

# Impact of Clinical and Subclinical Hypersensitivity to Asparaginase in Acute Lymphoblastic Leukemia

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Asparaginase is an essential element of acute lymphoblastic leukemia treatment. It depletes serum asparagine (an amino acid necessary for synthesis of cellular proteins), deprives leukemic blast cells of asparagine, and eventually results in cell death. To gain benefit from asparaginase, asparagine depletion must be ensured by giving intensive therapy and completing the full course of treatment. Three formulations of asparaginase exist; two are derived from *Escherichia coli*, a native form and pegylated form, and one is derived from *Erwinia chrysanthemi* (*Erwinia* asparaginase). Like many large proteins, asparaginases are immunogenic, and some patients develop antibodies to asparaginase. Antibodies may result in clinical hypersensitivity or subclinical hypersensitivity without symptoms, and both can result in a reduction in asparaginase activity and may affect therapeutic benefit. Clinical hypersensitivity is the most common reason for patients to stop asparaginase treatment. Subclinical hypersensitivity can only be identified by laboratory testing; therapeutic monitoring of asparaginase activity is used as a surrogate measure for asparagine depletion.

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Key words: hypersensitivity; antibodies; subclinical hypersensitivity; asparaginase; *Erwinia* asparaginase

Digital Object Identifier: 10.1188/14.CJON.E107-E112

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease, and treatment is selected on the basis of risk of relapse. Pediatric study groups classify patients into standard-, high-, and very high-risk groups, whereas adult study groups generally classify patients as standard or high risk (Pui & Evans, 2006). The risk of relapse is graded according to a number of factors including clinical features, cytogenetics, and initial response to therapy. Age at diagnosis and presenting leukocyte count are strong prognostic indicators. In pediatrics, standard-risk disease is usually defined as patients aged 1–9 years with a presenting leukocyte count of less than  $50 \times 10^9/L$ . In adults, prognosis worsens as age and leukocyte count increase (Pui & Evans, 2006).

Response to treatment has the greatest prognostic strength. Newer technological advances have made the measurement of minimal residual disease (MRD) to assess the proportion of leukemic cells remaining after induction therapy, a strong determining factor for treatment stratification; MRD of less than 0.01% identifies patients with an excellent outcome, whereas MRD of more than 1% after induction or more than 0.1% later

in treatment identifies patients with an extremely high risk of relapse (Pui & Evans, 2006). The use of MRD in terms of methodology, time points of testing, and appropriate cutoffs to identify different groups is an area of active investigation among all cooperative groups and continues to evolve.

Asparaginase is a cornerstone of treatment for ALL and is used in all treatment protocols (Pieters et al., 2011). To gain clinical benefit from asparaginase, patients must receive intensive therapy and complete the full course of treatment. A number of studies have shown significant benefit in terms of event-free survival (EFS), disease-free survival, and continuous complete remission rate with intensive asparaginase therapy (Rizzari et al., 2013).

## Asparaginase Products

### Mode of Action

Asparaginase is a naturally occurring enzyme in animals, plants, and microorganisms. It hydrolyzes asparagine to aspartic acid and ammonia, removing asparagine from the serum. Leukemic blast cells are unable to synthesize asparagine and, therefore,