with grade 0-2 hepatotoxicity (4.63 months vs 3.55 months; HR, 0.91; 95% CI, 0.68-1.23).

Retrospective Pooled Safety Study

Le Cesne et al (2012)[5] conducted a retrospective, pooled analysis of available safety data with YONDELIS as single-agent therapy in patients with advanced, solid tumors. The analysis included 1132 patients exposed to YONDELIS in 19 phase 2 trials, in which YONDELIS was administered as 1 of 3 schedules: a 24-hour infusion Q3W at starting dose of 1.5 mg/m^2 (n=570/2818 cycles), a 3-hour infusion Q3W at starting dose of 1.3 mg/m^2 (n=258/1003 cycles), or a 3-hour infusion for 3 consecutive weeks every 4 weeks at starting dose of 0.58 mg/m^2 (n=304/1198 cycles). Dexamethasone has been given prior to infusion at the recommended dose of 20 mg for over 30 minutes in the majority of studies. Most patients had received prior chemotherapy. The primary endpoint in the studies was antitumor activity, and safety was a secondary endpoint. A median of 3 YONDELIS cycles (range, 1-59 cycles) were administered over a median treatment duration of 9.4 weeks (range, 3.0-236.7 weeks).

There were 1390 (27.7%) cycles with dose delay >5 days. Grade 3-4 transaminase increases (ALT, 19.2%; AST, 9.2%) occurred in the cycle prior to dose delay. Transaminase

elevation peaked at days 5-7 and returned to grade ≤1 at approximately day 15 of each cycle. Overall, incidence and severity of ALT elevation decreased over cycles in those with the longest treatment duration; such AEs were manageable by dose adjustment. YONDELIS dose reductions were mandatory in the event that hepatobiliary disorders occurred between cycles (bilirubin elevation >ULN; alkaline phosphatase >2.5 x ULN; aminotransferases >2.5 x ULN that were not recovered by day 21 of the cycle).[5]

In a broader analysis, which included data from the Q3W 3-hour schedule, no new signals of hepatobiliary disorders or liver toxicities were found. However, the Q3W 24-hour schedule was associated with a higher incidence of severe liver test abnormalities.[5]

OTHER RELEVANT LITERATURE

The occurrence of hepatotoxicity during treatment with YONDELIS has also been described in other published studies[6-8] and case reports.[9-12] Three of these cases reported irreversible hepatoxicity secondary to YONDELIS use, with two of these cases being fatal.[10-12] Another case reported on a marked increase in liver lytic enzymes secondary to drug interaction with an herbal (chokeberry extract; *Aronia melanocarpa*), which gradually resolved following hospitalization and cessation of the offending agent.[9]

Studies evaluating cotreatment with dexamethasone as a measure against hepatotoxicity associated with YONDELIS have also been published.[13-15] One of these was a phase 2 study that assessed the efficacy, safety, and pharmacokinetic profile of YONDELIS, with or without prophylactic dexamethasone cotreatment, in patients with recurrent, advanced soft tissue sarcoma (N=41). Due to toxicity, the randomized study design was modified to open-label to make dexamethasone mandatory, and the initial dose (1650 µg/m^2) was reduced to 1500 µg/m^2, and then to 1300 µg/m^2. Transient, grade 3-4 AST and ALT elevations were observed in 23 (56%) and 27 (66%) patients, respectively, and grade 3 bilirubin elevations occurred in 2 (5%) patients. Most dose reductions were due to hepatic toxicity; dose reduction decreased incidence of grade 3-4 AST elevation from 76% to 25%. Dexamethasone was shown to reduce hepatotoxicity associated with YONDELIS.[13]

In another study involving 54 patients with advanced sarcoma, 23 patients did not receive dexamethasone premedication prior to YONDELIS, while the other 31 did. Grade 3-4 transaminase elevation was observed in 31% of patients and 12% of cycles. In all but 1 patient, hepatotoxicity was reversible to baseline within 15 days and was not clinically significant. Incidence of grade 3-4 transaminase (AST-ALT) elevation was as follows: without dexamethasone, 70% of patients and 34% of cycles; with dexamethasone premedication, 3% of patients and <1% of cycles.[15]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 11 October 2024.

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