Acute Lymphoblastic Leukaemia
A Guide to Asparaginase and Pegasparagase Therapy

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Summary

The cure rate for children with acute lymphoblastic leukaemia (ALL) has increased to approximately 70%, in part related to the use of the protein synthesis inhibitor drug asparaginase in multiagent chemotherapy regimens. Its lack of haematological toxicity allows its incorporation into phases of therapy in which myelosuppression would be expected either from the disease itself (induction therapy) or secondary to other chemotherapeutic agents (consolidation, intensification or reinduction phases of therapy). Its antileukaemic effect is related to the degree and duration of asparagine depletion.

The 2 native forms of L-asparaginase are derived from Escherichia coli and Erwinia chrysanthemi. The half-lives (t½) of these forms are approximately 1.2 and 0.6 days, respectively. In order to increase the biological t½, pegaspargase was synthesised by the covalent attachment of monomethoxypolyethylene glycol (PEG) to native E. coli L-asparaginase: it has a t½ of approximately 5.7 days. The duration of asparagine depletion, the substrate amino acid of the drug, is directly related to asparaginase t½.

Asparaginase is associated with several unique toxicities, including hyperglycaemia, hypolipoproteinaemia, hypoalbuminaemia, coagulation factor deficien-

1 A review from the Children's Cancer Group Asparaginase Task Force.
Asparaginase in Acute Lymphoblastic Leukaemia

Asparaginase plays an important role in the treatment of children with acute lymphoblastic leukaemia (ALL). Single agent response rates range from 25 to over 60% for patients in relapse after prior chemotherapy. Asparaginase does not cause substantial myelosuppression, thus allowing its use at full dosages in combination with other chemotherapeutic agents. More than 95% of children achieve initial remission with asparaginase-containing induction therapy. Asparaginase may also be useful in subsequent phases of treatment in prolonging the duration of remission and increasing the cure rate. It continues to have antileukaemic effect at relapse despite prior exposure.

Emerging data suggest that appreciable numbers of patients fail to maintain continuous asparagine depletion with conventional dosages and administration schedules of the various forms of asparaginase presently available for clinical use. Rapid disappearance of plasma asparaginase and abbreviated asparagine depletion have been linked to the appearance of high-titre IgG antibodies against asparaginase, which occurs frequently, even in the absence of clinical allergy. Patients with high-titre anti-asparaginase antibodies are less likely to respond to asparaginase-containing therapy than are patients with lower antibody titres. As an example, in the context of vincristine, prednisone, and daunomycin reinduction therapy for patients in relapse, intensive weekly pegaspargase is more effective than conventional every other week pegaspargase for providing reliable asparagine depletion and for successful remission reinduction. If failure to maintain asparaginase depletion is a significant cause of treatment failure, improving the dependability of asparagine depletion is an attractive therapeutic strategy.

1. Mechanism of Action

In the early 1950s, Kidd noted that certain mouse and rat lymphomas were destroyed by guinea pig serum. Kidd used guinea pig serum as a source of complement to enhance the antigen-antibody reaction between tumour cells and rabbit antilymphoma antiserum. Later, Broome found that asparaginase was the antitumour component of the guinea pig serum. Other investigators found that certain experimental neoplasms required asparaginase to support growth in tissue culture.

Many micro-organisms were screened as a pos-