Received: 17 March 2022 | Accepted: 10 June 2022

DOI: 10.1111/ijlh.13923

REVIEW

ISLH International Journal of Laboratory Hematology WILEY

To B- or not to B-: A review of lineage switched acute leukemia

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Abstract

Acute leukemia is a heterogeneous disorder of hematologic malignancies composed primarily of hematopoietic precursors that have acquired unregulated self-renewal and proliferation. Hematology classification systems typically divide these neoplasms into lymphoid (B- or T-) and myeloid-lineage subtypes, with therapy dependent upon this distinction. Infrequently, certain acute leukemias may undergo a complete lineage switch at relapse, subsequently complicating the diagnosis and treatment of these recurrent diseases. Transformation from B-lineage to myeloid lineage is the most common switch observed, and is frequently associated with a balanced 11q23 translocation, involving *KMT2A*. The mechanisms involved in the lineage-switch are unclear, but modern therapies targeting the B-cell-specific marker, CD19, have proven to promote this conversion as one means of treatment escape. Broadly speaking, therapy-mediated selection of alternate lineage-committed subclones derived from the same initial pluripotent progenitors, clonal evolution and reprogramming of lineage-committed blasts, and de novo clonally unrelated leukemias may account for the clinical impression of lineage switched acute leukemia during treatment. This review will explore the phenomenon and potential mechanisms of lineage transformation during the treatment of acute leukemia.

KEYWORDS
KMT2a, leukemia, lineage, lymphoblastic, myeloid

1 | INTRODUCTION

Leukemias develop because of mutations that cooperatively confer aberrant self-renewal capacity to leukemic cells, ultimately leading to dysregulated proliferation. For acute leukemias, these proliferating cells are composed of immature precursors (i.e., blasts) of myeloid or lymphoid lineage. Rarely, acute leukemia at relapse or during therapy demonstrates a lineage-switched immunophenotype (e.g., lymphoid leukemia to myeloid leukemia). To wit, the phenomenon of a lineage switched acute leukemia at relapse is fundamentally a clinicopathologic observation that is likely a description of a heterogeneous group of biological processes. The mechanisms by which this occurs are unclear, but may represent an expanded pre-therapy sub-clone, clonal evolution of the original leukemia, or development of a new clone that may be therapy-related. As such, relapsed acute leukemia with a lineage switch provides both a diagnostic and therapeutic challenge requiring further study.

The characterization of the lineage of an acute leukemia typically involves flow cytometric immunophenotyping, and occasionally immunohistochemistry.[1] Blasts that express a combination of the markers CD19, CD79a, and cytoplasmic CD22 generally make up B-lymphoblastic leukemias, whereas blasts expressing cytoplasmic CD3 typically represent T-lymphoblastic leukemia. Acute myeloid leukemia consists of blasts expressing myeloid markers, specifically myeloperoxidase (MPO) or monocytic markers such as CD64, CD11c, and CD14, usually in combination with other markers such as CD117, CD13, or CD33. The diagnosis of a lineage switch therefore requires detection (via either flow cytometry or immunohistochemistry) of the loss of markers associated

with one lineage and the gain of markers associated with another (e.g., loss of CD19, CD79a and CD22 and gain of MPO).

2 | LYMPHOID TO MYELOID SWITCH

The frequency of a lineage switch at relapse was initially estimated at 6.7% using FAB lineage assignment criteria; however, this number likely represents an overestimate when considering the advancement in immunophenotypic evaluation of leukemias since 1984 coupled with the more stringent lineage criteria employed by the current WHO classification system.[1–3] Most cases of lineage transformation involve a switch from acute lymphoblastic leukemia (ALL) to acute myeloid leukemia (AML).[2,4–15] Moreover, leukemic lineage switch is more frequently observed in infant leukemia and in young patients with gene rearrangements of the epigenetic and transcriptional regulator, lysine methyltransferase 2A, (*KMT2A*; formerly *MLL1*), and often occurs immediately after or even during induction chemotherapy.[5,16] The short interval between therapy and the change in lineage suggests a possible clonal selection facilitated by specific therapeutic agents.

2.1 | Anti-CD19 therapeutic agents causing lineage switch in B-ALL

Expression of the B-lineage-specific marker, CD19, characterizes B-ALL. Within the last decade, two therapies targeting CD19 have become quite prevalent, including the bispecific T-cell engager (BiTE), blinatumomab, and CD19-recognizing chimeric antigen receptor T cells (CAR-T). Both therapies direct the patient's T cells to attack the CD19-harboring leukemic blasts. It is not surprising, therefore, that some refractory leukemias develop CD19-negative blasts upon relapse.[17,18] While some relapsed CD19-negative leukemic blasts show an otherwise identical immunophenotype as the diagnostic disease, rare cases, particularly those that are *KMT2A*-rearranged (*KMT2Ar*), undergo lineage-switch at relapse as a mechanism to escape targeted destruction.[17–19] Lamble et al.[19] reported 12 of 163 (7.4%) B-ALL treated with CAR-T therapy demonstrated lineage switch, with 75% of the lineage switched relapses harboring *KMT2Ar*. Such cases provide a potential pitfall for lineage-specific minimal residual disease (MRD) assays that rely on using primarily lymphoid-associated markers, such as CD19, and suggest that myeloid-oriented flow panels may need to be routinely utilized for such cases.

KMT2Ar ALL has been observed to undergo lineage-transformation even prior to the advent of anti-CD19 targeted therapy, but due to its associated poor prognosis and propensity for relapse, anti-CD19 therapy is likely to be employed for many of these patients.[20,21] The potential for a lineage switch therefore provides a possible diagnostic challenge during the monitoring of patients during early treatment of *KMT2Ar* leukemia. As many patients can show circulating myeloid blasts after treatment, whether due to marrow regeneration or in response to growth factor therapy, pathologists and/or hematologists interpreting flow cytometry may be tasked with determining whether the detection of circulating myeloid blasts represents a reactive finding or the early signs of a myeloid lineage-switch. To this end, it should be noted that a majority of reported *KMT2Ar* lineage-switched myeloid blasts show a myelomonocytic or outright monocytic immunophenotype at relapse, a trait that may provide a diagnostic clue in this setting.[6–8,10,15,22,23,22(p)] As such, if myeloid-oriented MRD assays are to be used at the time of evaluation, a tube capable of evaluating immature monocytes, with markers such as CD64, CD11b, CD14, CD4, CD34, HLA-DR, CD33, and CD45 may be of utility.[24]

Of note, an alternate strategy for targeting leukemic B-lymphoblasts is to employ anti-CD22 therapy rather than targeting CD19. Interestingly, a study of 34 relapsed/refractory B-ALL patients treated with CD22 CAR-T therapy after failure of previous CD19 therapy did not uncover any cases of lineage switch.[25] Whether there is a fundamental difference between in the propensity for lineage switch when using anti-CD19 versus anti-CD22 therapy remains to be seen, but it may be that the mechanisms regulating CD19, such as PAX5, may be more essential for maintaining B-lineage commitment than those that control CD22.

3 | MYELOID TO LYMPHOID SWITCH

While most cases of lineage switch are from ALL to AML, AML to ALL transformations have also been reported, albeit rarely.[26–31] Rossi et al.[5] found that of their nine cases of lineage switch (identified from total of 1482 acute leukemia cases), two were from AML M5 to B-ALL. Nomani et al.[32] reported a case of a 54-year-old with AML with myelodysplasia related changes and monosomy 7 who experienced a lineage switch to MPAL, B/myeloid 180 days from initial diagnosis with the same karyotype and next generation sequencing (NGS) findings. Wu et al.[9] reported two patients with a lineage switch between B-ALL and AML intermediated by myelodysplastic syndrome (MDS). Cytogenetic analysis demonstrated complex abnormalities with evidence of sub-clone heterogeneity and clonal evolution. The latency interval between completion of induction and lineage switch appears to be longer in these cases and raises a question if chemotherapy induced the secondary leukemias.

4 | PATHOPHYSIOLOGY OF LINEAGE SWITCHED ACUTE LEUKEMIA

The underlying mechanisms for the apparent lineage switch are not well-known, and likely involve a multitude of pathways (Figure 1). At the simplest level, the apparent switch in phenotype may be artifactual, with the subsequent post-therapy "lineage-switched" acute leukemia representing an unrelated, de-novo leukemia. In contrast, the blasts at relapse may indeed be clonally related to the diagnostic neoplasm. In this case, a clonal relationship may reflect a common cell of origin for the leukemias, but a subsequent divergence in evolution prior to therapy.[33] Alternatively, it may be hypothesized that therapeutic intervention promotes evolution of the original blasts, resulting in lineage transformation.

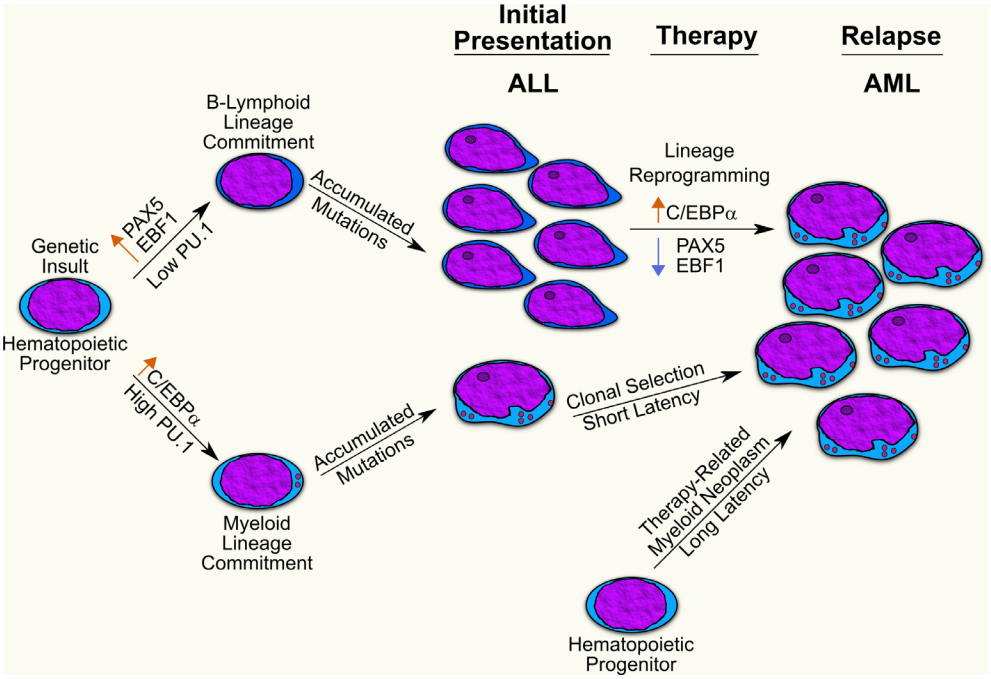

FIGURE 1 Proposed mechanisms of lineage switched acute leukemia. The figure illustrates possible mechanisms by which acute leukemia may undergo an apparent lineage switch at relapse using B-lymphoblastic leukemia as an example. (1) It is possible an early pluripotent hematopoietic stem cell acquires initial molecular abnormalities (e.g., *KMT2A* rearrangement), with subsequent downstream, more lineage-committed cells acquiring additional mutations leading to leukemogenesis. In this example the B-lymphoid blasts are the predominant clone at presentation, while neoplastic myeloid cells are rare. Initiation of therapy can promote a lineage switch at relapse by selecting against the dominant clone (e.g., anti CD19 therapy) and thus expanding the myeloid sub-clone. (2) Anti-ALL therapy may select for reprogrammed cells that have down-regulated B-lineage transcription factors, such as PAX5, and upregulated myeloid transcription factors, and thus undergone myeloid lineage-transformation. (3) Cytotoxic therapy itself may induce molecular alterations in bystander hematopoietic progenitors giving rise to a de-novo myeloid neoplasm. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia

4.1 | Clonal relation of initial diagnostic and relapsed leukemias

Comparison of the diagnostic and post-therapy *IgH* receptor rearrangement and/or cytogenetic and molecular signatures allows for assessment of a clonal relationship between the two blast populations. To this end, many reports of apparent lineage switch after therapy have indeed shown clonal relationships between the diagnostic and relapse samples.[7,34–37] A case report of a 25-year-old woman with pro-B ALL at diagnosis, B-ALL 2 years later at first relapse, and then monocytic leukemia 3 months at first relapse was shown by semi-nested PCR to have harbored *TAF15-ZNF384* translocations in all three samples.[36] Further, Rayes et al.[7(p)] identified a *KMT2Ar* infant leukemia that switched to acute monoblastic leukemia following 15 days of blinatumomab infusion and showed an identical clonal karyotype, [t(4;11)(q21;23), add(19)(p13)]. Moreover, a patient with congenital *KMT2Ar* B-ALL, with an abnormal karyotype, 46, XX, t(1;6)(p36.2; q25.3), t(4;11)(q21;q23), switched to myeloid lineage on day 100 of induction, yet retained the underlying cytogenetic abnormalities and JH rearrangement.[16] Clonal relationships have additionally been seen in *KMT2Ar* T-ALL, as demonstrated by an adolescent patient with early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) harboring a t(6;11)(q27;q23)/*KMT2A-AFDN* translocation which subsequently switched to a monoblastic leukemia by day 30 of induction therapy, while maintaining the underlying *KMT2A* rearrangement, structural chromosomal aberrations, and *TCR* gene rearrangement.[37] Finally, a patient with *KMT2Ar* B-ALL with 46,XX,add(1)(p36),t(4;11)(q21;q23)) at diagnosis, underwent blinatumomab therapy followed by a switch to AML lineage at relapse, suggesting a cytogenetic evolution with a newly acquired hyperdiploid karyotype, 54,XX,add(1)(p36),+2,t(4;11)(q21;q23),+der(4)t(4;11)x2,+6,del(7)(q22q32),+8x2,add(12)(p13),+add(12)(p13),+18x2, yet retention of the original *KMT2A* rearrangement and *IGH/TCRG* gene rearrangements.[23]

4.2 | Therapy-mediated selection of sub-clones from a common pluripotent progenitor

As mentioned above, clonal relationships might be accounted for by either a shared common cell of origin with pluripotency that acquired an initial hit and subsequently diverged into two neoplastic populations, or may represent lineage plasticity of the initial leukemia, which later reprogrammed upon treatment. Phylogenetic testing of the leukemic populations can provide a better understanding of when leukemic populations diverge. Performing a meta-analysis of 1665 transcriptomes from childhood ALL and AML, Khabirova et al.[38] found that *KMT2Ar* infant B-ALL displayed an early lymphocyte progenitor

(ELP) signature. ELPs (CD34+, CD127+, CD10-, and CD19-) have minimally or unrearranged IgH loci, and give rise to various lymphoid cells, including B cells (predominantly), as well as T cells and NK cells, but also show higher expression levels of CD15 and can generate small numbers of myeloid cells.[39] While it is tempting to speculate that the ELPs represent the cell of origin and that the pluripotency of this developmental stage might explain the lineage plasticity and subsequent lineage switches seen in infant *KMT2Ar* ALL, the reality of the situation is much less clear. Indeed, Khabirova et al.,[38] performed whole genome sequencing of diagnosis, remission, and relapse samples from a patient with *KMT2Ar* infant B-ALL with subsequent lineage switch to AML, and found that the initial *KMT2A*-rearrangement occurred in early embryonic development, prior to ELP stage commitment. Moreover, the diagnostic B-ALL and relapsed AML shared only six base substitutions in addition to the *KMT2A* rearrangement, indicating early divergence of the clones, prior to any subsequent therapy.[38]

With respect to *KMT2Ar* leukemias, the data suggest that clonally related "lineage switch" could be accounted for by small leukemic sub-clones of different lineage that then expand after the initial leukemia is targeted. Providing further support for this model, Chen et al.[40] reported two patients treated with CAR-T therapy that were found to have a pre-therapy blast population with myeloid potential as determined by scATAC-Seq. The first patient presented with *KMT2Ar* ALL and developed lineage switch after treatment with CART-19. Another *KMT2Ar* patient was treated with CART-19, relapsed with CD19-negative ALL, was subsequently treated with inotuzumab (targeting CD22), and ultimately CART-22 before relapsing with AML. In both instances, this pre-therapy blast population with myeloid potential expanded after application of selective treatment pressure. Of note, under the strictest sense, leukemias composed of two lineage clones at diagnosis exemplify the bilineal leukemias of mixed phenotype acute leukemia (MPAL) by WHO criteria, even if one population is small; indeed, "lineage switch" after diagnosis is considered a special type of MPAL.[41] As such, the lineage switch merely represents the expansion of a different initial clone. Nevertheless, detection of a smaller myeloid sub-clone depends on the sensitivity of the assays employed at diagnosis and may not always be possible.

4.3 | Clonal evolution and transcription factor reprogramming

While therapy-mediated clonal selection of leukemic sub-clones derived from a common progenitor may account for a subset of apparent lineage-switched acute leukemias, reprogramming of a lineage-committed leukemic clone remains a viable hypothesis for others. Using a transgenic murine model of E2A-PBX1 B-ALL treated with CAR-T cells, Jacoby et al.[42] demonstrated that early relapsed leukemia lost CD19 expression while later relapsed leukemias lost additional B-cell markers and gained a myeloid immunophenotype. In contrast to the early relapses, later relapse loss of CD19 expression was not due to alternative splicing of exon 2 of *Cd19*, but rather down-regulation of B-cell associated transcription factors, *Pax5* and *Ebf1*, with associated loss of H3K27ac signals at these promoter regions, and gains of H3K27ac signals in myeloid enhancers, including those for *Cebpa* and *Thap2*.[42] Moreover, single cell cloning of initial E2a-PBX1 leukemic cells showed expression of CD19, CD22, CD127, and CD43, with no overt CD19-negative myeloid leukemias detectable, arguing against CAR-T therapy selecting for a pre-treatment myeloid subclone.[42] Similar to the underlying transcriptional changes observed in E2a-PBX1 mouse model of lineage switched leukemia, Slamova et al.[43] identified increased hypomethylation in the *CEBPA* promoter and increased expression of C/EBPα in several patients with non-*KMT2Ar*, CD2+ B-ALL that switched to a monocytoid AML harboring similar Ig/TCR rearrangements. These findings are congruent with prior studies that show that ectopic expression of C/EBPα in various B-lineage cells can induce in vitro differentiation into myeloid cells, with C/EBPα and PAX5 playing antagonistic roles in myeloid and B-lymphoid lineage commitment, respectively.[44,45]

Interestingly, Wu et al.[9] report a case of a 23-year-old man who presented with BCR/ABL negative, *KMT2Ar*-negative B-ALL with complex cytogenetics, 45,X,−Y,der(10)t(5;10)(q26;q13)[4]/ 46,X,−Y,der(10)t(5;10)(q26;q13),+8[7]/46,XY[9], which relapsed 6.5 months after induction therapy as monocytic AML with further cytogenetic changes, 46,X,−Y,t(1;18)(q12;q21.1),t(4;21)(q12;q22),add(7)(p22),+8, der(10)t(5;10) (q26;q13),del(11)(q14q23),del(14)(q24q32),add(17)(q25)[20] (58.5% +5q31, 64% trisomy 8), but sharing the -Y, t(5;10) in some of the sub-clones, confirming a clonal link between the two leukmias. However, after switching to the AML-specific induction therapy, "7+3," the patient eventually relapsed again with B-ALL with an identical immunophenotype as the initial leukemia but with cytogenetics overlapping with some of the clones from the relapsed AML, 45,X,−Y,t(1;18)(q12;q21.1),t(4;21)(q12;q22),add(7)(p22),+8,−10, del(11) (q14q23),add(12)(q24.1),del(14)(q24q32),add(17)(q25), del(22)(q13) [cp14]/46,XX[5], specifically, the newly acquired t(1;18), t(4;21),add(7) abnormalities.[9] Such findings argue for a degree of lineage plasticity of the more committed leukemic blasts, with changes in lineage-specific therapy selecting for further evolved sub-cones present at each time point.

On a related note, the ability of these leukemias to adapt lineage based on the employed therapy are additionally illustrated by situations whereupon removal of the anti-CD19 selective pressure results in recurrence of the original B-lymphoblast population. Wölfl et al.[22] described a patient with *KMT2Ar* infant B-ALL that developed a CD19-negative monocytic AML harboring identical *KMT2A* and *IgH* rearrangements after 11 days of blinatumomab therapy, which subsequently reverted back to CD19+ B-ALL after cessation of blinatumomab. Similarly, a 40-year-old patient with *KMT2Ar* B-ALL who developed myeloid sarcoma after blinatumomab therapy, subsequently developed B/myeloid MPAL 6 weeks after removal of blinatumomab.[13]

4.4 | Neoplastic stem-like cells and increased plasticity of KMT2Ar infant leukemia

Therapy-mediated selection of pre-existing lineage committed sub-clones and clonal evolution with lineage transformation are not

necessarily mutually exclusive mechanisms by which a leukemia may evade therapy. Using single cell multi-omics approaches, Chen et al.[40] investigated some of these underlying mechanisms towards lineage plasticity. They showed that leukemic blasts from *KMT2Ar* infants <6 months of age are quite heterogeneous with respect to their stage of B-cell developmental arrest.[40] Moreover, they showed that the blasts from these patients possess a greater proportion of cells co-expressing both B- and myeloid-lineage genes, as well as sub populations of blasts that primarily mapped to a myeloid lineage.[40] Using scRNA-Seq and scATAC-Seq, Chen et al.[40] additionally showed that younger infants with *KMT2Ar* ALL have increased populations of circulating hematopoietic stem cell-like cells with *KMT2A* fusion transcripts, and that transplantation of these cells into mice could generate leukemias with a more myeloid immunophenotype. They also showed that engraftment of CD19+, CD34+, CD38- "immature" blasts and CD19+, CD33+ blasts could both generate leukemias predominantly composed of CD19+/CD33 negative blasts with a significant subpopulation of CD19+/CD33+ blasts.[40] These studies therefore highlight the plasticity of the blast clones of *KMT2Ar* leukemias, and indicate that both pluripotent leukemic progenitors as well as apparent lineage-committed blasts with the potential for lineage transformation can be present in the same leukemia, providing a multitude of ways for the neoplastic cells to evade targeted therapies.

4.5 | Therapy-related myeloid neoplasms masquerading as lineage switched relapse

Finally, it remains possible that a "lineage switch" identified at relapse may represent the development of a de novo clone that is unrelated to the initial acute leukemia. Gagnon et al.[35] report the conversion of ALL to AML in a 19-year-old female 30 months after treatment with vincristine-adriamycin-dexamethasone, with the relapse and diagnostic leukemias showing no cytogenetic overlapping features. Chung et al.[46] report a 9-year-old patient with B-ALL at diagnosis who relapsed with AML 9 months after induction and consolidation therapy, with the diagnostic and relapsed leukemias showing two markedly different abnormal karyotypes. One possible explanation for these cases lies in the cytotoxic therapies themselves promoting leukemogenesis. Intensive chemotherapy with alkylating agents, such as cyclophosphamide, and topoisomerases, such as etoposide, induce mutational changes that can promote a de-novo leukemia unrelated to the original neoplasm. Generally, alkylating agent-based therapy would be expected to produce losses of chromosomes 5 and 7, while topoisomerase-based therapy would expect to yield balanced translocations involving *KMT2A* at 11q23, *RUNX1* at 21q22 and *RARA* at 17q21.[47] Logically, assessment for a clonal relationship would involve a comparison of the original cytogenetic and molecular abnormalities identified at diagnosis and relapse, with the *KMT2Ar* relapses providing a potential challenge in that *KMT2A* is frequently rearranged at diagnosis in lineage-switched leukemia as well as in therapy-related acute leukemias.[48] The rapidity with which laboratories may carry out these studies clinically, however, will determine the usefulness of this assessment for disease management. Nevertheless, therapy-related myeloid neoplasms are generally later sequelae of cytotoxic therapy, and the latency with which alkylating agents (5–10 years) and topoisomerases (1–5 years) cause therapy-related acute leukemias make therapy-induced de novo leukemia less likely as an etiology for many of the leukemias with relapsed lineage switch occurring in the midst of the initial therapy.[47] Demonstrative of this latency period, Qing et al.[49] report the case of a 13-year-old boy who presented with B-ALL and an abnormal karyotype, 47,XY,+X,del(9)(p21p21)[4]/46,XY[16], was treated with vincristine, daunoruicin, prednisone, and PEG-asparaginase, as well as intrathecal cytrabine and methrotrexate, achieved initial remission followed by relapse treated by blinatumomab, but eventually developed AML with a normal karyotype but a de novo *KMT2A* rearrangement 4–5 years after the initial diagnosis. Similarly, Li et al.[50] report a case of Philadelphia chromosome-positive B-ALL that relapsed as AML therapy without a detectable BCR-ABL transcript 5 years and 4 months after standard induction, consolidation and CD19 CAR-T therapy.

5 | CONCLUSION

The lineage plasticity seen in some acute leukemias, particularly *KMT2Ar*, provides a diagnostic and therapeutic challenge in the modern age of hematology. While flow cytometric MRD assays for B-ALL are typically tailored to recognize atypical antigen expression on immature B cells, these assays typically employ few myeloid markers, decreasing the likelihood that a small population with an immunophenotypic shift will be detected.[51] As anti-CD19 therapy becomes more prevalent, recognition of lineage switch as an adaptive mechanism utilized by certain leukemias (e.g., *KMT2Ar* infant leukemia) to downregulate CD19 will be vital for future MRD assay development and gating strategies. At least for KMT2Ar, there may come a time that it will be necessary to run AML-associated MRD panels in addition to ALL-MRD assays during therapy. Relatedly, it is unclear what the therapeutic implications will be of early detection of a lineage switch prior to overt relapse. Moreover, the ideal treatment strategies to either prevent and/or manage lineage switched leukemia are unknown. Further work is thus necessary to understand the mechanisms of transformation and ultimately appropriately treat these challenging diseases.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. International Agency for Research on Cancer; 2017.
2. Stass S, Mirro J, Melvin S, Pui C, Murphy S, Williams D. Lineage switch in acute leukemia. *Blood*. 1984;64(3):701-706. doi:10.1182/blood.V64.3.701.701
3. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976;33(4):451-458.
4. Reardon DA, Hanson CA, Roth MS, Castle VP. Lineage switch in Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 1994;73(5):1526-1532. doi:10.1002/1097-0142(19940301)73:53.0.co;2-e
5. Rossi JG, Bernasconi AR, Alonso CN, et al. Lineage switch in childhood acute leukemia: an unusual event with poor outcome. *Am J Hematol*. 2012;87(9):890-897. doi:10.1002/ajh.23266
6. Gardner R, Wu D, Cherian S, et al. Acquisition of a CD19-negative myeloid phenotype allows immune escape of MLL-rearranged B-ALL from CD19 CAR-T-cell therapy. *Blood*. 2016;127(20):2406-2410. doi:10.1182/blood-2015-08-665547
7. Rayes A, McMasters RL, O'Brien MM. Lineage switch in MLL-rearranged infant leukemia following CD19-directed therapy. *Pediatr Blood Cancer*. 2016;63(6):1113-1115. doi:10.1002/pbc.25953
8. Balducci E, Nivaggioni V, Boudjarane J, et al. Lineage switch from B acute lymphoblastic leukemia to acute monocytic leukemia with persistent t(4;11)(q21;q23) and cytogenetic evolution under CD19-targeted therapy. *Ann Hematol*. 2017;96(9):1579-1581. doi:10.1007/s00277-017-3050-6
9. Wu B, Jug R, Luedke C, et al. Lineage switch between B-lymphoblastic leukemia and acute myeloid leukemia intermediated by "occult" myelodysplastic neoplasm: two cases of adult patients with evidence of genomic instability and clonal selection by chemotherapy. *Am J Clin Pathol*. 2017;148(2):136-147. doi:10.1093/ajcp/aqx055
10. Haddox CL, Mangaonkar AA, Chen D, et al. Blinatumomab-induced lineage switch of B-ALL with t(4:11)(q21;q23) KMT2A/AFF1 into an aggressive AML: pre- and post-switch phenotypic, cytogenetic and molecular analysis. *Blood Cancer J*. 2017;7(9):e607. doi:10.1038/bcj.2017.89
11. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):449-459. doi:10.1056/NEJMoa1709919
12. Oberley MJ, Gaynon PS, Bhojwani D, et al. Myeloid lineage switch following chimeric antigen receptor T-cell therapy in a patient with TCF3-ZNF384 fusion-positive B-lymphoblastic leukemia. *Pediatr Blood Cancer*. 2018;65(9):e27265. doi:10.1002/pbc.27265
13. He RR, Nayer Z, Hogan M, et al. Immunotherapy- (Blinatumomab-) related lineage switch of KMT2A/AFF1 rearranged B-lymphoblastic leukemia into acute myeloid leukemia/myeloid sarcoma and subsequently into B/myeloid mixed phenotype acute leukemia. *Case Rep Hematol*. 2019;2019:7394619. doi:10.1155/2019/7394619
14. Annesley C, Summers C, Pulsipher MA, et al. Clinical experience of CAR T cell immunotherapy for relapsed and refractory infant ALL demonstrates feasibility and favorable responses. *Blood*. 2019;134-(Supplement_1):3869. doi:10.1182/blood-2019-131447
15. Du J, Chisholm KM, Tsuchiya K, et al. Lineage switch in an infant B-lymphoblastic leukemia with t(1;11)(p32;q23); KMT2A/EPS15, following Blinatumomab therapy. *Pediatr Dev Pathol Off J Soc Pediatr Pathol Paediatr Pathol Soc*. 2021;24(4):378-382. doi:10.1177/10935266211001308
16. Jiang JG, Roman E, Nandula SV, Murty VVS, Bhagat G, Alobeid B. Congenital MLL-positive B-cell acute lymphoblastic leukemia (B-ALL) switched lineage at relapse to acute myelocytic leukemia (AML) with persistent t(4;11) and t(1;6) translocations and JH gene rearrangement. *Leuk Lymphoma*. 2005;46(8):1223-1227. doi:10.1080/10428190500086055
17. Braig F, Brandt A, Goebeler M, et al. Resistance to anti-CD19/CD3 BiTE in acute lymphoblastic leukemia may be mediated by disrupted CD19 membrane trafficking. *Blood*. 2017;129(1):100-104. doi:10.1182/blood-2016-05-718395
18. Shah NN, Fry TJ. Mechanisms of resistance to CAR T cell therapy. *Nat Rev Clin Oncol*. 2019;16(6):372-385. doi:10.1038/s41571-019-0184-6
19. Lamble A, Myers RM, Taraseviciute A, et al. Preinfusion factors impacting relapse immunophenotype following CD19 CAR T cells. *Blood Adv*. 2022;28:bloodadvances.2022007423. doi:10.1182/bloodadvances.2022007423
20. Hilden JM, Dinndorf PA, Meerbaum SO, et al. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. *Blood*. 2006;108(2):441-451. doi:10.1182/blood-2005-07-3011
21. Mitterbauer-Hohendanner G, Mannhalter C. The biological and clinical significance of MLL abnormalities in haematological malignancies. *Eur J Clin Invest*. 2004;34(Suppl 2):12-24. doi:10.1111/j.0960-135X.2004.01366.x
22. Wölfl M, Rasche M, Eyrich M, Schmid R, Reinhardt D, Schlegel PG. Spontaneous reversion of a lineage switch following an initial blinatumomab-induced ALL-to-AML switch in MLL-rearranged infant ALL. *Blood Adv*. 2018;2(12):1382-1385. doi:10.1182/bloodadvances.2018018093
23. Fournier E, Inchiappa L, Delattre C, et al. Increased risk of adverse acute myeloid leukemia after anti-CD19-targeted immunotherapies in KMT2A-rearranged acute lymphoblastic leukemia: a case report and review of the literature. *Leuk Lymphoma*. 2019;60(7):1827-1830. doi:10.1080/10428194.2018.1562185
24. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD working party. *Blood*. 2018;131(12):1275-1291. doi:10.1182/blood-2017-09-801498
25. Pan J, Niu Q, Deng B, et al. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. *Leukemia*. 2019;33(12):2854-2866. doi:10.1038/s41375-019-0488-7
26. Emami A, Ravindranath Y, Inoue S, Kaplan J, Lusher JM. Phenotypic change of acute monocytic leukemia to acute lymphoblastic leukemia on therapy. *Am J Pediatr Hematol Oncol*. 1983;5(4):341-343. doi:10.1097/00043426-198324000-00004
27. Marcus RE, Matutes E, Drysdale H, Catovsky D. Phenotypic conversion of TdT+ adult AML to CALLA+ ALL. *Scand J Haematol*. 1985;35(3):343-347. doi:10.1111/j.1600-0609.1985.tb01717.x
28. Lounici A, Cony-Makhoul P, Dubus P, Lacombe F, Merlio JP, Reiffers J. Lineage switch from acute myeloid leukemia to acute lymphoblastic leukemia: report of an adult case and review of the literature. *Am J Hematol*. 2000;65(4):319-321. doi:10.1002/1096-8652(200012)65:43.0.co;2-1
29. Krawczuk-Rybak M, Zak J, Jaworowska B. A lineage switch from AML to ALL with persistent translocation t(4;11) in congenital leukemia. *Med Pediatr Oncol*. 2003;41(1):95-96. doi:10.1002/mpo.10276
30. Dorantes-Acosta E, Arreguin-Gonzalez F, Rodriguez-Osorio CA, Sadowinski S, Pelayo R, Medina-Sanson A. Acute myelogenous leukemia switch lineage upon relapse to acute lymphoblastic leukemia: a case report. *Cases J*. 2009;2:154. doi:10.1186/1757-1626-2-154
31. van den Ancker W, Terwijn M, Regelink J, et al. Uncommon lineage switch warrants immunophenotyping even in relapsing leukemia. *Leuk Res*. 2009;33(7):e77-e80. doi:10.1016/j.leukres.2008.11.029
32. Nomani L, Cook JR, Rogers HJ. Very rare lineage switch from acute myeloid leukemia to mixed phenotype acute leukemia, B/myeloid, during chemotherapy with no clonal evolution. *Int J Lab Hematol*. 2019;41(4):e86-e88. doi:10.1111/ijlh.12977
33. Neame PB, Soamboonsrup P, Browman G, et al. Simultaneous or sequential expression of lymphoid and myeloid phenotypes in acute leukemia. *Blood*. 1985;65(1):142-148. doi:10.1182/blood.V65.1.142.142

34. Hershfield MS, Kurtzberg J, Harden E, Moore JO, Whang-Peng J, Haynes BF. Conversion of a stem cell leukemia from a T-lymphoid to a myeloid phenotype induced by the adenosine deaminase inhibitor 2′-deoxycoformycin. *Proc Natl Acad Sci U S A*. 1984;81(1):253-257. doi:10.1073/pnas.81.1.253
35. Gagnon GA, Childs CC, LeMaistre A, et al. Molecular heterogeneity in acute leukemia lineage switch. *Blood*. 1989;74(6):2088-2095. doi:10.1182/blood.V74.6.2088.2088
36. Grammatico S, Vitale A, La Starza R, et al. Lineage switch from pro-B acute lymphoid leukemia to acute myeloid leukemia in a case with t(12;17)(p13;q11)/TAF15–ZNF384 rearrangement. *Leuk Lymphoma*. 2013;54(8):1802-1805. doi:10.3109/10428194.2012.753450
37. Permikin Z, Popov A, Verzhbitskaya T, et al. Lineage switch to acute myeloid leukemia during induction chemotherapy for early T-cell precursor acute lymphoblastic leukemia with the translocation t(6;11)(q27;q23)/KMT2A-AFDN: a case report. *Leuk Res*. 2022;112:106758. doi:10.1016/j.leukres.2021.106758
38. Khabirova E, Jardine L, Coorens THH, et al. Single-cell transcriptomics reveals a distinct developmental state of KMT2A-rearranged infant B-cell acute lymphoblastic leukemia. *Nat Med*. 2022;28(4):743-751. doi:10.1038/s41591-022-01720-7
39. O'Byrne S, Elliott N, Rice S, et al. Discovery of a CD10-negative B-progenitor in human fetal life identifies unique ontogeny-related developmental programs. *Blood*. 2019;134(13):1059-1071. doi:10.1182/blood.2019001289
40. Chen C, Yu W, Alikarami F, et al. Single-cell multiomics reveals increased plasticity, resistant populations and stem-cell-like blasts in KMT2A-rearranged leukemia. *Blood*. 2021;138:2203. doi:10.1182/blood.2021013442
41. Borowitz MJ. Mixed phenotype acute leukemia. *Cytometry B Clin Cytom*. 2014;86(3):152-153. doi:10.1002/cyto.b.21155
42. Jacoby E, Nguyen SM, Fountaine TJ, et al. CD19 CAR immune pressure induces B-precursor acute lymphoblastic leukaemia lineage switch exposing inherent leukaemic plasticity. *Nat Commun*. 2016;7:12320. doi:10.1038/ncomms12320
43. Slamova L, Starkova J, Fronkova E, et al. CD2-positive B-cell precursor acute lymphoblastic leukemia with an early switch to the monocytic lineage. *Leukemia*. 2014;28(3):609-620. doi:10.1038/leu.2013.354
44. Heavey B, Charalambous C, Cobaleda C, Busslinger M. Myeloid lineage switch of Pax5 mutant but not wild-type B cell progenitors by C/EBPα and GATA factors. *EMBO J*. 2003;22(15):3887-3897. doi:10.1093/emboj/cdg380
45. Xie H, Ye M, Feng R, Graf T. Stepwise reprogramming of B cells into macrophages. *Cell*. 2004;117(5):663-676. doi:10.1016/S0092-8674(04)00419-2
46. Chung HJ, Park CJ, Jang S, Chi HS, Seo EJ, Seo JJ. A case of lineage switch from acute lymphoblastic leukemia to acute myeloid leukemia. *Korean J Lab Med*. 2007;27(2):102-105. doi:10.3343/kjlm.2007.27.2.102
47. Sill H, Olipitz W, Zebisch A, Schulz E, Wölfler A. Therapy-related myeloid neoplasms: pathobiology and clinical characteristics. *Br J Pharmacol*. 2011;162(4):792-805. doi:10.1111/j.1476-5381.2010.01100.x
48. Szczepanski T, Willemse M, Kamps W, van Wering E, Langerak A, van Dongen J. Molecular discrimination between relapsed and secondary acute lymphoblastic leukemia: proposal for an easy strategy. *Med Pediatr Oncol*. 2001;36(3):352-358.
49. Qing X, Panosyan E, Yue C, et al. Therapy-related myeloid neoplasm in an 18-year-old boy with B-lymphoblastic leukemia. *Exp Mol Pathol*. 2017;103(3):263-266. doi:10.1016/j.yexmp.2017.11.007
50. Li LZ, Sun Q, Fang Y, et al. A report on lineage switch at relapse of CD19 CAR-T therapy for Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia. *Chin Med J*. 2020;133(16):2001-2003. doi:10.1097/CM9.0000000000000962
51. Cherian S, Soma LA. How I diagnose minimal/measurable residual disease in B lymphoblastic leukemia/lymphoma by flow cytometry. *Am J Clin Pathol*. 2021;155(1):38-54. doi:10.1093/ajcp/aqaa242

How to cite this article: Kurzer JH, Weinberg OK. To B- or not to B-: A review of lineage switched acute leukemia. *Int J Lab Hematol*. 2022;44(S1):64-70. doi:10.1111/ijlh.13923