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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 DNA hypomethylating agent azacitidine as an 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 could not be improved compared to the previous studies.

ALL in infants less than one 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 one of the most difficult-to-cure types of leukemia, 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 success of the JPLSG MLL-10 study which resulted in 66% event-free survival rate for the 75 infants with KMT2A-r ALL, which was considered the effect of introducing high-dose cytarabine in early consolidation, adopting more stringent criteria for age-based chemotherapy dose reduction, and broader indication of 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 an introduction of FLT3 inhibitor lestaurtinib in their AALL0631 study.(9) The idea of the study was based on the gene expression profile studies that have shown a unique pattern of infant KMT2A-r ALL, particularly with high expression of *FLT3* gene. Overall, no significant difference in 3-year event-free survival rate was observed (36% in the lestaurtinib arm versus 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 patient plasma and *ex vivo* sensitivity of patient diagnostic blasts to lestaurtinib demonstrated an 88% event-free survival rate. 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 leukemia is still half-way down the road, their frontier spirit deserves full respect. Recently, the Interfant group conducted a single-arm pilot phase II study to evaluate the role of CD19/CD3 bi-specific T-cell engaging antibody blinatumomab combining with the Interfant-06 chemotherapy backbone and produced 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 on-going international non-randomized phase 3 study Interfant-21 (ClinicalTrials.gov identifier NCT05327894), for which the JCCG had 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 2 study 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 for the true improvement in outcomes of infant ALL.

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

Study	Accrual	Patients, N	HCT, N (%)	EFS, % (year)	OS, % (year)	Main findings/Main study questions for on-going 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 age≤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 consolidations.
COG AALL0631	2008–2014	146	0	34 (5)	41 (5)	No benefit of adding FLT3i (lestaurtinib)
JPLSG MLL-10	2011–2015	75	43 (57)	66.2 (5)	82.0 (5)	Early phase HDAC and adaptation of more 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 consolidations.
Interfant-21	2022–	NA	NA	NA	NA	Role of blinatumomab combined with chemotherapy.
COG AALL2321	2024–	NA	NA	NA	NA	Role of BCL2i (venetoclax) on top of blinatumomab-combined chemotherapy.

BCL2i, BCL2 inhibitor; CCG, Children's Cancer Group; COG, Children's Oncology Group; CR1, first complete remission; EFS, event-free survival; FLT3i, FLT3 inhibitor; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; JCCG, Japan Children's Cancer Group; JILSG, Japan Infant Leukemia Study Group; JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; NA, not available; OS, overall survival; POG, Pediatric Oncology Group.

*Disease-free survival