Asparaginase Therapy in Pediatric Acute Lymphoblastic Leukemia: A Focus on the Mode of Drug Resistance

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Key Words
acute lymphoblastic leukemia; asparaginase; chemotherapy; children; resistance

Asparaginase is one of the most important chemotherapeutic agents against pediatric acute lymphoblastic leukemia (ALL), the most common form of childhood cancer. The therapeutic efficacy (e.g., chemoresistance) and adverse effects of asparaginase (e.g., hypersensitivity and pancreatitis) have been investigated over the past four decades. It was suggested early on that leukemic cells are resistant to asparaginase because of their increased asparagine synthetase activity. Afterward, other mechanisms associated with asparaginase resistance were reported. Not only leukemic cells but also patients themselves may play a role in causing asparaginase resistance, which has been associated with unfavorable outcome in children with ALL. This article will briefly review asparaginase therapy in children with ALL and comprehensively analyze recent reports on the potential mechanisms of asparaginase resistance.

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1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children. An estimated 6000 new cases of ALL are diagnosed yearly in the United States; roughly 60% of cases occur in people aged younger than 20 years.1 Recent advances in intensive chemotherapy, as well as adequate supportive care, have made significant improvements in childhood ALL, so that approximately 80% of the children are cured (Table 1).2-11 According to the registry of the Taiwan Childhood Cancer Foundation, there are about 130–140 newly diagnosed ALL children (younger than 18 years), accounting for 25% of all childhood cancers in Taiwan. The treatment of childhood ALL in Taiwan has improved during the past decade. Overall survival improved significantly from 75.5% in 1997–2001 to 83.5% in 2002–2007.10 The high cure rate for ALL is attributable to the improved supportive care, more precise risk stratification, and personalized chemotherapy based on the characteristics of leukemic cells and hosts.12

Asparaginase is an enzyme isolated from various natural sources. However, only Escherichia coli and Erwinia chrysanthemi asparaginase are currently available for medical
use. Polyethylene glycol (PEG)—asparaginase is a conjugate of the native \textit{E. coli} asparaginase covalently linked to PEG at sites not affecting enzymatic activity. The characteristics of various asparaginase preparations are summarized in Table 2. Asparaginase has been highly successful for inducing remissions in acute leukemia since 1967. Asparaginase exerts its antileukemic activity by converting asparagine to aspartic acid in the extracellular fluid. Most normal cells can synthesize asparagine, but leukemic lymphoblasts are sensitive to the depletion of extracellular asparagine, putatively because they express low levels of asparagine synthetase (ASNS). However, data from some recent studies on the importance of ASNS are conflicting (Table 3). In addition to the leukemic cells, there is increasing evidence of host factors that can contribute to asparaginase resistance. In this article, the mechanisms of asparaginase resistance will be reviewed.

### 1.1. Baseline high ASNS expression level in leukemic cells

Horowitz et al.\textsuperscript{15} reported experiments on the ASNS activity of several transplanted mouse leukemias. Seven different regimens in pediatric ALL.\textsuperscript{21–23} Resistance to asparaginase has been demonstrated to be an unfavorable prognostic factor.\textsuperscript{24–27} One may reasonably postulate that resistant leukemic cells would have accesses to increase their asparagine in sufficient quantity to meet their needs. In recent years, considerable effort has been made to address fundamental questions about the role of ASNS in asparaginase resistance. However, data from some recent studies on the importance of ASNS are conflicting (Table 3). In addition to the leukemic cells, there is increasing evidence of host factors that can affect asparaginase resistance. In this article, the mechanisms contributing to asparaginase resistance will be reviewed.

### Table 1: Results of selected clinical trials for pediatric acute lymphoblastic leukemia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Years of study</th>
<th>No. of patients</th>
<th>Age range (y)</th>
<th>Event-free survival at 5 y (%)</th>
<th>Overall survival at 5 y (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFM-95</td>
<td>1995–1999</td>
<td>2169</td>
<td>0–18</td>
<td>79.6 ± 0.9</td>
<td>87.0 ± 0.7</td>
<td>Möricke et al\textsuperscript{1}</td>
</tr>
<tr>
<td>COG</td>
<td>2000–2005</td>
<td>7153</td>
<td>0–21</td>
<td>NA</td>
<td>90.4 ± 0.5</td>
<td>Hunger et al\textsuperscript{2}</td>
</tr>
<tr>
<td>DCOG-9</td>
<td>1997–2004</td>
<td>859</td>
<td>1–18</td>
<td>80.6 ± 1.4</td>
<td>86.4 ± 1.2</td>
<td>Veerman et al\textsuperscript{4}</td>
</tr>
<tr>
<td>DFCI 00-01</td>
<td>2000–2004</td>
<td>492</td>
<td>0–18</td>
<td>80.0 ± 2.0</td>
<td>91.0 ± 1.0</td>
<td>Vrooman et al\textsuperscript{5}</td>
</tr>
<tr>
<td>JCCLSG ALL 2000</td>
<td>2000–2004</td>
<td>305</td>
<td>1–15</td>
<td>79.7 ± 2.4</td>
<td>89.2 ± 1.8</td>
<td>Yamaji et al\textsuperscript{6}</td>
</tr>
<tr>
<td>Ma-Spore ALL 2003</td>
<td>2002–2011</td>
<td>556</td>
<td>0–18</td>
<td>80.6 ± 3.5</td>
<td>89.2 ± 2.7</td>
<td>Yeoh et al\textsuperscript{7}</td>
</tr>
<tr>
<td>MRC UKALL 2003</td>
<td>2003–2011</td>
<td>3126</td>
<td>1–25</td>
<td>87.2 ± 14</td>
<td>91.5 ± 1.2</td>
<td>Vora et al\textsuperscript{8}</td>
</tr>
<tr>
<td>NOPHO-2000</td>
<td>2002–2007</td>
<td>1023</td>
<td>1–15</td>
<td>79.4 ± 1.5</td>
<td>89.1 ± 11</td>
<td>Schmiegelow et al\textsuperscript{9}</td>
</tr>
<tr>
<td>TPOG-2002</td>
<td>2002–2007</td>
<td>788</td>
<td>0–18</td>
<td>77.4 ± 1.7</td>
<td>83.5 ± 1.6</td>
<td>Liang et al\textsuperscript{10}</td>
</tr>
<tr>
<td>SJCH XV</td>
<td>2000–2007</td>
<td>498</td>
<td>1–18</td>
<td>85.6 ± 2.9</td>
<td>93.5 ± 1.9</td>
<td>Pui et al\textsuperscript{11}</td>
</tr>
</tbody>
</table>


BFM = Berlin–Frankfurt–Münster; COG = Children’s Oncology Group; DCOG = Dutch Children’s Oncology Group; DFCI = Dana–Farber Cancer Institute Consortium; JCCLSG = Japanese Children’s Cancer and Leukemia Study Group; Ma-Spore = Malaysia–Singapore; MRC UKALL = Medical Research Council United Kingdom Acute Lymphoblastic Leukemia; NA = not available; NOPHO = Nordic Society of Pediatric Hematology and Oncology; TPOG = Taiwan Pediatric Oncology Group; SJCRH = St. Jude Children’s Research Hospital.

### Table 2: Main characteristics of various asparaginase preparations.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Native \textit{Escherichia coli} asparaginase</th>
<th>Erwinia chrysanthemi asparaginase</th>
<th>Pegylated form of native \textit{E. coli} asparaginase</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval</td>
<td>1978</td>
<td>2011</td>
<td>1994</td>
</tr>
<tr>
<td>Half-life (d)\textsuperscript{55,53,54}</td>
<td>1.08 – 1.35 (IM)</td>
<td>0.27 (IV)</td>
<td>5.5 – 5.7 (IM)</td>
</tr>
<tr>
<td>Route</td>
<td>IV, IM</td>
<td>IV, IM</td>
<td>IV, IM</td>
</tr>
<tr>
<td>Estimated equivalent doses for complete asparagine depletion for 2 wk</td>
<td>6000–20,000 U/m\textsuperscript{2} every 2–3 d</td>
<td>20,000–25,000 U/m\textsuperscript{2} every 2–3 d</td>
<td>2500–3500 U/m\textsuperscript{2} every 2 wk</td>
</tr>
<tr>
<td>Frequency of antiasparaginase antibody formation\textsuperscript{55–59}</td>
<td>20–42%</td>
<td>8–33%</td>
<td>2–11%</td>
</tr>
</tbody>
</table>

\textit{FDA} = Food and Drug Administration; IM = intramuscular; IV = intravenous.
Table 3  Summary of recent studies with conflicting conclusions on the impact of asparagine synthesis on asparaginase sensitivity in leukemic cells.

<table>
<thead>
<tr>
<th>Sample origin</th>
<th>Specific cell lines/ALL subtypes</th>
<th>Sample No.</th>
<th>Methods to determine ASNS activity</th>
<th>Relationship between ASNS and ASP sensitivity</th>
<th>The comparison of ASNS level in one subtype to other subtypes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI60 cancer cell lines *</td>
<td>6 Microarray</td>
<td>ASNS↑, GI50↑</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Scherf et al28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL TEL/AML1 and non-TEL/AML1 ALL</td>
<td>47 qRT-PCR</td>
<td>No correlation</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Stams et al32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL TEL/AML1 ALL</td>
<td>30 qRT-PCR</td>
<td>No correlation</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Stams et al32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL Non-TEL/AML1 ALL</td>
<td>17 qRT-PCR</td>
<td>No correlation</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Stams et al32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL Non-TEL/AML1 ALL</td>
<td>117 qRT-PCR and microarray</td>
<td>ASNS↑, LC50↑</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Stams et al32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemic cell lines</td>
<td>16 Microarray</td>
<td>ASNS↑, LC50↑</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Fine et al10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL</td>
<td>38 Microarray</td>
<td>No correlation</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Fine et al10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL</td>
<td>173 Microarray</td>
<td>ASNS↑, LC50↑</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Holleman et al39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL TEL ALL Non-TEL/AML1 ALL</td>
<td>20 qRT-PCR</td>
<td>Not mentioned</td>
<td>TEL ALL &gt; non-TEL ALL</td>
<td>Krejci et al31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL TEL/AML1 ALL Non-TEL/AML1 ALL</td>
<td>57 Microarray</td>
<td>Not mentioned</td>
<td>TEL ALL &lt; non-TEL ALL</td>
<td>Iwamoto et al35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL Hyperdiploid ALL Nonhyperdiploid ALL</td>
<td>51 Microarray</td>
<td>Not mentioned</td>
<td>Hyperdiploid ALL &lt; nonhyperdiploid ALL</td>
<td>Iwamoto et al35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary ALL T-ALL B-lineage ALL</td>
<td>47 Microarray</td>
<td>Not mentioned</td>
<td>T-ALL &gt; B-lineage ALL</td>
<td>Iwamoto et al35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemic cell lines Jurkat, SUP T1</td>
<td>2 qRT-PCR</td>
<td>ASNS↑, EC50↑</td>
<td>T-ALL &gt; B-lineage ALL</td>
<td>Estes et al60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemic cell lines MOLT-4, Nalm6, REH</td>
<td>3 qRT-PCR</td>
<td>No consistent correlation</td>
<td>T-ALL &gt; B-lineage ALL</td>
<td>Su et al36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemic cell lines MOLT-4, Nalm6, REH</td>
<td>3 Immunoblotting</td>
<td>ASNS↑, IC50↑</td>
<td>T-ALL &gt; B-lineage ALL</td>
<td>Su et al36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


ALL = acute lymphoblastic leukemia; ASNS = asparagine synthetase; ASP = asparaginase; EC50 = effective concentration leading to 50% cell death; GI50 = concentration with 50% growth inhibition of cells; IC50 = concentration with 50% growth inhibition of cells; LC50 = concentration lethal to 50% of cells.
* MOLT4, CEM, HL-60 (TB), SR, RPMI-8226, K562.
† Nalm20, Nalm21, Nalm29, Nalm30, SUP-B15, HB, RS411, BV173, HAL, UOC, MV, Nalm27, Nalm6, REH, 697, RCH-ACV.
asparaginase-sensitive mouse leukemias proved to have no or only slight ASNS activity. In contrast, asparaginase-resistant leukemias showed appreciable ASNS activity. Haskell and Canellos\textsuperscript{16} studied the ASNS levels in 18 leukemia patients who were subsequently treated with asparaginase. They found that the ASNS in leukemic cells was nearly undetectable prior to therapy regardless of subsequent response to asparaginase treatment, although the ASNS level in the asparaginase-resistant group was slightly higher than in the asparaginase-sensitive group. Kiriyama et al\textsuperscript{17} later showed that asparaginase-sensitive human leukemic cell lines exhibited a lower baseline ASNS level than asparaginase-nonsensitive ones. ASNS was also reported as one of the top genes with at least 2-fold expression level in two resistant T-ALL cell lines at different maturation stages.\textsuperscript{17}

Gene expression profiling studies by microarray analysis revealed conflicting results. Scherf et al\textsuperscript{28} showed that six leukemic cell lines had very high negative correlation between the ASNS expression and asparaginase sensitivity. Holleman et al\textsuperscript{29} found that ASNS was one of the genes discriminating asparaginase-sensitive and asparaginase-resistant leukemic cells from newly diagnosed pediatric ALL patients. Fene et al\textsuperscript{30} demonstrated that ASNS was one of the genes that had different asparaginase-sensitive and asparaginase-resistant cell lines in accordance with previous reports. However, baseline ASNS expression was not associated with asparaginase sensitivity in clinical ALL samples.

The t(12;21)\textsuperscript{+} ALL, which harbors the TEL/AML1 gene fusion and accounts for about 25% of pediatric ALL, was found to be significantly related to \textit{in vitro} drug sensitivity for asparaginase.\textsuperscript{31} The simple paradigm would be sensitivity to asparaginase in t(12;21)\textsuperscript{+} ALL emerged via a low baseline expression of ASNS. Surprisingly, Stams et al\textsuperscript{32} showed that the expression of ASNS in t(12;21)\textsuperscript{+} ALL was significantly higher than in t(12;21) ALL. The ASNS expression did not differ in sensitive and resistant t(12;21)\textsuperscript{+} ALL, either. The same trend was also demonstrated by Krejci et al.\textsuperscript{33} Both studies had only a small number of patient samples and used real-time quantitative polymerase chain reaction (RTQ-PCR) to determine ASNS mRNA expression. Although ASNS expression was not linked to asparaginase resistance in t(12;21)\textsuperscript{+} ALL, Stams et al\textsuperscript{34} later reported that the ASNS expression determined by either RTQ-PCR or microarray significantly differed between sensitive and resistant t(12;21)\textsuperscript{+} ALL. With a larger sample size and microarray analysis, a different result was shown by Iwamoto et al.\textsuperscript{35} The ASNS expression levels were found to be significantly lower in t(12;21)\textsuperscript{+} ALL compared to t(12;21) ALL.

Notably, the quantification of ASNS expression in leukemic cells by mRNA is limited by the fact that the relationship between the ASNS mRNA and intracellular protein concentrations in primary ALL has not been established. Su et al\textsuperscript{36} tested the correspondence between ASNS mRNA expression by RTQ-PCR and ASNS protein content by immunoblotting. Asparaginase resistance was estimated by half-maximal inhibitory concentration (IC\textsubscript{50}) after exposure to asparaginase. Their observations demonstrated that the correlation between ASNS protein and IC\textsubscript{50} was much better than that between the IC\textsubscript{50} and the ASNS mRNA content. This may imply that measuring the ASNS protein rather than mRNA can predict asparaginase resistance. More recently, Abbatiello et al\textsuperscript{37} developed a highly sensitive and selective nanoflow reversed-phase liquid chromatography-tandem mass spectrometry (RPLC-MS/MS) technique to quantify ASNS protein levels. They successfully measured the ASNS protein concentration directly in four patient blast samples. This new technique may help to reassess the correlation between ASNS expression and asparaginase resistance in the future.

In conclusion, a different sample size, determination of gene expressions, and origin of sample may account for the discrepancy in the results. However, these studies indicate that the baseline ASNS level plays a role but is not the only factor for leukemic cells’ resistance to asparaginase.

1.2. Upregulation of ASNS expression in leukemic cells in asparagine-depleted environment

In nine leukemia patients with paired ASNS activity determination before and during/after asparaginase treatment, the asparaginase-sensitive group showed no change in ASNS with therapy; however, there was a 7-fold increase in the mean level of ASNS levels in the asparaginase-resistant group.\textsuperscript{16} The difference between the ASNS levels in the sensitive and resistant groups, determined during/after asparaginase treatment, was highly significant.

Hutson et al\textsuperscript{38} also demonstrated that resistance to asparaginase in leukemic cell lines was mediated \textit{in vitro} by an upregulation of ASNS expression in response to asparagine depletion of the culture medium. Aslanian et al\textsuperscript{39} further examined the reversibility of the upregulation of ASNS caused by asparaginase treatment in asparaginase-resistant leukemic cells. They found that the elevated ASNS expression in the resistant cells was not fully reversed even 6 weeks after asparaginase had been removed from the culture medium.

However, asparaginase-sensitive leukemic cells were later revealed also to upregulate ASNS after asparaginase treatment. Stams et al\textsuperscript{40} exposed samples from t(12;21)\textsuperscript{+} and t(12;21) ALL patients in \textit{vitro} to asparaginase. Almost all samples showed upregulation of ASNS, which was independent from t(12;21) status and cellular sensitivity to asparaginase. Appel et al\textsuperscript{41} also demonstrated that the upregulation of ASNS occurred in both sensitive and resistant cases within 24 hours of \textit{in vivo} exposure to asparaginase. These data imply that mechanisms other than upregulated expression levels of ASNS contribute to cellular asparaginase resistance.

1.3. Increased substrates for ASNS reaction in leukemic cells

Aslanian and Kilberg\textsuperscript{42} found that multiple adaptive changes affect the ASNS substrate availability in asparaginase-resistant leukemic cell line. These changes appear to support increased asparagine biosynthesis by increasing the intracellular levels of aspartate and glutamine. Asparaginase-resistant cells produced more glutamine by an increase in glutamine synthetase (GS) activity. These cells also enhanced the uptake of extracellular glutamine via secondary active Na\textsuperscript{+}-dependent transporters. However, there was little or no aspartate uptake by these cells. Recently, Appel et al\textsuperscript{25}
demonstrated that the levels of intracellular amino acids did not significantly differ among different in vitro sensitivity cases or in vivo clinical responders. Therefore, the contribution of the ASNS substrate, aspartate, and glutamine's resistance to asparaginase remains unclear.

1.4. Influence on protein synthesis and apoptosis in leukemic cells

Protein synthesis is fundamental in all living cells, both benign and malignant. Amino acid deficiency impairs protein synthesis and leads to apoptosis and cell death. Many tRNA synthetases and amino acid transporters were shown to increase expression in human cells with amino acid starvation. In asparaginase-resistant ALL cells, several ribosomal protein genes were overexpressed, indicating the possible role of protein synthesis in asparaginase resistance. Holleman et al further analyzed the expression patterns of 70 apoptosis genes and tested the association between the expression of these genes and in vitro drug resistance in B-lineage ALL cells. Of the 70 apoptosis genes, three were associated with asparaginase resistance. Overexpression of BCL2L13, one of the genes associated with asparaginase resistance, was also associated with an unfavorable clinical outcome.

2. Host factors

There is increasing interest in the host factors resulting in asparaginase resistance of leukemic cells. Iwamoto et al described the protective effect of mesenchymal cells in leukemic cells against asparaginase treatment in bone marrow microenvironment. They showed that bone marrow mesenchymal cells express significantly higher amounts of ASNS than leukemic cells. They then showed that the resistance of leukemic cell lines and some specimens of primary leukemia to asparaginase correlated with the expression of ASNS by mesenchymal cells. Forced increased expression of ASNS by the mesenchymal cell leads to resistance of the ALL cells; conversely, reduced expression of ASNS by the mesenchymal cell leads to enhanced sensitivity of the ALL cells.

The childhood obesity problem has become epidemic in the United States and other industrialized countries. In vivo and in vitro models have shown that obesity impairs the efficacy of chemotherapeutics against ALL cells, likely mediated by adipocytes. Ehsanipour et al examined bone marrow biopsy specimens from four obese and four lean adolescent leukemia patients for expression of ASNS and GS. They found that the GS expression was markedly increased in bone marrow adipocytes after induction chemotherapy, whereas ASNS expression appeared to be unaltered after treatment. They further cultured ALL cells over fibroblasts or adipocytes in media with asparaginase. They observed that adipocytes protected ALLs from asparaginase treatment via release of glutamine, which complemented the previous finding from Iwamoto et al. The protective effect from such microenvironment is still open to debate.

In recent years, pharmacogenetics/pharmacogenomics in childhood ALL has become a major field of research. The genetic variation is a key determinant for the interindividual differences in treatment resistance. Luo et al identified that the single nucleotide polymorphism in the promoter region of the ASNS gene, −92G>A, is associated with increased ASNS expression and is more common in pediatric leukemic patients than among normal control individuals. We used an agnostic genome-wide approach to identify inherited genomic variants that contribute to asparaginase resistance using normal lymphoblastoid cell lines from 87 trio members of European ancestry and 54 primary ALL leukemic blast samples at diagnosis. We found that the top-ranked pathway was that of aspartate metabolism, which may be linked directly to the mechanism of action of asparaginase. The two most highly ranked genes (ADSL and DARS) in this pathway encompassed seven single nucleotide polymorphisms. Moreover, we found that more sensitive ALL subtypes (hyperdiploid and TEL-AML1) had lower ADSL expression than the more resistant subtypes (T-ALL), which is consistent with higher ADSL expression associated with resistance.

Because asparaginase is a foreign protein, hypersensitivity reactions due to anti-asparaginase antibody production are common, occurring in up to 45% of patients. The development of these antibodies appears to be more commonly observed in native E. coli asparaginase than in the pegylated enzyme. The development of anti-asparaginase antibodies may shorten the half-life of asparaginase, prevent or delay absorption after intramuscular injection of asparaginase, or interfere with asparaginase activity. Therefore, it confers resistance to asparaginase therapy and reduced therapeutic efficacy in some clinical studies.

3. Conclusion

The intensive administration of asparaginase improved the treatment outcomes in children with ALL. It is crucial to recognize the mechanisms for the development of both in vitro and in vivo resistance by leukemic cells. The role of the host factor is increasing. Adequate asparaginase exposure may result in a lower clearance of steroids, which may potentiate the cytotoxicity of vincristine. Therefore, it is important for clinicians to choose the appropriate management in patients with asparaginase resistance. Switching to another preparation may be a difficult choice. Measurement of asparaginase level during asparaginase treatment may help to guide the decision of switching preparations or dose escalation. Further studies should continue investigating and promoting effective asparaginase therapy individually.

Conflicts of interest

The author has no conflicts of interest relevant to this article.

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Asparaginase in acute lymphoblastic leukemia


