Venous thromboembolism in patients with acute lymphoblastic leukemia (ALL) treated with eryaspase (L-asparaginase encapsulated in red blood cells)

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Background

L-asparaginase (ASNase) is a key drug in the treatment of ALL. Its toxicity includes venous thromboembolism (VTE) which can be serious and potentially fatal. The reported prevalence of VTE among children and adults with ALL ranges between 1% and 37%. The rate is dependent on cofounding factors such as higher age, presence of indwelling venous catheters, the use of prophylactic antithrombin replacement or anticoagulation, inclusion of asymptomatic cases, and other risk factors unrelated to the use of ASNase. ASNase leads to serum asparagine depletion, inhibiting the synthesis of anti-coagulation factors such antithrombin III (AT), protein C, and protein S, which leads to increase in thrombin generation and risk of TE.

ASNase is derived from *E. coli* (native or the long acting pegylated forms) or *Erwinia chyrsanthemi* bacteria. Eryaspase is an investigational product under development that uses a novel system to deliver native *E. coli* ASNase encapsulated within donor-derived matched red blood cells (RBCs) by a proprietary osmotic-based method. The aim is to improve the tolerance and prolong the activity of this enzyme. After eryaspase infusion, plasma asparagine is actively transported into RBCs, where it is hydrolyzed. As a result, asparagine in the plasma is depleted. ASNase activity of eryaspase is longer that the native *E. coli*. RBC encapsulation is done at GMP facilities in a process that typically takes 24 hours from obtaining donor-matched RBC to shipment of the product to the investigator's center. Eryaspase is delivered directly to the Investigator for immediate transfusion over 1 hour. We are reporting on the occurrence of VTE after eryaspase treatment in patients with ALL, given the use of RBC and its distinct manufacturing process.

Methods

Integrated safety data from 5 studies of eryaspase in ALL were retrospectively analyzed using MedDRA coding. Treatment with eryaspase was in combination with chemotherapy during induction and consolidation phases. The cut-off date for analysis was 28 Feb 2017.

Results

A total of 125 patients were included in this series, with median age of 20 years (range, 2 - 77). Treatment was generally well tolerated. 8 (6.4%) patients (7 adults; one child) had VTE; 6 (4.8%) were serious events. VTE was considered related to eryaspase in 6 (4.8%) patients. The most common event was reported as venous thrombosis (n=6 (4.8%)). None of the events had a fatal outcome. Decreased AT was found in 35 (28%) of the patients. In a subset of patients randomized to eryaspase (n=26) or to native ASNase (n=28), laboratory coagulation abnormalities were observed in 11.5% and 71.4% during induction, respectively.

Conclusion

The risk of VTE with eryaspase treatment in our ALL patients was low and seen mostly in adults. The low incidence of these events may be related to decreased incidence of impaired coagulation parameters. We conclude that eryaspase is not associated with an increased rate or severity of VTE toxicity.