REVIEW SERIES

KMT2A-rearranged acute lymphoblastic leukemia in infants: current progress and challenges

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Abstract

Chromosomal translocation of the *KMT2A* gene represents the cytogenetic hallmark of acute lymphoblastic leukemia diagnosed in infants (<1 year of age), driving a highly aggressive malignancy. For decades the event-free survival rates for these very young patients were at best ~40%. However, recent advances adding immunotherapy in the form of the bi-specific T-cell engager blinatumomab to the treatment led to encouraging results. In the present review we describe the current progress made, as well as the challenges that still lie ahead in terms of drug-related toxicity, the implementation of less toxic agents, acquired drug resistance, central nervous system involvement, and lineage switches. In addition, we touch on the benefit of preclinical models that can assist in guiding new treatment strategies.

Introduction

Although the 5-year event-free survival of childhood acute lymphoblastic leukemia (ALL) currently reaches 90%, treatment of infants (i.e., patients <1 year of age) with ALL remains challenging. In approximately 75% of infants, the leukemia is driven by chromosomal translocations of the *KMT2A* (formerly known as *MLL*) gene.[1,2] Wildtype *KMT2A* encodes a large multi-domain methyltransferase with critical functions in embryonic development and hematopoiesis. In the case of a *KMT2A* translocation, the N-terminus of *KMT2A* on chromosome 11q23 fuses to the C-terminus of one of its translocation partners. In infant ALL cells *KMT2A* most commonly fuses with *AFF1* (or *AF4* on chromosome 4), *MLLT1* (also known as *ENL* on chromosome 19), or *MLLT3* (also known as *AF9* on chromosome 9).[3,4] The resulting *KMT2A* fusion genes encode chimeric KMT2A-fusion proteins that represent strong oncogenic drivers imposing considerable changes in the transcriptomic landscape that strongly favor leukemia development. The leukemogenic activity of these fusion proteins largely depends on their direct interactions with two complementary oncogenic co-factors, menin and DOT1L, which are critical for KMT2A-fusion-driven transformation. The DNA-binding/scaffold protein menin serves as an adaptor that allows stable formation of the KMT2A-fusion protein complex to the chromatin. Subsequent recruitment of the histone H3K79 methyltransferase DOT1L results in inappropriately enhanced gene expression at loci targeted by the KMT2A-fusion protein complex through binding of menin, which is critical for the onset and maintenance of leukemia.[5-10]

With 5-year event-free survival rates of at best 45% the outcome of infants diagnosed with *KMT2A*-rearranged ALL remained poor for decades.[1,2,11,12] However, recent advances incorporating immunotherapy in the treatment strategy have introduced a significant change in the paradigm for this high-risk group of very young patients.[13] This review explores the advancements achieved In the treatment of *KMT2A*-rearranged infant ALL, the challenges encountered in creating advanced therapeutic strategies, and the role of preclinical research in guiding the development of novel treatment strategies to overcome these obstacles.

Treatment and outcomes: the past, present and future

Collaborative groups such as the Interfant Study Group, the Children's Oncology Group (COG), and the Japan Children's Cancer Group (JCCG) have made significant strides

in improving outcomes for infants with ALL.[1,2,11,12,14,15] Trials led by these three collaborative groups involved hybrid chemotherapy combining an ALL backbone with elements of the treatment of acute myeloid leukemia (AML), guided by the cytarabine sensitivity displayed by infant ALL blasts *in vitro*[16] (Table 1). High-risk patients are identified by clinical characteristics (i.e., age <6 months, high white blood cell counts at diagnosis and central nervous system [CNS] disease), where minimal residual disease (MRD) response additionally proved highly informative in identifying patients at high risk of relapse.[12,17] While both the Interfant and JCCG consortia advocate that high-risk *KMT2A*-rearranged infant ALL patients should receive hematopoietic stem cell transplantations in first complete remission,[12,18] this is not the strategy the COG takes forward.[19]

Although the outcome of infants with *KMT2A*-rearranged ALL in large clinical trials did not exceed 5-year event-free survival rates of 50%, the Japanese MLL-10 trial clearly stood out with a 3-year event-free survival of 66%.[12] Interestingly, this trial contained treatment elements that were comparable to those of the Interfant and COG trials. However, aggressive supportive care guidelines and stricter age-related dosing, which generally resulted in higher dosages, may underly the more beneficial event-free survival achieved in the MLL-10 trial.

The observation that higher doses of chemotherapy may contribute to improved outcomes is particularly intriguing and warrants further exploration. However, further intensification of already intense chemotherapeutic regimens comes with high risks of acute and long-term side effects. Regarding the latter, our current knowledge on the quality of life of surviving patients is still extremely limited. Long-term complications have been shown to occur across nearly all organ systems[20-22] and considering the health burden for children with ALL older than 1 year of age treated with less intense therapies,[23] the long-term effects for infant ALL patients may not be mild, as recently reviewed.[24] Hence, reducing the intensity of classical chemotherapeutic agents and introducing more targeted and less toxic small molecule inhibitors and/or immune therapies should be the way forward.

In line with that notion, various efforts implementing novel and to some extent more targeted agents, such as retinoic acid,[25] lestaurtinib (an inhibitor of the receptor tyrosine kinase FLT3),[11] azacitidine (a demethylating agent),[26] and vorinostat (a histone deacetylase inhibitor)[27] as upfront therapies have been tested in clinical trials. Unfortunately, none of these efforts led to significant improvements in clinical outcome (Table 1). In contrast, the addition of a single post-induction course of the bispecific T-cell engager molecule blinatumomab targeting CD19 to the Interfant-06 treatment protocol in the Interfant Blina pilot study has been ground-breaking. This treatment strategy achieved impressive early results without the addition of significant toxicity, dramatically increasing the 2-year disease-free survival from 49% to 82%, and the overall survival from 66% to 93%.[13] These promising results have led to the inclusion of blinatumomab after induction chemotherapy in current trials (Table 2). Additionally, other promising drugs that will be tested in phase II clinical trials include the BCL2 inhibitor venetoclax (NCT06317662), and the menin inhibitor revumenib (NCT05761171) (Table 2). Lastly, chimeric antigen receptor (CAR) T-cell therapy is also promising in *KMT2A*-rearranged infant ALL. Even though infants were excluded

Table 1. Summary of outcomes for infants with *KMT2A*-rearranged acute lymphoblastic leukemia.

Trial phase	Clinical trial	Drug(s) tested	Trial period	N of patients included	5-year EFS, %	5-year OS, %	Reference
III	COG-P9407	-	2001-2006	100	35.5	-	Dreyer *et al.*[14]
	COG AALL0631	R-lestaurtinib	2008-2014	146	34	41	Brown *et al.*[11]
	Interfant-99	R-VIMARAM	1999-2005	311	35.9 (6 y)	43.2	Pieters *et al.*[1]
	Interfant-06	R-ADE/MAE	2006-2016	476 - 334‡ - 142†	36.4 (6 y)* - 40.7 - 28.1	48.0 - 52.3 - 38.1	Pieters *et al.*[2]
	JPLSG MLL03	-	2004-2009	62	43.2 (4 y)	67.2	Koh *et al.*[15]
	JPLSG MLL10	-	2011-2015	75	66.2	82	Tomizawa *et al.*[12]
	JCCG-MLL17	Clofarabine	2019-2024	44	Awaited	Awaited	-
	MLL-Baby	Retinoic acid	2003-2016	100	36 (6 y)	44	Fechina *et al.*[25]
II	Interfant Blina pilot	Blinatumomab	2018-2021	30	81.6 (2 y)	93.3	van der Sluis *et al.*[13]
	TINI1	Bortezomib, vorinostat	2017-2021	30	44.8 (3 y)	62	Gruber *et al.*[27]
	AALL15P1	Azacytidine priming	2017-2019	53	34.7	64	Guest *et al.*[26]

*Outcome in Western countries (‡) was ±10% higher than that in non-Western countries (†). EFS: event-free survival; OS: overall survival; R: randomization; VIMARAM: vincristine, high-dose methotrexate and high-dose cytarabine; y: years; ADE: cytarabine, doxorubicin, etoposide; MAE: mitotraxone, cytarabine, etoposide.

Table 2. Current and planned trials for infant acute lymphoblastic leukemia, upfront and relapse.

Clinical trial	Phase	Line of treatment	Starting year	N of patients included	*KMT2A*-r status	IMP, new drugs	NCT number
Interfant-21	III (single arm)	First line	2023	160	*KMT2A*-r	Blinatumomab	NCT05327894
TINI2	I/II (single arm)	First line	2023	90	*KMT2A*-r + *KMT2A*-wt	Blinatumomab, bortezomib, vorinostat Ziftomenib only for *KMT2A*-r patients ≤90 days of age at diagnosis OR *KMT2A*-r patients >90 days of age at diagnosis with MRD-positive disease after induction intensification	NCT05848687
CCCG-iALL/ MPAL-2022	III (randomization)	First line	2022	200	*KMT2A*-r + *KMT2A*-wt	Blinatumomab, venetoclax (all patients receive venetoclax in induction and post-induction blinatumomab, randomization of additional courses of venetoclax during maintenance treatment)	ChiCTR2200064906
ALL-Baby-2021	III (single arm)	First line	2021	80	*KMT2A*-r + *KMT2A*-wt	Blinatumomab for high-risk patients followed by HSCT	NCT05029531
COG – AALL2321	II (randomization)	First line	Opening 2025	70	*KMT2A*-r	Blinatumomab, venetoclax (randomization of venetoclax in induction and consolidation)	NCT06317662
COG -AALL2121	I/Ib (single arm)	Second line	2024	66	*KMT2A*-r	Revumenib, added to lymphoid-directed or myeloid-directed induction therapy	NCT05761171

KMT2A-r: *KMT2A*-rearranged; IMP: investigated medicine product; *KMT2A*-wt: *KMT2A*-wildtype; MRD: minimal residual disease; HSCT: hematopoietic stem cell transplantation.

from the pivotal ELIANA trial,[28] retrospective real-world data have revealed similar positive outcomes.[29,30] There are no specific trials open for infant ALL at the moment.

Challenges in improving treatment of *KMT2A*-rearranged infant acute lymphoblastic leukemia

Infants are not just small children

Age-based dose reductions

Traditionally, the dose of chemotherapy is adjusted for infants compared to children, a practice that is not based on pharmacokinetic data but on anecdotal experience, focusing of safety rather than efficacy. In Interfant, COG, and JCCG trials, the dose is calculated per square meter and reduced for infants less than 1 year of age, given the relatively large body surface area of infants. The Japanese MLL-10 trial, however, changed the dose reduction guidelines and gave full dosages to children from the age of 4 months. As mentioned above, this trial showed a remarkably good outcome with a 3-year event-free survival of 66% for infants with *KMT2A*-rearranged ALL.[12] Therefore, the less strict reduction in age-related dosing may well have played an important role in improving this survival rate. This is supported by the differences in end-of-induction MRD remission rates (< 0.01%) according to age-based dose reductions between the Japanese MLL-10 and Interfant-06 (Table 3). In particular, infants older than 6 months at diagnosis had better end-of-induction MRD responses when treated with the full dose in MLL-10. Although there are no pharmacokinetic data to support this,[31-35] infant ALL patients might be underdosed if dose reduction guidelines are applied. This possibility informed the design of Interfant-21, in which patients received full dosages from 6 months of age. However due to a higher rate of infectious deaths in induction compared to that in Interfant-06, the dosing guidelines were reverted to those of Interfant-06.

Developmental changes in pharmacokinetics

Developmental changes in physiological factors can cause age-related variations in drug metabolism and disposition. Factors such as size, weight, body composition, and physiology play significant roles in drug absorption, distribution, metabolism, and excretion, and change particularly during the first year of life. For instance, differences in gastric pH and bile secretion may affect *absorption*. Changes in body composition, such as a decrease in total body water and increase in body fat during the first year of life, can affect *distribution*. *Metabolism* can be influenced by the change of expression of cytochrome P450 enzymes. For example,

Table 3. Differences in end-of-induction minimal residual disease between MLL-10 and Interfant-06 according to age-based dose reductions.

Age category	Study	Age-based dose intensity*	EOI MRD remission % (N of patients)
0-2 months	MLL-10	Two-thirds	27 (3/11)
	Interfant-06	Two-thirds	32 (8/25)
≥2-4 months	MLL-10	Three-quarters	63 (12/19)
	Interfant-06	Two-thirds	49 (25/51)
≥4-6 months	MLL-10	Full	59 (16/27)
	Interfant-06	Two-thirds	48 (21/44)
≥6-12 months	MLL-10	Full	89 (16/18)
	Interfant-06	Three-quarters	54 (52/97)

*Dosages were either two-thirds or three-quarters of the prescribed dose. EOI: end of induction: MRD: minimal residual disease. Adapted from the Interfant-21 protocol, version 1.3, Sept 2022.

CYP3A4 expression increases during the first week of life and reaches adult levels by 1-2 years of age. Similarly, drug *elimination*, which depends on the glomerular filtration rate and active tubular secretion, reaches adult levels by 6 to 12 months of age.[36,37] Consequently, developmental changes in drug absorption, distribution, metabolism, and excretion will affect the pharmacokinetics of various drugs differently. Therefore, dose adaptations might be essential for some drugs, but not for all.

Although not studied for all chemotherapeutic components administered to infants with *KMT2A*-rearranged ALL, the pharmacokinetics of vincristine, daunorubicin, methotrexate and PEGasparaginase has been evaluated in infants.

Vincristine is a vinca-alkaloid which binds to β-tubulin. Lee *et al*. suggested a 5-fold higher β-tubulin binding capacity in children compared to adults, which may play a role in differences in clearance of vincristine.[38] Consistently, two studies using population pharmacokinetic modeling showed that neonates and infants are potentially underdosed with doses below 0.05 mg/kg,[33,35] and Nijstadt *et al*. suggested that due to an increased β-tubulin binding young children could tolerate higher doses compared to adults.[35]

The pharmacokinetics of daunorubicin as well as high-dose methotrexate in infants was studied in Interfant 99.[31,34] Infants showed a lower area under the concentration curve for daunorubicin compared to older children due to dose reductions. The dose reductions also resulted in a lower area under the curve for its active metabolite, daunorubicinol.[31] Similarly, age-based dose reductions of high-dose methotrexate resulted in comparable steady-state concentrations for infants of all ages. However, the median methotrexate steady-state concentration was much lower than steady-state concentrations achieved in older children, which might hamper effectiveness in infants.[34] Therefore, these studies concluded that there was no indication of age-dependent pharmacokinetics of daunorubicin and methotrexate in infants.

Lastly, a recent population pharmacokinetic model of PEGasparaginase making use of data from 68 infants with ALL showed that the pharmacokinetic profiles in these infants were similar to those in older children. Based on this study the same dose without dose adaptations was recommended for infants in future trials.[39]

Overall, for many drugs used in infant ALL pharmacological evidence for dosing is limited. However, findings from the MLL-10 study suggested that higher dosages would result in better outcomes. Therefore, a pharmacokinetic study (PATIO study) has been set up within Interfant-21 with the aim of gaining better insight in the pharmacokinetics of chemotherapeutic agents in infant ALL, considering the influence of maturation and body size in the first year of life.

Comprehensive preclinical models to guide adaptation of toxic induction treatments

As described above, the addition of a single post-induction course of blinatumomab to a standard Interfant-06 treatment protocol showed very promising results.[13] Nonetheless, blinatumomab is particularly effective in patients with a low leukemia burden[40,41] and therefore relies on (and requires) effective first-line induction therapy. The current induction therapy for *KMT2A*-rearranged infant ALL patients consisting of five different drugs (i.e., dexamethasone, vincristine, *L*-asparaginase, daunorubicin, and cytarabine) is intense and comes with high risks of acute and severe toxicities. In addition, over 80% of *KMT2A*-rearranged infant ALL patients still display MRD (half of whom at high levels) at the end of induction therapy.[17] Therefore, less toxic induction strategies achieving similar or preferably better efficacy, are urgently needed. In an attempt to improve efficacy while decreasing toxicity, the upcoming phase II randomized COG trial (NCT06317662) will test the replacement of cytarabine with venetoclax, a BCL-2 inhibitor which we and others have recently identified as highly effective against primary *KMT2A*-rearranged infant ALL samples.[46,47]

The implementation of novel agents into current treatment protocols is, however, complicated as novel agents need to work alongside existing therapies. Furthermore, as *KMT2A*-rearranged infant ALL is a rare malignancy, there is

a limited number of patients available for clinical testing, and even in relatively large cohorts of patients the implementation of novel agents by the Interfant, COG, and JCCG does not guarantee success (Table 1). Hence, preclinically identified and promising new treatments that qualify for clinical testing need to be selected carefully. For this, patient-derived xenograft mouse models of *KMT2A*-rearranged infant ALL that mimic disease remission and relapse occurrence following induction therapy would represent useful tools. Following the development of such models in the laboratory of Richard Lock, which recapitulate the response to vincristine, dexamethasone, and *L*-asparaginase in pediatric ALL,[42,43] we recently established similar models for *KMT2A*-rearranged infant ALL (Figure 1, *unpublished data*). To render our models comparable to the Interfant-style induction therapy,[1,2] we added high-dose cytarabine to a vincristine, dexamethasone, and *L*-asparaginase backbone. As in actual patients, the addition of cytarabine significantly increased the burden of treatment for the mice and often led to dose-limiting toxicities. Additionally, our models achieved complete responses followed by relapsing disease after lifting the intensive induction treatment (Figure 1D, E, *unpublished data*). Hence, our models accurately recapitulate the treatment responses to contemporary induction therapy as observed in actual *KMT2A*-rearranged infant ALL patients. However, the use of immunodeficient patient-derived xenograft models has its limitations as a native immune system is lacking. This obscures the role of the immune system in therapy response, as well as complicating the assessment of immunomodulatory drugs or bispecific T-cell engagers that are based on the immune system. Nonetheless, especially in the case of rare malignancies such as *KMT2A*-rearranged infant ALL, for which a limited number of patients is available for clinical testing, these preclinical models may very well represent the next best available system and therefore are widely regarded as the gold standard. As such, the combination of patient-derived xenograft models with Interfant-style induction therapy represents an ideal platform to test novel agents or drug combinations alongside currently applied (chemo)therapy or as a replacement of one or several toxic components of standard treatment.

Moreover, these mouse models can now be used to preclinically test any desired drug (combination) addition and/or omission in a clinically relevant manner. As examples, more targeted approaches using small molecule inhibitors disrupting the specific oncogenic consequences of the formation of KMT2A-fusion proteins including DOT1L inhibitors (e.g., pinometostat) and menin inhibitors (e.g., revumenib and ziftomenib) may be attractive options.[5-10] Unfortunately, the efficacy of these inhibitors as single agents is short-lived due to readily emerging acquired resistance as observed in exposed leukemia samples *in vitro* as well as in actual patients treated with these agents during clinical trials.[44-47] An efficient solution to avoid this may involve combinatorial treatment of various agents simultaneously disrupting the oncogenic KMT2A-fusion multiprotein complex.[48] This could be especially relevant for *KMT2A*-rearranged ALL in which, in contrast to *KMT2A*-rearranged AML, the response to revumenib is quick and highly synergistic with that to the DOT1L inhibitor, pinometostat.[45] Moreover, the combined inhibition of menin and DOT1L may be further complemented by additional agents specifically disrupting critical interactions in KMT2A-fusion protein complexes, such as BET Inhibitors targeting BRD4[49,50] or recently developed inhibitors targeting the YEATS domains in MLLT1 (also known as ENL) and MLLT3 (or AF9). While MLLT1 and MLLT3 are known translocation fusion partners of KMT2A, wildtype forms of both proteins are also present in KMT2A-fusion containing multiprotein complexes, regardless of the type of KMT2A translocation.[51] In fact, in a CRISPR-cas9 loss-of-function screen in *KMT2A::AFF1*$^{+}$ acute leukemia cells, the YEATS domain of MLLT1 was identified to be essential for leukemic growth both *in vitro* and *in vivo*.[52] Subsequently emerging YEATS domain inhibitors such as TDI-11055 and SR-0813 appeared to display anti-cancer activity especially against *KMT2A*-rearranged acute leukemias.[53-55]

To remain acute lymphoblastic leukemia or to become acute myeloid leukemia (-like)

Clonal heterogeneity underlying relapse occurrence

About two-thirds of *KMT2A*-rearranged infant ALL patients relapse within 2 years of diagnosis while still being actively treated,[1,2] usually leading to refractory disease with a fatal outcome.[56] Currently, many hypotheses regarding cancer relapse emergence involve cellular heterogeneity,[57-63] with residual populations with different properties initiating disease re-emergence. Interestingly, a high degree of clonal heterogeneity has been observed in *KMT2A*-rearranged infant ALL.[64-67] To gain further insights into the mechanism(s) underlying relapse, we recently applied single-cell RNA sequencing to analyze diagnostic *KMT2A*-rearranged infant ALL samples from patients who experienced early relapses and patients who remained disease-free for at least 7 years.[68] This led to the identification of subsets of therapy-resistant and quiescent stem-like leukemic cells, the presence of which accurately predicted relapse occurrence. Strikingly, these 'relapse-predictive cells' were largely absent in diagnostic samples derived from *KMT2A*-rearranged infant ALL patients who remained disease-free for more than 7 years. Hence, elimination of these cells during induction therapy may well represent the key to developing curative treatments for infants diagnosed with *KMT2A*-rearranged ALL.

High end-of-induction minimal residual disease levels correlate with acute myeloid leukemia-like features

A *post-hoc* analysis of Interfant-06 identified that outcome according to the received treatment was influenced by the end-of-induction MRD response. Patients with MRD levels (≥0.05%) at that timepoint had better survival rates with

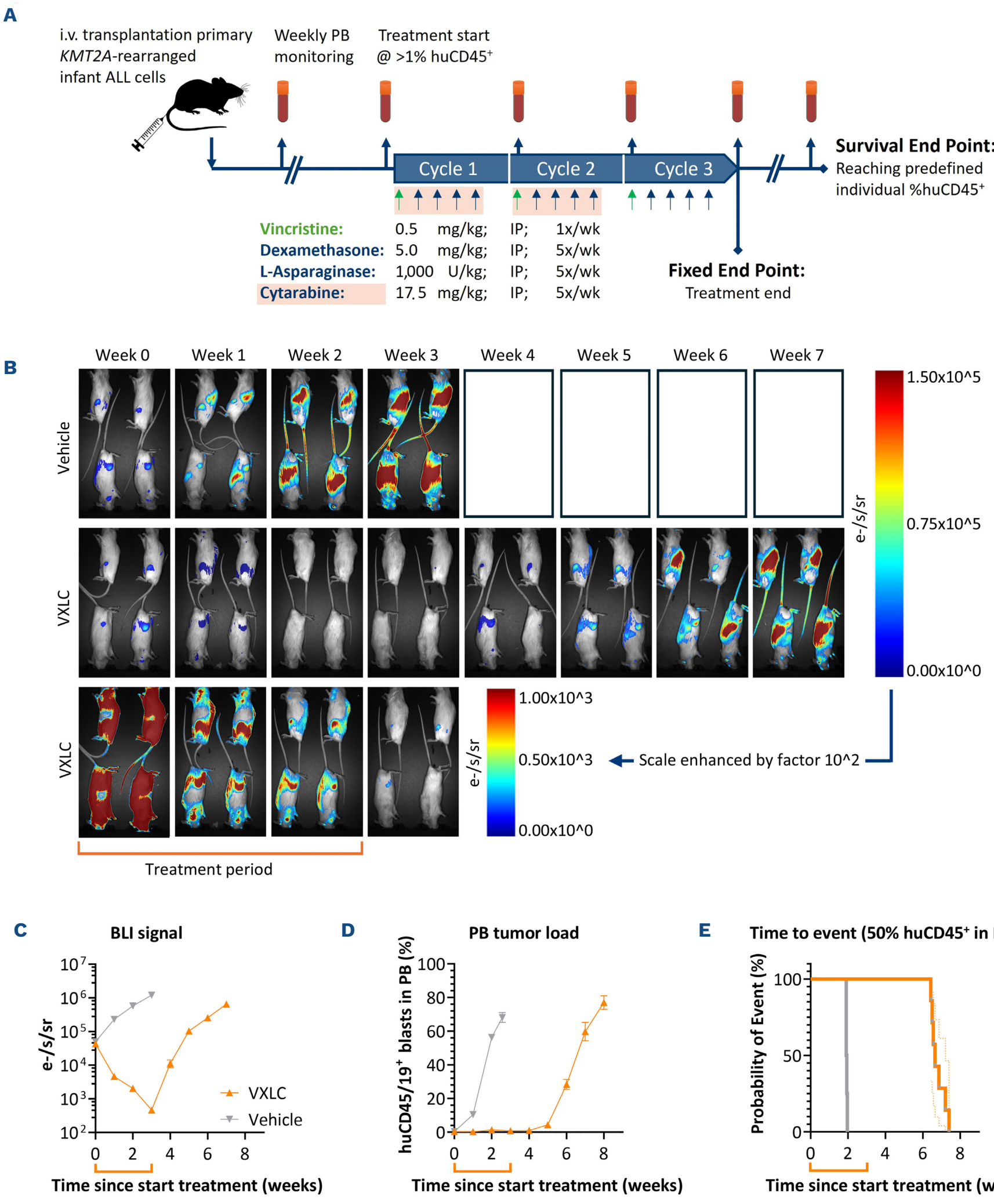

Figure 1. Representative luciferase-expressing patient-derived xenograft mouse model of *KMT2A*-rearranged infant acute lymphoblastic leukemia mimicking disease remission and leukemia re-emergence following induction therapy. (A) Schematic representation of the experimental design. Primary *KMT2A*-rearranged infant acute lymphoblastic leukemia (ALL) cells with transgenic expression of luciferase were injected intravenously into immunodeficient NRGS mice. Engraftment was monitored by quantifying the fraction of human CD19/CD45-positive cells weekly in the peripheral blood and treatment was commenced upon

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reaching >1% human CD19/CD45-positive cells. Mice were treated with either vehicle, or a mouse-adapted version of the Interfant induction treatment (designated VXLC) consisting of vincristine (V), dexamethasone (X), L-asparaginase (L), and cytarabine (C). Experimental endpoints were reached after mice succumbed to leukemia in the case of 'survival' experiments or directly after treatment cessation in the case of 'fixed endpoint' experiments. (B) Graphical depiction of weekly bioluminescence imaging (ordered horizontally) of animals transplanted with a luciferase-expressing patient-derived xenograft model and treated with vehicle or VXLC. The images in the third row (VXLC) are of the same animals at the same timepoints as the second row (VXLC), however, the scale is enhanced by a factor of 100 to allow for visibility of minimal residual disease during treatment. The treatment period is depicted by the orange bar. (C) Overall disease burden quantified by determining the average radiance, in electrons/s/sr, emitted per mouse monitored weekly until the experimental endpoint. (D) Disease development monitored by quantifying the fraction of human CD19/CD45-positive cells weekly in the peripheral blood, displaying a significant delay in reaching the experimental endpoint upon treatment. (E) Survival analysis illustrated by a Kaplan-Meier plot, with an event defined as reaching 50% of human CD19/CD45-positive cells in the peripheral blood. Similar to the clinical picture, animals appear to reach complete remission in peripheral blood in response to treatment, although leaving minimal residual disease visible according to the bioluminescent signal resulting in subsequent relapse. i.v.: intravenous; ALL: acute lymphoblastic leukemia; huCD45^{+}: human CD19/CD45-positive cells; IP: intraperitoneal; wk: week; BLI: bioluminescent imaging; PB: peripheral blood.

myeloid consolidation (6-year disease-free survival: 46% *vs*. 23%). In contrast, those with negative MRD achieved greater benefit from lymphoid consolidation (6-year disease-free survival: 78% *vs*. 45%).[17] In addition, it was noted that patients with high end-of-induction MRD more often exhibited co-expression of myeloid markers (80% *vs*. 50% for those with negative MRD). Therefore, it appears that an ALL-like induction regimen leads to selection of patients: patients with high MRD exhibit a more 'AML-like leukemia' (or multi-lineage type of leukemia) and benefit from the addition of AML consolidation (cytarabine, etoposide, daunorubicin/methotrexate) treatment, while patients with low or no MRD have a more 'ALL-like leukemia' and predominantly benefit from ALL consolidation (IB) therapy. Interestingly, this may well fit the hypothesis that relapse-initiating cells represent a stem cell-like phenotype that grants these cells the plasticity to either thrive as a lymphoblastic or myeloid leukemia.[68,69] ALL in infants may be cured by ALL-style therapies,[17] whereas the leukemia in high-risk patients probably originates from a more stem-like progenitor, requiring specific treatments that eliminate the hypothetical leukemic stem cell.

Therapy-induced lineage switching

Although it is a rare event, the capacity for lineage switch is a known characteristic of *KMT2A*-rearranged acute leukemias. Lineage switches comprised only 2% (5 of 231) of all relapses in first remission in Interfant-06 (Interfant-06 Study report, 2017). Treatment-induced lineage switching from B-ALL to AML with identical initial *KMT2A* breakpoints suggests a common origin rather than therapy-related secondary leukemia.[70] The pathogenesis of lineage switching involves increased lineage plasticity and infidelity, a hallmark of *KMT2A*-rearranged ALL cells, particularly in infants less than 6 months of age.[69] Mechanistically, this plasticity may arise from the presence of bipotential progenitor cells capable of differentiating into either myeloid or lymphoid lineages.[71] Additional contributing factors include cellular reprogramming, clonal selection under therapy-induced pressures, dedifferentiation, and epigenetic dysregulation.[72] It is hypothesized that *KMT2A*-rearranged B-ALL cells are more plastic in the context of immunological stimuli, since lineage switching seems to be more frequently observed with the broader use of CD19- and CD22-directed immunotherapies.[73-75] However, there are also studies with blinatumomab and CD19-directed CAR T-cell therapy in which hardly any lineage switched occurred,[13,29,30] suggesting that lineage switching is dependent on the intrinsic disease heterogeneity and plasticity rather than CD19 pressure.

Recent studies suggest that lineage switching is driven by changes in gene regulatory networks and chromatin accessibility, with myeloid relapses frequently linked to mutations or disruptions in epigenetic regulators such as CHD4.[72] These insights highlight the role of epigenetic abnormalities in maintaining the switched lineage phenotype. The switch may also reflect therapy-resistant subclones with inherent myeloid lineage potential, which emerge under selective pressure from ALL-directed treatments,[69] as has been hypothesized in the former paragraph as well. Treatment of lineage-switched *KMT2A*-rearranged ALL remains highly challenging, as outcomes are poor due to the aggressive nature of the disease and resistance to standard therapies. Current approaches typically involve AML-like regimens for myeloid relapses, such as cytarabine- and anthracycline-based chemotherapy or a combination of venetoclax and azacitidine.[76] However, these therapies often achieve limited success, and novel strategies are urgently needed. Investigational therapies, including menin inhibitors, hold promise by addressing the underlying epigenetic dysregulation. Nonetheless, lineage switches upon treatment with menin inhibitors have also been reported.[77] Likewise, Schneider *et al*. recently demonstrated that acquired resistance to the DOT1L inhibitor pinometostat in *KMT2A*-rearranged ALL cells was accompanied by the acquisition of specific myeloid-associated cell-surface antigens and gene expression.[44] Directly targeting the KMT2A-fusion protein complex should probably involve combinations of agents that simultaneously disrupt its oncogenic features to avoid lineage switching and the development of acquired resistance.

Central nervous system involvement

The incidence of CNS involvement at diagnosis is notably higher in *KMT2A*-rearranged infant ALL compared to non-infant ALL cases. This is especially true for infants with *KMT2A::AFF1*$^{+}$ ALL and a pro-B immunophenotype. In the Interfant-06 study, CNS involvement was reported in 13.8% of cases at diagnosis.[2] In non-infant pediatric ALL the CNS involvement rates are only 2-5% at diagnosis.[78] CNS involvement has been associated with worse outcome in *KMT2A*-rearranged infant ALL,[79,80] and was a high-risk feature in Japanese trials.[12]

A great proportion of relapses involve the CNS; in Interfant-06, 213 of 442 patients in first complete remission experienced a relapse of which 24% (N=50) involved the CNS, including 11% of cases with isolated CNS relapse and 13% with combined bone marrow and CNS relapse.[2] Even though the percentage of CNS relapses is not higher than that in non-infant pediatric ALL (i.e., 28% in AALL1331[81] and 20% in DCOG ALL11[82]), the absolute number of CNS relapses was higher (50 out of 442 [11%]) in infants with *KMT2A*-rearranged ALL in Interfant-06 compared to 1-2% in childhood ALL.[81,82]

CNS treatment strategies for *KMT2A*-rearranged infant ALL include intrathecal chemotherapy combined with systemic CNS-active agents, such as dexamethasone, high-dose methotrexate and high-dose cytarabine. With blinatumomab now integrated into most treatment protocols and some protocols omitting high-dose methotrexate, there might be challenges in treating the CNS compartment, since blinatumomab does not penetrate the CNS. Recent findings support this concern. In the Interfant blinatumomab pilot study, all relapses (4/30) involved the CNS, despite a lack of CNS involvement at diagnosis.[13] Similarly, a COG trial showed fewer bone marrow relapses with blinatumomab but no impact on CNS relapse rates.[83] These observations emphasize the importance of ensuring that novel therapies adequately address CNS disease.

Since blinatumomab mainly prevents bone marrow relapses, improvement in CNS treatment is needed to prevent CNS relapses. It has been hypothesized that triple intrathecal therapy might prevent CNS relapses better than single intrathecal therapy. Hence, the current Interfant-21 protocol uses triple intrathecal therapy for all *KMT2A*-rearranged infant ALL patients. The beneficial effect of triple intrathecal therapy on outcome is controversial. In studies in non-infants, triple intrathecal therapy seems to reduce CNS relapses but might increase bone marrow relapses as a competing event (CCG-1952).[84] However, this appears to be dependent on the intensity of the treatment backbone, because with increasing intensity this paradoxical effect was lost (AALL1331).[81] As mentioned above, CD19-directed CAR T-cell therapy is promising, also in the light of CNS relapses, since CAR T cells, unlike blinatumomab, are active at clearing CNS disease.[85,86] Moreover, Prieto *et al*. recently showed that neuron-glial antigen 2 (NG2) expression is associated with CNS infiltration in *KMT2A*-rearranged infant ALL.[87,88] Consequently, NG2-directed therapy may reduce CNS disease and relapse,[87,88] provided that such therapies are able to cross the blood-brain barrier and/or the blood-cerebrospinal fluid barrier.

Other than this, our understanding of CNS infiltration in *KMT2A*-rearranged infant ALL is limited and warrants further investigation to develop therapeutic strategies that effectively target CNS disease at diagnosis or prevent CNS infiltration during treatment.

Conclusions

Overall, the addition of post-induction blinatumomab treatment has proven to be highly beneficial. However, *KMT2A*-rearranged ALL remains a high-risk subtype of pediatric ALL, treated with an intense chemotherapeutic regimen. Hence, to further revolutionize the treatment of *KMT2A*-rearranged infant ALL we should now concentrate on lowering the toxicity of current therapies, while developing novel, preferably more effective treatment strategies as alternatives to intensive chemotherapy. Better insights into the differences in pharmacokinetics in infants will help fine-tune current chemotherapeutic protocols, optimizing efficacy while minimizing adverse effects. Additionally, targeted therapies focused on the *KMT2A*-fusion complex may aid in eradicating the subsets of therapy-resistant and quiescent stem-like leukemic cells present at diagnosis, subsequently inducing deeper remissions and preventing relapses, CNS involvement, and lineage switching.

Disclosures

No conflicts of interest to disclose.

Contributions

JS and RWS conceived the study, wrote the original draft, then reviewed and edited the manuscript. IMdvS, KSV and RP conceived the study, and reviewed and edited the manuscript.

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