3602 Open-Label Bendamustine for Pediatric Patients with Relapsed or Refractory Acute Leukemia: Safety and Efficacy Outcomes

Program: Oral and Poster Abstracts
Type: Poster
Session: 615. Acute Myeloid Leukemia - Therapy, excluding Transplantation: Poster III
Monday, December 12, 2011, 6:00 PM-8:00 PM
Hall GH (San Diego Convention Center)

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Background

Acute leukemias, consisting of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), are the most common form of childhood cancers. New treatments are needed for patients whose disease progresses or recurs following established therapies.

Bendamustine is an alkylating agent that has demonstrated activity in adults with chronic lymphoblastic leukemia and rituximab-refractory non-Hodgkin lymphoma (NHL). Bendamustine has antileukemic activity in adults with AML and myelodysplastic syndrome; however, there are few data regarding bendamustine in children or in childhood acute leukemia specifically. This study is a single-arm, phase 1/2 dose-escalating trial to determine the recommended phase 2 dose (RP2D), schedule, pharmacokinetics, and safety profile of bendamustine in pediatric patients with relapsed and refractory acute leukemia.

Methods

Subjects were children aged 1-20 years with relapsed or refractory ALL or AML and without the opportunity for curative therapy. Acute toxic effects of prior therapy (ended ≥2 weeks prior to first dose of study drug) had resolved to grade 2 or less.

Bendamustine was infused IV over 60 minutes on days 1 and 2 of each 21-day cycle, with delays allowed up to 2 weeks for neutrophil and platelet recovery. The starting dose was 90 mg/m^2/dose with planned escalation to 120 and 150 mg/m^2 in cohorts of 3. The dose of 150 mg/m^2 was to be implemented only if 120 mg/m^2 was safe, but produced subtherapeutic plasma levels compared with data from adults.

In phase 2, patients were enrolled at the RP2D in phase 1. Patients were followed until disease progression, withdrawal due to safety or other reasons, loss to follow-up, or a maximum of 12 cycles. After the end of treatment, patients were evaluated every 3 months for 12 months after the last dose, or until progression, death, or start of new cancer treatment.

Overall response rate was assessed in all recipients and defined as complete response (CR) or CR without platelet recovery (CRp). Duration of response was assessed in patients who achieved CR or CRp. Biologic activity (≥ partial response [PR]) was also recorded. Safety assessments included adverse events (AEs), concomitant medication throughout treatment, vital signs, and clinical laboratory values.

Results

Eleven patients were treated in phase 1 and 32 patients in phase 2. There were 27 patients with ALL and 16 with AML. Twenty-five patients had received >3 chemotherapy regimens and 20 patients had received prior hematopoietic cell transplant in addition to chemotherapy regimens. In phase 1, 5 patients received 90 mg/m^2/dose, and 6 received 120 mg/m^2/dose. Because no dose-limiting toxicities were observed and therapeutic levels were obtained at 120 mg/m^2, the RP2D was determined to be 120 mg/m^2. In phase 2, 32 patients received 120 mg/m^2.

Responses in patients with ALL included 2 patients with CR at 90 mg/m^2, 1 had PR, and 7 had stable disease at 120 mg/m^2. Two patients with AML had stable disease at 120 mg/m^2. Duration of response ranged from 1-8 months with one patient still in remission after unrelated stem cell transplant. Three deaths due to progressive disease occurred in phase 1 and 13 in phase 2. None were considered treatment-related. Thirty-seven patients had at least one grade 3 AE and 19 had at least one grade 4 AE. Twenty patients had grade 3/4 thrombocytopenia (47%), 20 had grade 3/4 anemia (46.5%), and 15 had grade 3/4 febrile neutropenia (35%). Most frequent grade 3/4 non-hematologic AEs were hyperkalemia (21%), dyspnea (9.3%), and tumor lysis syndrome (9.3%). No patients withdrew due to AEs.

Conclusions

In pediatric patients with multiple relapsed and refractory ALL and AML, preliminary data suggest that bendamustine has an acceptable safety profile. The RP2D was established as 120 mg/m^2, which is identical to that used to treat adults with rituximab-refractory NHL. Response data for the study population suggest that bendamustine has minimal activity in heavily pretreated patients with relapsed and refractory ALL, but not in AML. Further studies will be required to evaluate the role of this agent in combination with regimens that are the backbone of current leukemia therapy in children.

This research was sponsored by and conducted by Cephalon, Inc., Frazer, PA.

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