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50 Years Ago in *The Journal of Pediatrics*

L-Asparaginase Therapy in Pediatric Acute Lymphoblastic Leukemia: Optimizing Efficacy and Minimizing Toxicity

Pratt CB, Simone JV, Zee P, Aur RJ, Johnson WW. Comparison of daily vs weekly L-asparaginase for the treatment of childhood acute leukemia. J Pediatr 1970;77:474-83.

L-asparaginase is a chemotherapeutic agent that was discovered in the 1950s and first administered to patients in the 1960s. By 1970, several studies had shown that L-asparaginase therapy could induce temporary bone marrow remission in patients with leukemia; however, its toxicity was underappreciated. For example, a study from 1969 reported the efficacy of L-asparaginase therapy and asserted that it was "relatively nontoxic…" and that "it does not possess the toxicity associated with conventional treatment."[1] Nevertheless, some oncologists at the time were beginning to observe substantial and unique toxicities with L-asparaginase therapy as it became more frequently administered.[2]

In this study, Pratt et al sought to more fully characterize L-asparaginase toxicity and to evaluate whether an alteration in its dosing regimen could ameliorate the toxicity while preserving its efficacy. The investigators treated 19 children with relapsed acute leukemia, 16 with acute lymphoblastic leukemia (ALL) and 3 with acute myelogenous leukemia. Patients were randomized to either conventional daily dosing or weekly dosing of L-asparaginase for 2 weeks as monotherapy. The authors performed extensive laboratory, clinical, and postmortem examinations to assess toxicity. L-asparaginase therapy was found to alter liver function studies and coagulation measures, as well as to cause nausea, vomiting, and weight loss in the majority of patients. The authors observed single instances of severe pancreatitis, hemorrhage, and hypersensitivity, all of which are now well-characterized toxicities with L-asparaginase therapy. Notably, thrombosis is an important toxicity that was not observed in this study. The authors found a trend toward diminished L-asparaginase toxicity in the weekly dosing group and similar efficacy in inducing bone marrow remission in the daily and weekly dosing groups.

This study is an early instance of a paradigm in designing treatment protocols for pediatric ALL: striving to optimize outcomes while minimizing toxicity from treatment. In 2020, L-asparaginase therapy is an integral part of all pediatric ALL treatment protocols both in the US and internationally. Numerous studies have demonstrated the important contribution of L-asparaginase therapy to the improved outcomes in pediatric ALL seen over the last 50 years, with regards to both its initial inclusion in treatment protocols and further upon intensification of treatment (an excellent review has been provided by Pieters et al[3]). Other advances in L-asparaginase therapy, and in some instances continuing areas of investigation, include using different formulations of L-asparaginase as well as altering the dosage, timing, and duration of L-asparaginase therapy.

Wallace Bourgeois, MD
Pediatric Hematology-Oncology Fellow
Boston Children's Hospital/Dana-Farber Cancer Institute
Boston, Massachusetts

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