YONDELIS® (trabectedin)
Use of YONDELIS in Pediatric Patients

SUMMARY

- YONDELIS is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.[1]
- Safety and effectiveness in pediatric patients have not been established.[1]
  - Safety (n=61) and efficacy (n=58) were assessed across five open-label studies (NCT00006463, NCT01453283, NCT00005625, NCT00070109, and ET-B-023-00) in pediatric patients (aged 2 to <17 years) with pediatric histotypes of sarcoma (predominantly rhabdomyosarcoma, osteosarcoma, Ewing sarcoma, and non-rhabdomyosarcoma soft tissue sarcoma). No new safety signals were observed in pediatric patients across these studies.[1]
  - Pharmacokinetic parameters in 17 pediatric patients (aged 3 to 17 years) were within the range of values previously observed in adults given the same dose per body surface area.[1]
- Limited efficacy was observed in a phase 2 study of YONDELIS in children with recurrent rhabdomyosarcoma, Ewing sarcoma, or nonrhabdomyosarcoma soft tissue sarcomas (NRSTSs). Among 42 evaluable patients, 1 partial response (PR) was observed in a patient with rhabdomyosarcoma and stable disease (SD) was observed in 3 patients (1 each with rhabdomyosarcoma, spindle-cell sarcoma, and Ewing sarcoma). Grade 3/4 dose-limiting toxicities (DLTs) included fatigue, alanine aminotransferase (ALT) elevations, aspartate aminotransferase (AST) elevations, gamma-glutamyl transferase (GGT) elevations, myelosuppression, and deep vein thrombosis (DVT).[2]
- In a phase 1 study of YONDELIS in children and adolescents with refractory or relapsed solid tumors, DLTs included anorexia, fatigue, dehydration, and GGT elevation. The maximum tolerated dose (MTD) was determined to be 1.5 mg/m^2 given intravenously (IV) over 24 hours every 21 days (Q21D). Pharmacokinetic parameters were similar to those observed in adults. PR was achieved in 1 patient (neuroendocrine carcinoma), and SD was observed in 3 patients (osteosarcoma, n=2; desmoplastic small round cell tumor, n=1).[3]
- In a phase 1 study of YONDELIS in children with refractory solid tumors, DLTs included prolonged grade 4 neutropenia and reversible grade 4 ALT elevation. The MTD was determined to be 1100 mcg/m^2 given IV over 3 hours Q21D. Complete response (CR) was achieved in 1 patient with metastatic Ewing sarcoma after completing 6 courses of treatment.[4]

CLINICAL DATA

To provide the most relevant information, the summary below is limited to prospective phase 1 and 2 studies with enrollment restricted to pediatric patients.

Phase 2 Study

Baruchel et al (2012)[2] evaluated the safety, efficacy, and pharmacokinetics of YONDELIS in children with recurrent rhabdomyosarcoma, Ewing sarcoma, or NRSTSs (N=50).

Study Design/Methods

- Two-part study (dose-finding phase evaluating safety and phase 2 component evaluating efficacy)
- Select inclusion criteria: patients aged ≥12 months and ≤21 years at initial diagnosis with histologic diagnosis of rhabdomyosarcoma, Ewing sarcoma, or NRSTS, measurable disease according to Response Evaluation Criteria in Solid Tumors, and performance score by Karnofsky or Lansky of ≥50%
- *Dose-finding phase:* Patients were enrolled in cohorts of 6 to evaluate the safety of 2 doses (1.3 and 1.5 mg/m^2) administered as a 24-hour infusion.

- If <2 patients experienced DLTs during the first cycle, the dose was increased to 1.5 mg/m^2. If ≥2 patients experienced DLTs during the first cycle, the dose was decreased to 1.1 mg/m^2. If ≤1 patient experienced DLTs during the first cycle of 1.5 mg/m^2, then this was considered the recommended dose and patients would move on to the 2-stage design of the phase 2 component.
- DLTs were defined as: (1) grade 3-4 nonhematological toxicity considered possibly, probably, or likely related to YONDELIS (except for grade 3 nausea/vomiting, grade 3 ALT/AST that returned to grade 1 or baseline prior to next cycle, and grade 3 fever, infection, or alopecia) OR (2) grade 4 neutropenia >7 days or grade 4 thrombocytopenia >7 days which required transfusion >2 times in 7 days or which caused delay of >14 days in start of next cycle. Grade 3-4 GGT elevation was also considered a DLT.

- *Phase 2 component:* Efficacy was then evaluated using a 2-stage design (10 + 10) at the 1.5 mg/m^2 dose.
  - Ten patients in each disease strata of NRSTS, Ewing sarcoma, and rhabdomyosarcoma were enrolled in the first stage. If none had CR or PR, enrollment to that stratum was closed. If ≥6 objective responses (ORs) were observed, enrollment to that stratum was closed. Otherwise, enrollment continued to a total of 20 patients. If ≥3/20 patients had OR, then YONDELIS activity was deemed as warranting further investigation.
  - Responders were considered patients with 2 consecutive evaluations of SD, complete remission, or PR.
- YONDELIS was administered as a 24-hour IV infusion Q21D; patients received dexamethasone 2.5 mg/m^2 orally the evening before YONDELIS and every 12 hours on days 1, 2, and 3 of each cycle.
- Pharmacokinetics (day 1 and steady state) were performed during cycle 1.

Results

Patient Characteristics

- Mean age was 15.5 years (range, 4-24), 62% were males, and 76% were white.
- Patient diagnosis included rhabdomyosarcoma in 46% (n=23), Ewing sarcoma in 32% (n=16), and NRSTS in 22% (n=11); sarcoma not otherwise specified and desmoplastic small round-cell tumor (n=1 for each); alveolar soft-part sarcoma, spindle-cell sarcoma, undifferentiated sarcoma, and synovial sarcoma (n=2 for each).

Dose-Finding Phase

- Fourteen patients were enrolled, receiving YONDELIS 1.3 mg/m^2 (n=8) or 1.5 mg/m^2 (n=6); 11 patients were evaluable for toxicity (3 were not due to disease progression prior to completing cycle 1).
- One of 6 patients treated at the 1.3 mg/m^2 dose had DLTs of fatigue and grade 3 GGT elevation; no DLTs were observed in the 5 patients treated at the 1.5 mg/m^2 dose.
- Reversible grade 3 myelosuppression and elevation of AST/ALT were reported in 7 patients.

Phase 2 Component - Efficacy

- A total of 42 patients were evaluated, of which 6 were from the YONDELIS 1.5 mg/m^2 dose group in the dose-finding phase, and 36 from the phase 2 component. Forty of these patients were fully evaluable for response.
- PR was observed in 1 patient with rhabdomyosarcoma after 6 cycles.
- SD was achieved in 3 patients (1 with rhabdomyosarcoma after 15 cycles [for duration of 2 cycles], 1 with spindle-cell sarcoma after 2 cycles [for duration of 3 cycles], and 1 with Ewing sarcoma after 4 cycles [for duration of 15 cycles]).
- Patients received a median of 4 cycles (range, 1-15).

Phase 2 Component - Safety

- Forty-one patients were evaluable for toxicity.
- DLTs were reported in 9/41 (22%) patients, with 8 DLTs occurring during cycle 1, including the following: grade 3 fatigue (n=1), grade 3 GGT elevation (n=7), grade 3 AST elevation (n=2), grade 3 ALT elevation (n=2), grade 4 absolute neutrophil count (ANC) toxicity (n=1), and grade 3 DVT (n=1).
- Toxicities observed in ≥5% of patients included: ANC (34%), elevated ALT (32%), leukocytes (27%), elevated AST (24%), lymphopenia (17%), elevated GGT (15%), platelets (12%), hemoglobin (7%), fatigue (5%), hypokalemia (5%), and thrombosis/embolism (vascular-related access; 5%).

Pharmacokinetics

- A pharmacokinetic analysis was conducted using plasma samples of 10 patients treated at the 1.5 mg/m^2 dose. Plasma clearance was 24.3 ± 16.2 L/h/m^2, maximum plasma concentration was 2.49 ± 2.25 ng/mL, area under the curve$_{0-\infty}$ was 112.6 ± 132.5 ng/mLxh, and half-life was 52.6 ± 18.4 hours. Trough drug concentrations were greater than the concentrations associated with antitumor activity in preclinical model systems.

Phase 1 Studies

Chuk et al (2012)[3] conducted a phase 1 and pharmacokinetic study of YONDELIS in children and adolescents (4-16 years of age) with refractory or relapsed solid tumors to determine the MTD, safety profile, and pharmacokinetics of a 24-hour continuous IV infusion of YONDELIS (N=12). YONDELIS (starting dose of 1.1 mg/m^2, with escalation to 1.5 and 1.7 mg/m^2) was administered as a 24-hour infusion through a central venous catheter Q21D; prophylactic dexamethasone and growth factor support were also administered. A total of 58 cycles were administered, with a median of 2.5 cycles/patient (range, 1-18 cycles). Three, 6, and 3 patients received YONDELIS at 1.1, 1.5, and 1.7 mg/m^2, respectively. One patient experienced dose-limiting (grade 3) anorexia and fatigue at 1.5 mg/m^2, while 2 patients experienced dose-limiting (grade 3) dehydration and GGT elevation at 1.7 mg/m^2, respectively. Nausea, emesis, myelosuppression, fatigue, and elevation of serum transaminases were noted as non-DLTs. The MTD was determined to be 1.5 mg/m^2 IV over 24 hours Q21D. Pharmacokinetic parameters were found to be similar to those observed in adults in previous studies. PR was observed in a patient with neuroendocrine carcinoma, while SD ≥6 cycles was observed in 3 patients (osteosarcoma, n=2; desmoplastic small round-cell tumor, n=1).

Lau et al (2005)[4] conducted a phase 1 study of YONDELIS in 12 evaluable children <18 years of age with refractory solid tumors. The starting dose of YONDELIS was 1100 mcg/m^2, with planned escalations of 200 mcg/m^2 increments; treatment was administered as a 3-hour IV infusion via central venous catheter Q21D. Prophylactic therapy consisted of ondansetron/granisetron with or without dexamethasone. Six patients were treated at the first dose level (1100 mcg/m^2) and 6 at the second level (1300 mcg/m^2; 1 patient was reduced to 1100 mcg/m^2 due to grade 4 creatine phosphokinase elevation). One DLT (prolonged grade 4 neutropenia) was observed at the first dose level (1100 mcg/m^2), and 2 DLTs (reversible grade 4 ALT elevations) were observed at the second dose level (1300 mcg/m^2). The MTD was therefore defined as 1100 mcg/m^2. Reversible hepatotoxicity, the most common adverse event, occurred in 58% of patients. Hematologic toxicity consisted of 2 episodes of grade 3 neutropenia, 1 episode of grade 4 neutropenia, and 1 episode of grade 4 anemia. Among 11 patients evaluable for response, 1 CR (duration of 10 months) was observed in a patient with metastatic Ewing sarcoma after completion of 6 courses; the patient experienced recurrence 3 months following cessation of treatment.

Case Reports

Trabal et al (2018)[5] reported the use of YONDELIS (1.2 mg/m^2 IV) in a 17-year-old male with metastatic, refractory synovial sarcoma to the lungs that progressed following failure of several chemotherapy regimens. After 2 cycles of YONDELIS treatment, the patient no longer required oxygen therapy or ambulatory assistance. Radiological imaging showed significant reduction in number and size of lung nodules. Safety results were not reported.

Colli et al (2012)[6] evaluated the efficacy and safety of YONDELIS (1.3 to 1.5 mg/m^2 IV over 24 hours Q21D for 13 cycles) in 4 pretreated, pediatric patients with relapsed or progressive, advanced sarcomas. One patient with a triton tumor had significant response, but her tumor progressed after 4 cycles, eventually leading to death. No other patient responded to YONDELIS. Nausea/vomiting and fatigue were reported in 61.5% of the cycles. The following were also reported: anemia (30.6%), neutropenia (15.3%), elevated ALT (15.3%), elevated AST (15.3%), elevated GGT (7.7%), and lipasemia/amylasemia (7.7%). One patient presented with significant transaminasemia/pancreatitis likely related to steroids and died following the first cycle due to invasive ductal carcinoma.

Farah et al (2011)[7] reported on the use of YONDELIS (1.3 mg/m^2 IV over 24 hours for 2 cycles) in an 8-year-old boy with nonmetastatic, alveolar rhabdomyosarcoma of the right forearm (group 3, stage 3) following failure of several other chemotherapy regimens and disease progression. Within 48 hours, improvement in the patient's quality of life was noted, with a significant decrease in daily morphine doses and ability to tolerate oral intake again. He experienced transient neutropenia and ultimately died after experiencing increasing respiratory failure with disease progression 28 months after initial diagnosis.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 20 April 2023.

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