Asparaginases develop innovative “tumor starvation” conditions for all antileukemia treatments; however, administrations are limited by the toxicities of this drug. Patients exhibiting moderate toxicity have optimal treatment outcomes. Certain asparagine synthetase (ASNS) polymorphisms may contribute to severe host toxicities in divergent subsets of patients, whereas others do not. Clinical correlations should be evaluated. Clin Cancer Res; 21(2); 230–2. ©2014 AACR. See related article by Tanfous et al., p. 329.

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The authors demonstrated a new insight into the pharmacogenetics of asparaginase-related treatment complications in ALL. It is imperative to emphasize that the article by Tanfous and colleagues (1) showed that a polymorphism of ASNS (haplotype “1”) was associated with reduced sensitivity to ASNS in vitro (1). However, should this haplotype be linked with lower rates of host toxicity, one may wonder if this is also correlated to poorer clinical PD activity by ASNS. Another question is whether the patients with lower host toxicities will also have reduced PD contribution by ASNS in the combination regimens, would they also be vulnerable to a higher risk for relapse. In either case, this novel methodology and provided data that can be used in individualizing treatments in patients with ALL and lymphomas by selecting an appropriate ASNS with optimal glutaminase coactivity. Such an ASNS can nullify the Asn biosynthesis by ASNS, thus achieving greater Asn depletion strategies.

**Glutamine Sources**

Glutamine (Gln, Q) is a cosubstrate of ASNS; therefore, it is indispensable to investigate the sources of this nonessential AA under physiologic conditions. Gln becomes essential in certain pathologic tissues (ALL cells); thus, it becomes a "conditionally essential" AA (4). In rapidly growing malignancies, severe burns, stress and trauma, skeletal muscle and the liver are unable to maintain normal plasma Gln concentrations because of intensely increased requirements for Gln by the gastrointestinal tract, immune system, inflammatory, and malignant cells. Also, Gln is essential for healthy cellular function and must be provided in the diet or synthesized via the catalysis by glutamine synthetase (GS) in muscle, adipose tissue, liver, brain, etc. (5, 6). Gln crosses the blood–brain barrier, where it is used as an energy source and a precursor for neurotransmitter substances in the neurons (GABA receptor ligands).

**Asparagine Synthetase**

ASNS consists of approximately 560 AA with oligo-peptide repeats in various isoforms (molecular weight 62–64 KDa). Only the 561 AA isoform has been experimentally confirmed, and it has been found upregulated in nutrient-deprived mammals. ASNS protein is cytoplasmic, but a small fraction shows nuclear localization. Moreover, mesenchymal cells express and release ASNS in...
ASNS Isoforms and Asparaginase Toxicity

Clinical Data on Asn Deamination and ASNS

The biochemical relationships between ASNSase enzymatic activity and Asn or Gln levels have been examined in 274 pairs of pre- and post-ASNSase serum specimens from 200 patients with high-risk ALL (9). The asparaginase PD results from patients with high-risk and standard-risk ALL were superimposable (9–12). The percentages of Asn and Gln deamination were predicted by population of ASNSase activity in patients’ sera. Further PD analyses strongly suggested that >90% deamination of Gln must occur before optimal Asn deamination (>90% deamination, <3 µmol/L/mL) takes place in vivo at ASNSase concentrations of 0.3 IU/mL after intramuscular administration, serum levels at trough times (9, 10). These PD analyses also demonstrated the same beneficial PD effect in antibody-positive patients to Escherichia coli ASNSase who were then switched to Erwinase (currently licensed by the FDA as Erwinaze (asparaginase Erwinia chrysanthemi)) to Jazz Pharmaceuticals treatments (CCG-1961), which has greater glutaminase coactivity and faster \( k_{cat} \) than the E. coli ASNSase (11). These findings strongly suggested that greater deamination of Gln must occur first for optimal Asn deamination under similar ASNSase serum concentrations (9–11). Taken together, these findings suggested that Gln deamination plays an important role in the antileukemic contribution of ASNSase, due to the inhibition of the de novo Asn biosynthesis by mammalian ASNS in leukemia cells in vitro (7, 9, 10). This phenomenon was also observed in vivo (10). Unfortunately, the process of estimating additive error biochemical parameter requires intense pharmacokinetics–PD sampling and analyses in each patient. Hence, it is not reasonable to expect this process to be applied in most clinical oncology centers.

Our clinical experience in over 1,000 patients with ALL reinforces that moderate-to-severe host toxicity is associated with better event-free survival and long-term outcomes (9–11). Thus, it is easily inferred that patients with ALL with the triple repeat allele (3R) of the ASNS gene may have improved event-free survival and outcomes, whereas patients with haplotype ‘1’ may have lower PD activity by ASNSase (9–12). The clinical PD relationships between ASNSase and ASNS, even though well understood, were not fully elucidated until the recent articles on the polymorphisms of ASNS. Therefore, the article by Tanfous and colleagues (1) is a seminal paper directly associating specific ASNS isoforms with severe toxicity and presumably, effective outcome in patients with ALL. Moreover, if these new polymorphism methods are applied in real-time in leukemia treatment centers, they will benefit refractory patients by selecting an appropriate alternative ASNSase with greater glutaminase coactivity (Erwinase), which has been associated with improved event-free survival (10, 11).

Conclusions

This article shows a groundbreaking and promising genomic methodology in identifying patients with leukemia with ASNS isoforms. This work fulfills an unmet medical need, which may yield improved individualized treatments in patients with ALL.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
References


Asparagine Synthetase Polymorphisms and Toxicity and Efficacy of Asparaginases

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