

## Current therapeutic approaches in pediatric acute lymphoblastic leukemia.\*

### Esquemas terapéuticos actuales en leucemia linfoblástica aguda pediátrica

Hiroto Inaba

#### Abstract

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. The current approach to treating ALL uses risk stratification based on the biological features of the leukemic cells and the response to treatment. However, to further improve survival to as close to 100% as possible and to reduce the adverse effects of treatment, innovative approaches are needed. Currently, many frontline ALL treatment protocols are incorporating novel precision-medicine strategies based on inherited and leukemia/lymphoma-specific genomic features and targeted treatment approaches, which could lead to improved cure rates and reduced toxicities.

**KEYWORDS:** Acute lymphoblastic leukemia; Immunotherapy.

#### Resumen

La leucemia linfoblástica aguda es el cáncer pediátrico más común. Los esquemas terapéuticos actuales de la leucemia linfoblástica aguda usan estratificación del riesgo con base en las características biológicas de las células leucémicas y la respuesta al tratamiento. Sin embargo, para mejorar la supervivencia lo más cercano posible al 100% y para reducir los efectos adversos del tratamiento se necesitan enfoques innovadores. En la actualidad muchos protocolos de tratamiento de primera línea contra la leucemia linfoblástica aguda están incorporando nuevas estrategias de medicina de precisión basadas en características genómicas heredadas y específicas de la leucemia-linfoma y enfoques de tratamiento dirigido, que podrían mejorar las tasas de curación y reducir la toxicidad.

**PALABRAS CLAVE:** Leucemia linfoblástica aguda; inmunoterapia.

\* Presented at LIX National Congress of Hematology, 25-29 April, 2018. Nuevo Vallarta, Mexico.  
Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN 38105.

**Received:** 9 April 2018

**Accepted:** 11 April 2018

#### Correspondence

Hiroto Inaba  
hiroto.inaba@stjude.org

#### This article must be quoted

Inaba H. Current therapeutic approaches in pediatric acute lymphoblastic leukemia. Hematol Méx. 2018 April-June;19(2):91-94.

## BACKGROUND

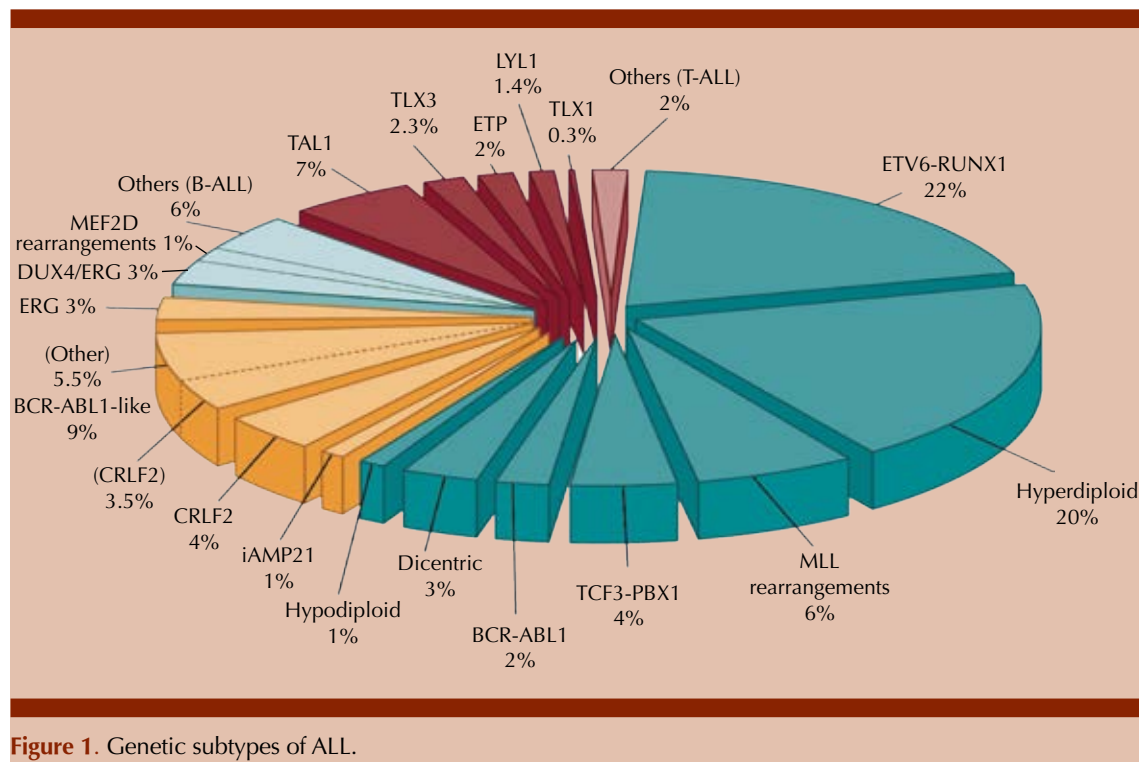
Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. Over the past few decades, the survival of children with ALL has improved significantly; the St. Jude Children's Research Hospital Total XV study demonstrated a 5-year overall survival of around 94%.<sup>1</sup> The current approach to treating ALL uses risk stratification based on the biological features of the leukemic cells and the response to treatment, treatment modification based on the patients' pharmacodynamics and pharmacogenomics, and improved supportive care.<sup>2</sup> However, to further improve survival to as close to 100% as possible and to reduce the adverse effects of treatment, innovative approaches are needed. Next-generation sequencing of leukemia samples (whole-genome, exome, and transcriptome sequencing), as well as of germline samples (whole-genome and exome sequencing), can be used to study leukemogenesis, to define new ALL subtypes, to identify new prognostic markers and therapeutic targets to facilitate personalized precision medicine, to monitor treatment response with sensitive assays, and to predict adverse effects.<sup>3</sup>

It is considered that ALL pathogenesis starts in utero and that promotional exposure events are probably important for disease emergence.<sup>4</sup> Infection is the strongest candidate for a causal exposure in pediatric ALL.<sup>5</sup> The incidence of ALL is significantly lower in infants who were placed in day care during their first few years of life than in those who were not placed in day care during that time. Immune-cell programming occurs with infection during infancy. Good hygiene can prevent infection, but infection after infancy can cause aberrant/pathologic immune responses that may lead to a second hit for leukemogenesis. In addition, genome-wide association studies of childhood ALL that compared the whole genomes of a large series of ALL patients to those

in an ethnically matched control group identified leukemia-susceptibility genes as common allelic variants in *IKZF1*, *ARID5B*, *CEBPE*, and *CDKN2A* and as rare germline mutations in *PAX5*, *ETV6*, and *TP53*.<sup>6</sup>

High-resolution profiling of genetic alterations in leukemia samples has transformed our understanding of the genetic basis of ALL.<sup>2,6</sup> ALL can be subdivided into more than 20 genetic subtypes, which is important for risk stratification and for selecting an appropriate treatment strategy (**Figure 1**). Although the outcomes are excellent for patients with National Cancer Institute (NCI) standard-risk ALL (e.g., those with the *ETV6-RUNX1* fusion or hyperdiploid ALL), significant improvements are needed in the cure rates for patients with NCI high-risk and very high-risk ALL, such as those with *MLL* rearrangements (especially infants), hypodiploid ALL, *iAMP21*, *BCR-ABL1*-like ALL, or *MEF2D* rearrangements. *BCR-ABL1*-like ALL (also known as Ph-like ALL) has a gene-expression profile similar to that of *BCR-ABL1*-positive (Ph-positive) ALL; a diverse range of genetic alterations activating tyrosine kinase signaling; the mutation of lymphoid transcription factor genes such as *IKZF1* (in 70%–80% of cases); and a poor outcome.<sup>7</sup> The kinase-activating alterations can be targetable with tyrosine kinase inhibitors (TKIs), such as dasatinib/imatinib (for ABL-class fusions) and ruxolitinib (for mutations that cause JAK-STAT signaling alterations). **Table 1**

Minimal residual disease evaluation is critical for evaluating treatment response and risk classification in contemporary ALL protocols.<sup>8</sup> Flow cytometry analysis uses aberrant immunophenotypes to detect leukemia cells and has a sensitivity of approximately 1 in 10<sup>4</sup> cells. PCR can monitor immunoglobulin and T-cell receptor genes or fusion transcripts with a sensitivity of approximately 1 in 10<sup>5</sup> cells. However, next-generation massive parallel sequencing technology



may allow analysis with even greater sensitivity (capable of detecting as few as 1 in  $10^6$  cells). Patients with persistent minimal residual disease after conventional chemotherapy may be considered for immunotherapy (with chimeric antigen receptor T cells and/or antibody therapy [e.g., blinatumomab/inotuzumab]).<sup>9-11</sup>

Analysis of inherited genomic features can identify genotypes associated with treatment toxicities. For example, individuals with the TT genotype in the *CEP72* promotor regions have a higher incidence of vincristine-associated peripheral neuropathy than do those with the CC or CT genotype.<sup>12</sup> The *TPMT* and *NUDT15* genotypes are associated with 6-mercaptopurine tolerability.<sup>13</sup> *TPMT* deficiency is common in patients with European ancestry and *NUDT15* deficiency is often seen in patients with Asian or American Indian ancestry. This information

can be used for dose adjustments of chemotherapeutic agents.

Currently, many frontline ALL treatment protocols are incorporating novel precision-medicine strategies based on inherited and leukemia/lymphoma-specific genomic features and targeted treatment approaches, which could lead to improved cure rates and reduced toxicities.

#### Acknowledgement

We thank Keith A. Laycock, PhD, ELS, (St. Jude Children's Research Hospital) for editorial assistance.

#### Conflict of interest statement

Hiroto Inaba: Bristol-Myers-Squibb and Incyte provided drug support.

**Table 1.** Kinase rearrangements and therapeutic targets in *BCR-ABL*-like ALL

Kinase	Tyrosine kinase inhibitor	Number of gene partners	Fusion partner genes
<i>ABL1</i>	Dasatinib	12	<i>CENPC, ETV6, FOXP1, LSM14, NUP153, NUP214, RCSD1, RANBP2, SNX2, SFPQ, SPTAN1, ZMIZ1</i>
<i>ABL2</i>	Dasatinib	3	<i>PAG1, RCSD1, ZC3HAV1</i>
<i>CSF1R</i>	Dasatinib	3	<i>SSBP2, MEF2D, TBL1XR1</i>
<i>PDGFRB</i>	Dasatinib	7	<i>ATF7IP, EBF1, ETV6, SSBP2, TNIP1, ZEB2, ZMYND8</i>
<i>PDGFRA</i>	Dasatinib	1	<i>FIP1L1</i>
<i>CRLF2</i>	JAK2 inhibitor	2	<i>IGH, P2RY8</i>
<i>JAK2</i>	JAK2 inhibitor	19	<i>ATF7IP, BCR, EBF1, ETV6, PAX5, PCM1, PPFIBP1, RFX3, SSBP2, STRN3, TERF2, TPR, USP25, ZNF274, GOLGA5, SMU1, HMBOX1, SNX29, ZNF340</i>
<i>EPOR</i>	JAK2 inhibitor	4	<i>IGH, IGH, LAIR1, THADA</i>
<i>TSLP</i>	JAK2 inhibitor	1	<i>IQGAP2</i>
<i>DGKH</i>	Unknown	1	<i>ZFAND3</i>
<i>IL2RB</i>	JAK1/JAK3 inhibitor	1	<i>MYH9</i>
<i>NTRK3</i>	TRK inhibitor	1	<i>ETV6</i>
<i>PTK2B</i>	FAK inhibitor	3	<i>KDM6A, STAG2, TMEM2</i>
<i>TYK2</i>	TYK2 inhibitor	3	<i>MYB, SMARCA4, ZNF340</i>
<i>FLT3</i>	FLT3 inhibitor	1	<i>ZMYM2</i>
<i>FGFR1</i>	Sorafenib/dasatinib	1	<i>BCR</i>

### Funding

This work was supported by grant no. CA21765 from the National Institutes of Health and by ALSAC.

### REFERENCES

1. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med* 2009;360:2730-41.
2. Inaba H, Greaves M, Mullighan CG: Acute lymphoblastic leukaemia. *Lancet* 2013;381:1943-55.
3. Inaba H, Azzato EM, Mullighan CG. Integration of next-generation sequencing to treat acute lymphoblastic leukemia with targetable lesions: the St. Jude Children's Research Hospital approach. *Front Pediatr* 2017;5:258.
4. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. *Nat Rev Cancer* 2003;3:639-49.
5. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer* 2006;6:193-203.
6. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med* 2015;373:1541-52.
7. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014;371:1005-15.
8. van Dongen JJ, van der Velden VH, Brüggemann M, et al. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. *Blood* 2015;125:3996-4009.
9. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* 2018;378:439-48.
10. Kantarjian H, Stein A, Gökbuğten N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017;376:836-47.
11. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016;375:740-53.
12. Diouf B, Crews KR, Lew G, et al. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. *JAMA* 2015;313:815-23.
13. Yang JJ, Landier W, Yang W, et al. Inherited *NUDT15* variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. *J Clin Oncol* 2015;33:1235-42.