Asparagine Synthetase Polymorphisms and Toxicity and Efficacy of Asparaginases

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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 asparaginase synthetase 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.

In this issue of Clinical Cancer Research, Tanfous and colleagues (1) evaluate certain polymorphisms of asparagine synthetase (ASNS) and host toxicity. Specific ASNS polymorphisms were associated with adverse effects after asparaginase (ASNase) treatment; these innovative findings elucidate the variable toxic effects that are seen in patients with acute lymphoblastic leukemia (ALL).

Combination chemotherapy regimens, including ASNase, are successful against ALL. Repetitive administration of ASNase initiates events in patients by deaminating L-asparagine (Asn) and l-glutamine (Gln). Amino acid (AA) deprivation in serum initiates a response to ASNase. These pharmacodynamic (PD) events plus obesity are obstacles to successful treatment in all patients.

Isozymes of ASNS may differ in AA sequence, but catalyze the same biochemical reaction of the de novo Asn biosynthesis from aspartate, Gln, ATP in the presence of Mg2+ ion (Fig. 1A). These investigations validate the polymorphisms of ASNS reported previously (2, 3). Moreover, the authors show that specific isoforms of ASNS are associated with severe host toxicities (1).

Earlier work resolved the crystalline resolution of ASNS and showed that altering one AA (Gys-1 to Ala or Ser) eliminated the Gln-dependent activity, leading to lack of Asn biosynthesis by these mutants. In these proteins, Gln became an inhibitor of ASNS instead of a cosubstrate (2). Other investigators demonstrated two 14-bp tandem repeat (2R, wild-type) sequences in the first intron of the ASNS gene isolated from human ALL cells. The 14-bp sequence is similar to the three GC boxes (GC-I, -II, and -III) found in the promoter region of the ASNS gene. Approximately 75% of all samples exhibited the 2R sequence in both alleles; however, 20% and 3% of ALL samples had three (3R) and four (4R) 14-bp tandem repeats in one allele, respectively. The authors concluded that based on the increased number of tandem repeats, the ASNS gene produces variable Asn biosynthesis activity (1, 3). 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 ASNase 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 ASNase. 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 ASNase with optimal glutaminase coactivity. Such an ASNase 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 ASNS enzyme catalyzing the de novo biosynthesis of Asn from Gln and aspartic acid with the energy provided by ATP hydrolysis in the presence of Mg++. Asn is the target amino acid of ASNS in leukemia treatments. B, diagrammatic depiction of the enrichment of Asn concentration in blood circulation via the nutrients and via the de novo biosynthesis catalyzed by ASNS in many tissues. The INPUT and additive rate of Asn accumulation in central circulation are calculated by integrating the population pharmacokinetic equation of ASNase elimination in patients fused with the Michaelis-Menten equation. The fused equations are then integrated per minute for 43,200 minutes (a month), and many iterations, to minimize the variability errors, thus yielding best-fit PD values of Asn INPUT and its additive rate values. Of interest is that the INPUT values (µmol/L/mL/min) are increasing with time, and therefore it becomes highly similar in most patient populations; however, the additive error values (nmol/L/mL/min) are increasing with time, and therefore it becomes highly similar in most patient populations; however, the additive error values (nmol/L/mL/min) are increasing with time. 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 ASNS with greater glutaminase coactivity (Erwinase), which has been associated with faster kcat value than the E. coli ASNS (11). These findings strongly suggested that greater deamination of Gln must occur first for optimal Asn deamination under similar ASNase serum concentrations (9–11). Taken together, these findings suggested that Gln deamination plays an important role in the antileukemic contribution of ASNS, 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 ASNS (9–12). The clinical PD relationships between ASNS 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 ASNS 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

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