YONDELIS® (trabectedin)
Use of YONDELIS in Patients with Hepatic Impairment

SUMMARY

- Mild hepatic impairment is not associated with a clinically significant effect on the pharmacokinetics of YONDELIS.[1]
- The mean YONDELIS exposure was (97%) higher in patients with moderate (bilirubin levels greater than 1.5 to 3 times the upper limit of normal [ULN], and aspartate aminotransferase [AST] and alanine aminotransferase [ALT] less than 8 times the ULN) hepatic impairment compared to patients with normal (total bilirubin ≤ the ULN, and AST and ALT ≤ the ULN) liver function. Reduce YONDELIS dose in patients with moderate hepatic impairment.[1,2]
- The recommended dose of YONDELIS is 0.9 mg/m^2 in patients with moderate hepatic impairment (bilirubin levels greater than 1.5 times to 3 times the ULN, and AST and ALT less than 8 times the ULN).[1]
- Do not administer YONDELIS to patients with severe hepatic impairment (bilirubin levels above 3 times the ULN, and any AST and ALT).[1]
- The effect of severe hepatic impairment on YONDELIS exposure is unknown.[1]
- Hepatotoxicity, including hepatic failure, can occur with YONDELIS.[1]
- Assess liver function tests (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.[1]
- In a phase 1/2a, open-label, multicenter, single-dose, nonrandomized study, use of YONDELIS in patients with hepatic impairment resulted in higher plasma exposures versus controls.[2]
- Please refer to the DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, USE IN SPECIFIC POPULATIONS, CLINICAL PHARMACOLOGY, and PATIENT COUNSELING INFORMATION sections of the full Prescribing Information.[1]

CLINICAL DATA

Phase 1/2a Study

Calvo et al (2018)[2] evaluated the pharmacokinetics of YONDELIS in patients with locally advanced or metastatic solid tumors and moderate hepatic impairment (N=15).

Study Design/Methods

- Phase 1/2a, open-label, multicenter, single-dose, nonrandomized study (NCT01273493)
- Patients were stratified by hepatic function, based on serum total bilirubin and ALT concentrations.
  - In the control group, patients without hepatic dysfunction (n=9) received a single-dose of YONDELIS 1.3 mg/m^2 as a 3-hour intravenous (IV) infusion.
  - Patients with hepatic impairment, defined as having stable serum total bilirubin concentrations >1.5x to ≤3x ULN for at least 8 days at baseline and AST or ALT concentrations <8x ULN, received YONDELIS 0.58 mg/m^2 (n=3) or 0.9 mg/m^2 (n=3) as a 3-hour IV infusion.
- Select inclusion criteria: locally advanced or metastatic disease (any solid tumor except hepatocellular carcinoma), intolerant to or had relapsed or progressive disease following standard-of-care chemotherapy, Eastern Cooperative Oncology Group performance status ≤2, and adequate organ function
- Exclusion criteria: prior exposure to YONDELIS, intrinsic liver disease (eg, cirrhosis or hepatitis), therapy known to exacerbate hepatic impairment within 2 weeks of YONDELIS administration, use of potent inducers or inhibitors of CYP3A4 activity within 3 weeks before YONDELIS administration, and significant cardiovascular disease or abnormality

- For pharmacokinetic evaluations, blood samples were collected pre-dose and at 0.5, 1.5, 2 hours 50 minutes, 3.5, 4, 5, 8, 24, 48, 72, 120, and 168 hours during and after the infusion.
- **Primary objective:** characterize the pharmacokinetic profile of YONDELIS in patients with advanced malignancies and hepatic impairment
- **Secondary objectives:** assess survival and safety of YONDELIS when administered to patients with hepatic impairment

Results

Patient Characteristics

- Fifteen patients (n=6 in the hepatic impairment group; n=9 in the control group) were included in the study.

Pharmacokinetics

- For both the control and hepatic impairment groups, mean YONDELIS plasma concentration-time profiles from pre-dose to 168 hours post-dose increased over the 3-hour infusion period, followed by a rapid decline after completion of the infusion and a slow terminal elimination phase.
- Mean pharmacokinetic parameters for YONDELIS in patients with hepatic impairment and in the control group are shown in Table: Mean (SD) Pharmacokinetic Parameters for YONDELIS in Patients with Hepatic Impairment and Control Patients.
- The unbound fraction of YONDELIS in plasma averaged 1.24% (range, 0.969%-1.56%) in the hepatic impairment group and 2.20% (range, 0.918%-3.50%) in the control group.
- Geometric mean ratios (90% confidence interval) were 1.40 (0.99-1.99) and 1.97 (1.20-3.22) for dose-normalized maximum plasma concentration and area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration, respectively, in patients with hepatic impairment compared to control patients.

Mean (SD) Pharmacokinetic Parameters for YONDELIS in Patients with Hepatic Impairment and Control Patients[2]

Variable	Hepatic impairment group		Control group
	YONDELIS 0.58 mg/m² n=3	YONDELIS 0.9 mg/m² n=3	YONDELIS 1.3 mg/m² n=9
Actual dose, mg	1.12 (0.29)	1.59 (0.12)	2.41 (0.28)
t_{max}, hours[a]	2.83 (2.83-2.83)	1.58 (1.50-2.80)	2.83 (0.52-3.45)
$t_{1/2}$, hours	104 (20.0)[b]	NAs	94.7 (13.3)[c]
C_{max}, ng/mL	6.29 (1.92)	9.84 (3.05)	10.4 (3.72)
AUC_{48}, ng·hour/mL	28.0 (9.79)	55.6 (23.5)	42.5 (20.4)
AUC_{last}, ng·hour/mL	41.6 (18.1)	105 (59.4)	62.8 (32.3)
AUC_{∞}, ng·hour/mL	40.5 (19.8)[b]	NAs	76.4 (46.3)[c]
V_z, L	4090 (2110)[b]	NAs	5290 (2720)[c]
CL, L/h	29.1 (19.6)[b]	NAs	38.6 (19.0)[c]
Fraction unbound	0.0121 (0.00256)	0.0127 (0.0406)[b]	0.0220 (0.00928)[d]

Abbreviations: AUC_{48}, area under the plasma concentration-time curve from time 0 to 48 hours after the start of YONDELIS infusion; AUC_{last}, area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration of YONDELIS; AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinity (calculated as the sum of AUC_{last} and $C_{last}/\lambda z$, where C_{last} is the last observed quantifiable concentration and λz is the first-order rate constant associated with the terminal portion of the curve); CL, total clearance of drug after intravenous administration (calculated as dose/AUC_{∞}); C_{max}, maximum plasma concentration; NAs, not assessable (AUC_{∞}, $t_{1/2}$, V_z, and CL were not calculated if r^2 adjusted was below 0.8 or if $AUC_{\infty,ex}$ was greater than 20%); SD, standard deviation; $t_{1/2}$, elimination half-life; t_{max}, time to reach C_{max}; V_z, apparent volume of distribution (calculated as dose/λz x AUC_{∞}]).
[a]Median (range); [b]n=2; [c]n=6; [d]n=7.

Safety

- All 15 enrolled patients were evaluable for safety.
- One patient in the control group had a treatment-emergent adverse event (TEAE; sepsis, unrelated to treatment) that led to treatment discontinuation.
- The most frequently reported TEAEs were vomiting in the hepatic impairment group (n=3) and nausea in the control group (n=4).
- Grade 3-4 drug related TEAEs were increased AST, increased bilirubin, leukopenia, and neutropenia (n=1 in each case) in the hepatic impairment group, and increased ALT (n=1), increased AST (n=2), neutropenia (n=2), thrombocytopenia (n=1), and anemia (n=1) in the control group.
- Three patients had serious TEAEs considered to be related to YONDELIS (1 in the hepatic impairment 0.9 mg/m^2 cohort, 2 in the control group).
- There were 2 deaths within 30 days of YONDELIS administration. The death in the hepatic impairment group was due to progressive disease. The death in the control group was related to a TEAE (sepsis). Neither deaths were considered related to YONDELIS.

Survival Follow-up

- Of the 15 enrolled patients, 13 died (5 in the hepatic impairment group and 8 in the control group), 2 within 30 days of dosing (1 in each of the 2 groups).
  - Nine patients died within 0 to <6 months, 3 died within 6 to <12 months, and 1 died within 12 to <18 months after receiving the single dose of YONDELIS.
  - The remaining 2 patients were lost to follow-up.

Retrospective Pooled Analysis

In a population pharmacokinetic analysis of 5 phase-1 and 9 phase-2 studies involving 603 patients with cancer, plasma clearance of YONDELIS in patients with mild hepatic impairment was similar to that seen in patients with normal hepatic function (total bilirubin ≤1.5-fold greater than ULN, AST and ALT levels ≤2.5-fold greater than ULN).[3]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 18 September 2024.

REFERENCES

1. YONDELIS (trabectedin) [Prescribing Information]. Horsham, PA: Janssen Products, LP;https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/YONDELIS-pi.pdf.

2. Calvo E, Azaro A, Rodon J, et al. Hepatic safety analysis of trabectedin: results of a pharmacokinetic study with trabectedin in patients with hepatic impairment and experience from a phase 3 clinical trial. *Invest New Drug*. 2018;36(3):476-486.

3. Perez-Ruixo JJ, Zannikos P, Hirankam S, et al. Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients. *Clin Pharmacokinet*. 2007;46(10):867-884.