BLOOD RESEARCH
Volume 49 · Number 1 · March 2014
http://dx.doi.org/10.5045/br.2014.49.1.3

Perspective

How do we prepare ourselves for a new paradigm of medicine to advance the treatment of pediatric acute lymphoblastic leukemia?

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The immunotherapeutic approaches that have been realized in clinical settings have begun a new era in the treatment of acute lymphoblastic leukemia (ALL). Gene-engineered autologous T-cell therapy, called "living drug," has killed leukemic cells and had kept 88% of refractory adult patients with ALL alive in successful molecular remission [1]. We are fully armed with tailored chemotherapy, hematopoietic stem cell transplantation, and gene-engineered T-cell immunotherapy to fight ALL.

Over the past several decades, there have been remarkable advances in childhood ALL. In recent clinical trials, which had better defined risk stratification using minimal residual disease, the 5-year survival rate was more than 85% in developed countries [2]. This improvement is the result of active chemotherapeutic agents being developed, a better understanding of prescribing doses and combining these agents, and the significant progress made in supportive care through multicenter clinical trials. However, we still have to fight a treatment failure of 10–15%. Continued research is required to identify and target specific molecular and genetic abnormalities within leukemic cells as well as to better understand and address individual differences in the pharmacogenetics of chemotherapeutic agents.

Genomic sequencing and adequate analytic platforms, such as gene expression profiling, single-nucleotide polymorphism arrays, and next-generation sequencing, have become available in the treatment of childhood ALL. Molecular biology techniques have revealed many different childhood ALL subtypes that bear features such as iAMP21, CRLF2 rearrangements, IKZF1 alteration, JAK1/2 mutations, *BCR-ABL1*-like signatures, and early T-cell precursors that are associated with poorer outcomes [3]. In addition, recent analysis has identified new genomic alteration-associated prognosis; therefore, these genomics can be translated into a better risk stratification that will make tailored therapy available in the near future. The increasing number of genomic alterations that have been discovered recently gives us important information for designing future studies. The first is whether these genotypes can be used to improve patient stratification; the second concerns the role of new discoveries in genetics and molecular biology in determining specific treatment modalities.

Pharmacogenomics in cancer treatment hold great promise for yielding genetic polymorphisms that could be used to individualize antileukemic agent dosages. Thus far, the only well-established clinical effect refers to mercaptopurine and the genetic polymorphism status of the *thiopurine methyltransferase* (*TPMT*) gene. Indeed, tailoring the dosages of methotrexate and mercaptopurine to the limits of tolerance has been associated with a better outcome [4]. Therefore, customizing the dosage of mercaptopurine based on preemptive testing for *TPMT* status will likely decrease the risk of mercaptopurine-induced toxicities associated with an inherited *TPMT* deficiency. This, in turn, might reduce the likelihood of acute myelosuppression (without compromising disease control) and the risk for developing mercaptopurine-induced myeloid malignancy. *TPMT* also

has a significant impact on thioguanine pharmacokinetics because patients with this enzyme deficiency are at an increased risk for developing hepatic venoocclusive disease. It is possible that, in the near future, genetic guidance might ensure a better use of standard drugs, improved efficacy, and reduced toxicity and long-term side effects. *TPMT* mutations in the Asian populations are rare (about 2–3%) compared with that in the Western populations (about 10%) [5]. However, this cannot account for the reduced tolerance to mercaptopurine among the Asian populations. Further study is needed to ascertain whether polymorphisms of genes encoding enzymes involved in folate metabolism, or perhaps other genes, affect the response to antimetabolites in the Asian populations.

Korea has many centers with enhanced resources that can adapt new technologies to clinical practices [6]. However, in Korea, where the national health insurance system controls the application of new laboratory tests or treatments to clinical practice, national health insurance policy limitations hinder the addition of these advances to standard practice guidelines, which would be unlikely in the United States or Europe [7]. In the past, our management guidelines in pediatric ALL have been based mainly on treatment experiences in the United States or Europe, and those guidelines are often different in each institution. However, several years ago, we started multi-center clinical trials for high-risk pediatric ALL patients and have finished patient enrollment. Currently, we are developing new protocols for newly diagnosed high-risk and relapsed ALL patients. In these trials, risk assignment, bone marrow response, and minimal residual disease measurements will be performed on day 7 or day 15 by flow cytometry and reverse transcription PCR (HemaVision). *TPMT* studies will be carried out for pharmacogenetics.

Because defining the complete genetic repertoire of ALL and the progressive availability of new targeted therapy will make patient subgroups smaller, we will be asked to participate in international collaborative trials. For this to become a reality, we have to keep up with global standards. Now is the time to come together.

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