YONDELIS® (trabectedin)
YONDELIS – Rhabdomyolysis

SUMMARY

- YONDELIS can cause rhabdomyolysis and musculoskeletal toxicity. In the phase 3 registration 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, rhabdomyolysis leading to death occurred in 3 (0.8%) of the 378 patients receiving YONDELIS. 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%). The median time to first occurrence of grade 3 or 4 CPK elevations was 2 months (range, 1 to 11.5 months). The median time to complete resolution was 14 days (range, 5 days to 1 month).2
- Assess CPK levels prior to each administration of YONDELIS. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.2
- In a retrospective analysis of 10,841 patients with advanced solid tumors treated with YONDELIS, the incidence of rhabdomyolysis was 0.7%. The majority of cases occurred during the first 2 cycles of treatment. The incidence of fatal cases was 0.3%.3
- Please refer to the DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, 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 (N>10,000). Additional studies reporting the occurrence of rhabdomyolysis 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] evaluated the efficacy and safety of YONDELIS vs dacarbazine in patients (N=550) with unresectable, 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 (1.5 mg/m^2 intravenously [IV] via central venous access over 24 hours every 21 days; n=378) or dacarbazine (1 g/m^2 over 20-120 minutes every 21 days; n=172). All patients treated with YONDELIS were required to receive dexamethasone 20 mg IV injection 30 minutes prior to the start of each YONDELIS infusion. Major prognostic factors were well balanced among patients, and most patients received ≥2 prior lines of chemotherapy. The median duration of exposure to YONDELIS was 13 weeks (range, 1 to 127 weeks), with 30% of patients exposed for >6 months and 7% of patients exposed for >1 year.

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Retrospective Safety Analysis

Grosso et al (2012)[3] conducted a retrospective safety analysis to determine the incidence of rhabdomyolysis events reported during YONDELIS treatment since the first phase 1 study conducted in April 1996, up to September 2010.

Study Design/Methods

- Cases of rhabdomyolysis and clinically relevant CPK increases without acute renal failure were identified from 10,841 adult patients with advanced solid tumors who received YONDELIS as a single-agent or in combination with doxorubicin or pegylated liposomal doxorubicin.
- Multivariate analyses evaluated potential predictive risk factors for rhabdomyolysis in the subset of 2321 patients who received YONDELIS in the clinical trial setting.

Results

- The overall incidence of rhabdomyolysis was 0.7% (75/10,841 patients), with most cases occurring in cycle 1 (13.3%) or cycle 2 (57.3%) of treatment.
- Median age of patients with rhabdomyolysis was 55 years (range, 21 to 83 years), and 54.7% were females.
- The incidence of fatal rhabdomyolysis was 0.3% (31/10,841).
- The median time for CPK peak was day 13.5 after the last dose (range, 2.0 to 33.0 days); grade 3/4 CPK increase was observed in 33.3% of patients.
- Treatment consisted of either dialysis, IV hydration, or urine alkalinization.
- CPK increases without acute renal failure were observed in 0.4% (48/10,841) of patients (grade 2, 5.2%; grade 3, 43.1%; grade 4, 34.5%); all patients had normal renal function without relevant clinical impact.
- Multivariate analyses did not identify any potential factor that could be predictive or represent a significantly higher risk of developing rhabdomyolysis.

OTHER RELEVANT LITERATURE

The occurrence of rhabdomyolysis during treatment with YONDELIS has also been described in other published studies[4-12] and case reports[13-19]. Some of these rhabdomyolysis events were fatal.[4-8,10,16] Two of these case reports described severe muscle pain and a marked increase in serum levels of myoglobin, CPK, and lactate dehydrogenase, leading to a conclusive diagnosis of rhabdomyolysis secondary to drug interactions with an herbal agent (chokeberry extract; *Aronia melanocarpa*) in one patient and a bioflavonoid (diosmin) in another patient. Both patients gradually recovered following hospitalization and cessation of the offending agent.[13,18]

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 24 September 2024.

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