Erwinia asparaginase for acute lymphoblastic leukemia in children with hypersensitivity to *E coli*-derived asparaginase

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Asparaginase *Erwinia chrysanthemi*, an asparaginase derived from the bacterium *E chrysanthemi*, was recently approved by the Food and Drug Administration as a component of multiagent chemotherapy in patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *Escherichia coli* (*E coli*)-derived asparaginase and pegaspargase.[1] Hypersensitivity to *E coli*-derived asparaginase may occur in up to 30% of patients[2] with ALL, a common childhood cancer. Leukemic cells are not able to synthesize the amino acid asparagine, which is required for protein metabolism and survival, because of a lack of asparagine synthetase activity. *Erwinia*-derived asparaginase reduces circulating levels of asparagine by catalyzing the deamidation of asparagine to aspartic acid and ammonia. The reduction of circulating asparagine results in cytotoxicity specific for leukemic cells by depriving them of their source of the amino acid.

The approval of *Erwinia* asparaginase treatment was based on a multicenter, open-label study in 58 children and teenagers (median age, 10 years; range, 2-18) who had ALL and who were not able to continue receiving pegaspargase or asparaginase derived from *E coli* because of allergic reactions to those two therapies.[1] The major efficacy outcome was achievement of sustained serum asparaginase activity levels of at least 0.1 IU/mL, a level that is known to result in the depletion of asparagine to levels that predict efficacy.

The patients received *Erwinia* asparaginase 25,000 IU/m^2 intramuscularly 3 times weekly for 2 weeks (for a total of 6 doses) as a replacement for each scheduled dose of pegaspargase remaining in their original treatment protocol. More than half of the patients (59%) were male; 78% were white, 10% were black or African American, 5% were Asian, and 5% were Hispanic or Latino. The planned number of courses of *Erwinia* asparaginase (2 weeks, 6 doses) ranged from 1 to 8. In all, 32 patients (55%) completed the planned therapy and 9 stopped therapy before completion—4 because of allergic reactions, and 5 because of physician or patient choice.

A total of 48 patients were considered evaluable for efficacy based on the pharmacokinetics measurements that were recorded during their first course of *Erwinia* asparaginase. Of those, 35 patients had asparaginase

What's new, what's important

Acute lymphoblastic leukemia (ALL) is the most common form of childhood leukemia. It accounts for about 75% of all leukemias in children. The cure rate for ALL is very high, approaching 90%. Combination chemotherapy is the cornerstone of leukemia treatment.

Asparaginase, native *Escherichia coli*-derived is the cornerstone of the ALL chemotherapy regimens. However, about 30% of patients develop allergic reaction to E coli-derived asparaginase. Pegaspargase (PEG-A) has been approved by the Food and Drug Administration for the treatment of patients with newly diagnosed ALL or in patients with a history of hypersensitivity to native L-asparaginase.

Recent findings have shown that between 15% and 20% of ALL patients develop hypersensitivity to *E coli*-derived asparaginase, including PEG-A, representing about 450-600 children in the United States each year. *Erwinia* asparaginase (derived from *Erwinia chrysanthemi*) has now been approved by the FDA for this subset of patients who are allergic reaction to native asparaginases.

The dose of 25,000 IU/m^2 is given intramuscularly 3 times a week for 2 weeks for a total of 6 doses. The common side effects included systemic allergic reactions (17%), pancreatitis (4%), liver function abnormalities (4%), and fever (3%).

Erwinia asparaginase is an important lifesaving treatment option for a subset of patients with ALL.

— Jame Abraham, MD

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How I treat ALL

There are several regimens that are used for the treatment of patients with newly diagnosed acute lymphocytic leukemia (ALL) and they all have a common theme of induction, followed by consolidation, maintenance, and central nervous system (CNS) prophylaxis. I use either the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin (also known as adriamycin), and dexamethasone) chemotherapy regimen or the CALGB (Cancer and Leukemia Group B) regimen. Both yield a similar complete response (CR) rate of 85%-90% and a 5-year survival of 40%.

The main differences between the two regimens are that the hyper-CVAD is usually given inpatient with supportive care in between cycles as an outpatient, whereas the CALGB regimen is outpatient after induction; CNS prophylaxis in the hyper-CVAD regimen is achieved with intrathecal therapy (IT) and high-dose methotrexate, whereas in the CALGB regimen it is achieved with cranial radiation and IT therapy; and the hyper-CVAD regimen does not include asparaginase, whereas the CALGB regimen does. In patients with Philadelphia chromosome-positive (Ph+) ALL, hyper-CVAD with either imatinib or dasatinib has yielded excellent results. However, hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1) remains the standard of care at this time.

Three separate retrospective studies[1-3] found improved outcome for adolescents and young adults treated with pediatric ALL regimens when compared with treatment with adult regimens. Based on those findings, there is an intergroup study in which adults who are younger than 40 years are treated with a pediatric regimen (CALGB 10403, an intergroup phase 2 clinical trial for adolescents and young adults with untreated ALL). I treat all patients under 40 years old with that protocol.

HSCT in first remission is indicated for patients with Ph+ ALL and in patients with the t(4;11) translocation. Its role in patients younger than 35 years remains controversial. In the UKALL XII/ECOG E2993 study, patients who were younger than 35 years benefited from HSCT in CR1, with a 10% difference in overall survival compared with standard chemotherapy. However, because the chemotherapy used was an adult ALL regimen, we consider the adult ALL regimen an inferior regimen in patients younger than 35 years old in light of the aforementioned data mentioned.

— Ehab Atallah, MD

References

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activity of at least 0.1 IU/mL at 48 hours after the last dose, and 13 had activity at that level 72 hours after the last dose.

The safety data were derived from the 58 patients in the open-label trial and from 572 patients with ALL or lymphoblastic lymphoma who were enrolled in an *Erwinia* asparaginase expanded-access program after they developed systemic hypersensitivity to an *E coli* asparaginase. The latter group of patients had a median age of 9 years (range, 1-66), 62% were male, and 97% had ALL. They received doses of *Erwinia* asparaginase that ranged from 20,000-25,000 IU/m^2. The planned number of doses ranged from 3 to 48, and 75% of patients were able to receive all planned doses. Common adverse events were similar in severity and incidence to those attributable to *E coli* asparaginase. Of the total 630 patients, the most common adverse events were systemic allergic reactions (17%), pancreatitis (4%), liver function abnormalities (4%), and fever (3%). Grade 3 or 4 adverse events consisted of allergic reaction/hypersensitivity in 9% of patients in the open-label trial, and 5% of patients in the expanded access population; elevated transaminases in 2% of patients in the open-label trial, and less than 1% of expanded access patients; and hyperglycemia in 2%, pancreatitis in 1%, thrombosis in 1%, and hemorrhage in less than 1% of expanded access patients.

Erwinia asparaginase carries warnings/precautions for serious hypersensitivity reactions, including anaphylaxis, severe or hemorrhagic pancreatitis, glucose intolerance, thrombosis, and hemorrhage. There have been no adequate, well-controlled studies of *Erwinia* asparaginase in pregnant women, it is not known if it is secreted in human milk, and its safety and efficacy have not been studied in elderly patients.

References

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