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Asparaginase in Acute Lymphoblastic Leukemia

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Abstract

Cure rates in pediatric acute lymphoblastic leukemia have significantly improved over the past decades. Now, almost 90% of children will survive the disease. The cure rates in adolescents, young adults, and adults have not kept pace with the improvements in younger patients, even though almost an equal proportion of adult patients achieve complete remission as their pediatric counterparts. Differences in treatment regimens might be important. Intensive use of asparaginase has been a key component of successful pediatric therapy. In this review, we focus on the use of asparaginase and the potential of optimizing asparaginase use via monitoring to minimize adverse drug events and improve efficacy of the drug.

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Introduction

Survival in pediatric patients with acute lymphoblastic leukemia (ALL) has significantly improved over time with almost 90% of children are cured.[1-6] This has been achieved by dose intensification and by extending the duration of chemotherapeutic agents.[6-10] One chemotherapeutic agent, which has been central to pediatric therapies, is asparaginase. Pediatric studies support the use of asparaginase, and some groups have demonstrated that asparaginase dose intensification might improve outcome in pediatric ALL.[6,10-15] However, there has been less improvement in adolescents and young adults (AYAs) or adults with ALL, and the long-term disease-free survival (DFS) in many studies is < 50%.[5,16,17] In retrospective comparisons, adolescents treated with pediatric-based regimens have better outcome compared with those treated with adult-based regimens.[9,18-22] There are several differences in pediatric and adult treatment regimens, including the intensive use of asparaginase in pediatric regimens.[9,23,24] Studies using pediatric-based regimens in AYAs and adult patients with greater use of asparaginase have shown promising results.[25-28] However, AYAs and adult patients are more prone to severe Grade 3 to 4 toxicities including thrombosis, pancreatitis, and chemical hepatitis compared with pediatric patients.[29-32] Pharmacokinetic (PK) studies suggest that adult patients might have a decreased bodily clearance and consequently greater exposure to asparaginase, which might contribute (along with other risk factors) to the increased incidence of severe adverse drug events.[33,34] In this review, we discuss the effect of asparaginase on outcomes and toxicities especially in AYAs and adult patients, and the potential use of therapeutic drug monitoring to minimize adverse events, while maintaining the therapeutic efficacy of asparaginase.

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Discussion

Asparaginase Mechanism of Action and Its Different Preparations

Asparaginase is an enzyme that catalyzes the hydrolysis of the amino acid asparagine to aspartic acid thereby depleting asparagine levels in the serum. Asparagine is a nonessential amino acid for normal tissues, because they can synthesize it via asparagine synthetase, but is an essential amino acid for malignant cells because they cannot synthesize it and rely on extracellular asparagine in the serum.[35-37] Asparagine is important for synthesis of protein, DNA, and RNA. Asparaginase is derived from bacteria and the current preparations are: (1) native asparaginase (Elspar [Lundbeck], Kidrolase [Jazz Pharmaceuticals, Inc.], Crasnitin [Bayer AG], Leunase [Kyowa Hakko Kirin], Asparaginase medac [Kyowa-Hakko]) derived from *Escherichia coli*; (2) pegylated form of native *E. coli* asparaginase (Oncaspar [Sigma-Tau Pharmaceuticals, Inc.]; pegaspargase); and (3) *Erwinia* asparaginase (Erwinaze, and Erwinase [Jazz Pharmaceuticals, Inc.]), which is isolated from *Erwinia chrysanthemi*. It is important to mention that some asparaginase preparations are discontinued and no longer available in all countries. In addition, a pegylated recombinant *Erwinia* asparaginase (mPEG-r-crisantaspase) is undergoing phase I evaluation (NCT015515124). There is also a preparation of asparaginase that is packaged in red blood cells.[38]

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Effect of Asparaginase on Treatment Outcomes in Pediatric ALL

Asparaginase is used during induction, consolidation, and maintenance phases of pediatric ALL therapy. In the Pediatric Oncology Group 8704 study involving T-cell ALL and lymphoblastic lymphoma patients randomized to *E. coli* asparaginase (25,000 IU/m^2 weekly for 20 weeks) during consolidation had improved complete continuous remission compared with patients randomized to the nonasparaginase arm (71.3% vs. 57.8% at the end of 4 years).[12] Similarly, in a study carried out by the Associazione Italiana Ematologia Oncologia Pediatrica, standard-risk ALL children treated with Berlin-Frankfurt-Munich (BFM)-type chemotherapy were randomized to receive asparaginase (25,000 IU/m^2 weekly for 20 weeks) or not receive asparaginase. Children who received asparaginase had a significantly increased 10-year DFS and overall survival (OS) (87.5% vs. 78.7% and 93.7% vs. 88.6%, respectively) compared with those who were not treated with asparaginase.[39] In the Dana-Farber Cancer Institute (DFCI) Consortium Protocol 91-01, it was observed that prolonged asparaginase intensification significantly improved outcome in pediatric ALL, and patients who received 25 or fewer weeks of asparaginase had significantly worse outcome than those who tolerated at least 26 weeks of asparaginase treatment (5-year event-free survival [EFS] was 73% vs. 90%).[6]

Effect of Asparaginase on Treatment Outcomes in AYA and Adult ALL

Recent retrospective comparisons indicate that young adults treated with pediatric-based protocols might have better outcomes than similar patients treated with adult regimens. This has resulted in renewed interest in asparaginase and subsequent toxicities in AYAs and adults.[9,25-28,40] In their retrospective analysis, Stock and colleagues found that young adults (16-20 years of age) treated according to Children's Cancer Group (CCG) protocols had better outcomes than similar patients treated according to adult protocols from the Cancer and Leukemia Group B (CALGB). The 7-year EFS and OS were 63% and 67% compared with 34% and 46%, respectively, in patients treated according to CCG and CALGB protocols.[9] The major difference in the 2 protocols was a greater dose of dexamethasone, vincristine, L-asparaginase, and methotrexate. For asparaginase the CCG protocols used a cumulative dose of 318,000 IU/m^2 compared with 50,000 IU/m^2 in CALGB protocols. The French Group for Research on Adult Acute Lymphoblastic Leukemia reported an improved DFS of 56% in patients (aged 15-55 years) after an increase in the cumulative asparaginase dose from 20,000 IU/m^2 in the LALA-94 (Lymphoblastic Acute Leukemia in Adults 94) trial to 132,000 IU/m^2 (doses of prednisolone and vincristine were also increased).[40] Similarly, the German Multicenter Study Group For Adult ALL reported a significant improvement of treatment outcome in AYAs aged 15 to 35 years treated with a pediatric-derived adult protocol.[27] The 07/03 protocol intensified treatment with asparaginase and methotrexate and added targeted therapies such as rituximab and imatinib, and minimal residual disease-based stratification (it also included stem cell transplant for high-risk and very high-risk patients). The dose for pegaspargase was increased from 1000 to 2000 IU/m^2 in induction, and from 500 to 2000 IU/m^2 in consolidation therapy (combined with high-dose methotrexate and mercaptopurine) for patients aged between 15 and 55 years.[28] Of the 1529 AYA patients, 642 were treated according to the 05/03 protocol and 887 were treated according to the 07/03 protocol. Compared with the 05/03 protocol, complete remission and OS increased from 88% to 91% and 86% to 90%, respectively, with 73% OS in patients aged 15 to 17 years.[27]

Toxicities Associated With Asparaginase

Although inclusion of asparaginase in treatment regimens has improved treatment outcomes, there are several dose-limiting toxicities that make the management of asparaginase therapy difficult. Because asparaginase is a foreign protein derived from bacteria, patients commonly develop allergic reactions and antibodies against the enzyme, which significantly hampers its efficacy and results in suboptimal treatment response. In the St Jude Total XV study, patients who developed antibodies to native asparaginase had a 6.5-fold greater risk of developing central nervous system relapse.[41] Other notable toxicities, which in some cases can be fatal, include pancreatitis, bleeding, thrombosis, hyperglycemia, hyperlipidemia, hyperbilirubinemia, and liver dysfunction.[31,42,43] In pediatric patients, asparaginase-induced allergy and silent hypersensitivity are major challenges.[44-46] When patients develop allergy or silent hypersensitivity to *E. coli* asparaginase, they are switched to pegaspargase and then *Erwinia* asparaginase. Because of the greater incidence of allergic reactions to native asparaginase, pegaspargase is now used as first-line treatment in the United States and other countries.[47]

Although pegaspargase sometimes circumvents the problem of allergic reaction and enzyme-neutralizing antibodies, the problem might still persist. Furthermore, it is not clear whether the anti-pegaspargase antibody titer is capable of causing significant neutralization of pegaspargase. In contrast, the therapeutic benefits of asparaginase in AYAs and adults are less certain because of serious adverse drug toxicities which are not seen at such high frequencies in pediatric patients.[29-31] In adults, no large body of data exists, but Stock and colleagues compared toxicities with intravenously (I.V.)-administered pegaspargase in 76 adult patients treated at the Cleveland Clinic, the University of Texas M.D. Anderson Cancer Center, and the University of Southern California with those for 1274 pediatric patients, administered with intramuscular pegaspargase treated at member institutions of the Children's Oncology Group.[31] Older patients suffered greater incidence of Grade 3 to 4 toxicities of the pancreas and liver, such as increased transaminase level (20% vs. 36%), hyperbilirubinemia (3% vs. 14%), hypofibrinogenemia (3% vs. 14%), hyperglycemia (7% vs. 25%), and pancreatitis (2% vs. 5%), and thrombosis (3% vs. 8%). These adverse effects were further exacerbated with use of the pegaspargase, which has a longer elimination half-life. The U.K. phase III multicenter trial, UKALL 14, reported that pegaspargase was "definitely or probably" implicated in 11 of 18 induction deaths.[48] The incidence of nonfatal pegaspargase toxicities during induction was 36% (n = 33). Liver dysfunction was most common (24.5%) followed by coagulopathy (7.7%) and thrombosis (5.6%). Age and Philadelphia (Ph) chromosome status were independent factors for risk of induction deaths. The odds ratio for age > 40 years and > 55 years were 5.27 and 4.47, respectively, and 6.08 for Ph-positive disease. Older age