A new frontier in the battle against infant acute lymphoblastic leukemia

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In this issue of *Haematologica*, Guest *et al.* report the results of the Children's Oncology Group (COG) trial AALL15P1, which evaluated the role of the DNA hypomethylating agent azacitidine as epigenetic priming for chemotherapy for infants with acute lymphoblastic leukemia (ALL).[1] Although the treatment was well tolerated with decreased DNA methylation in nearly 90% of the cases, as demonstrated by the analysis using the patients' peripheral blood mononuclear cells, overall outcome was not improved compared to that in previous studies.

ALL in infants less than 1 year old is rare (<5% of pediatric ALL) and 70%-80% of the patients present with a very aggressive leukemia characterized by *KMT2A* gene rearrangements (*KMT2A*-r). In order to improve the outcome of this type of leukemia, which is one of the most difficult to cure, multi-institutional cooperative study groups in North America (COG, formerly the Children's Cancer Group [CCG] and the Pediatric Oncology Group [POG]), Europe (Interfant), and Japan (the Japan Children's Cancer Group [JCCG], formerly the Japan Infant Leukemia Study Group [JILSG], later the Japanese Pediatric Leukemia/Lymphoma Study Group [JPLSG]) have each conducted clinical trials specific to infant ALL from the late 1990s (Table 1). Until recently, most of these trials focused on intensifying conventional chemotherapy (Interfant 99, Interfant-06, CCG1953, POG9407, and COG P9407)[2-5] or aggressive use of allogeneic hematopoietic stem cell transplantation (JILSG MLL96/MLL98 and JPLSG MLL03),[6,7] but ended up with event-free survival rates of no more than 40%-50%. One exception was the successful JPLSG MLL-10 study that resulted in a 66% event-free survival rate in 75 infants with *KMT2A*-r ALL, which was considered the effect of introducing high-dose cytarabine in early consolidation, adopting less stringent criteria for age-based chemotherapy dose reduction, and broader indication for allogeneic stem cell transplantation compared to the other two groups, but along with comprehensive supportive care measures.[8]

It is obvious that further improvement in outcomes of infant *KMT2A*-r ALL cannot be achieved without introduction of novel therapies based on biological rationale. In this regard, COG investigators have always been pioneers leading the way. The first challenge was the introduction of a FLT3 inhibitor, lestaurtinib, in their AALL0631 study.[9] This idea was based on gene expression profile studies that have shown a unique pattern of infant *KMT2A*-r ALL, particularly with high expression of the *FLT3* gene. Overall, no significant difference in 3-year event-free survival rate was observed (36% in the lestaurtinib arm *vs*. 39% in the chemotherapy arm, *P*=0.67), but the patients who had shown both inhibition of the FLT3-activated cell line by lestaurtinib-treated patients' plasma and *ex vivo* sensitivity of patients' diagnostic blasts to lestaurtinib had an event-free survival rate of 88%. The next challenge was the pilot study AALL15P1. Recent genomic studies have revealed that infant *KMT2A*-r leukemia cells are characterized by an aberrant methylated genomic state with very few cooperating gene alterations. Infant *KMT2A*-r leukemogenesis is driven by specific histone modifications, such as H3K79 dimethylation induced via DOT1L recruitment by KMT2A fusion proteins, which leads to site-specific hypermethylation and to aberrant transcription of leukemogenic genes. Thus, epigenetic modifiers, such as hypomethylating agents including azacitidine and/or histone deacetylase inhibitors, became attractive targeting agents for infant *KMT2A*-r ALL. However, the 3-year event-free survival rates for the 53 patients who received at least one dose of azacitidine remained as low as 34.7%.[1] The final results of the two consecutive infant ALL clinical trials by the COG investigators may not be what they had expected; however, their attitude to rise to the challenge reminds me of the legendary phrase "we stand today on the edge of a new frontier..." spoken by John F. Kennedy in his acceptance speech of the Democratic nomination for president in the 1960 United States presidential election. Although the challenge against this intractable

Table 1. Major clinical trials for infants with *KMT2A*-rearranged acute lymphoblastic leukemia in chronological order.

Study	Accrual	Patients, N	HCT, N (%)	EFS, % (years)	OS, % (years)	Main findings/Main study questions for ongoing trials
JILSG MLL96/98	1995–2001	80	49 (61)	38.6 (5)	50.8 (5)	Intensive chemotherapy followed by HCT in CR1 may be beneficial
CCG1953/ POG9407	1996–2000	79/53	37 (47)/16 (30)	33.6 (5)/NA	NA/NA	No benefit of HCT
Interfant-99	1999–2005	308	37 (12)	36.9 (4)	NA	No benefit of delayed intensification
COG P9407	2001–2006	100	0	35.5 (5)	NA	Poor prognosis of infants aged ≤90 days
JPLSG MLL03	2004–2009	62	44 (71)	43.2 (4)	67.2 (4)	No benefit of HCT in earlier phase
Interfant-06	2006–2016	476	84 (18)	36.4 (6)	48.0 (6)	No difference between myeloid- and lymphoid-early consolidation
COG AALL0631	2008–2014	146	0	34 (5)	41 (5)	No benefit of adding FLT3 inhibitor (lestaurtinib)
JPLSG MLL-10	2011–2015	75	43 (57)	66.2 (5)	82.0 (5)	Early phase HDAC and adaptation of less stringent age-based chemotherapeutic dosing are likely to be beneficial
COG AALL15P1	2017–2019	53	0	34.7 (3)	64.0 (3)	No benefit of azacitidine priming
Interfant-pilot	2018–2021	30	9 (30)	81.6 (2)*	93.3 (2)	Addition of blinatumomab is likely to be highly effective and safe
JCCG MLL-17	2019–2024	NA	NA	NA	NA	Role of clofarabine in early and delayed consolidation
Interfant-21	2022–	NA	NA	NA	NA	Role of blinatumomab combined with chemotherapy
COG AALL2321	2024–	NA	NA	NA	NA	Role of BCL2 inhbitor (venetoclax) on top of blinatumomab-combined chemotherapy

*Disease-free survival. HCT: hematopoietic cell transplantation; EFS: event-free survival; OS: overall survival; JILSG: Japan Infant Leukemia Study Group; CR1: first complete remission; CCG: Children's Cancer Group; POG: Pediatric Oncology Group; NA: not available; COG: Children's Oncology Group; JPLSG: Japanese Pediatric Leukemia/Lymphoma Study Group; HDAC: high-dose cytarabine; JCCG: Japan Children's Cancer Group.

leukemia is still half-way down the road, the frontier spirit of the COG researchers deserves full respect. Recently, the Interfant group conducted a single-arm pilot phase II study to evaluate the role of the CD19/CD3 bispecific T-cell engaging antibody blinatumomab combined with the Interfant-06 chemotherapy backbone and documented a remarkable 2-year disease-free survival rate of 81.6% in 30 infants with *KMT2A*-r ALL.[10] Given the promising results of the pilot study, blinatumomab-combined therapy will be evaluated in a larger number of patients in the ongoing international non-randomized phase III study Interfant-21 (ClinicalTrials.gov identifier NCT05327894), for which the JCCG has also joined the force. Meanwhile, COG investigators will evaluate the role of the BCL-2 inhibitor venetoclax on top of the Interfant-backbone chemotherapy combined with blinatumomab in their next frontline infant ALL trial AALL2321 (ClinicalTrials.gov identifier NCT06317662). Additionally, a phase II study AALL2121 for relapsed/refractory *KMT2A*-r infant ALL evaluating the menin inhibitor revumenib in combination with chemotherapy has been initiated (ClinicalTrials.gov identifier NCT05761171). These continuing global efforts and challenges to incorporate novel therapeutics should lead to an effective solution enabling true improvement in outcomes of infant ALL.

Disclosures

No conflicts of interest to disclose.

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