BMC Pediatrics

CASE REPORT Open Access

A long-term survivor of congenital KMT2A-R B-lymphoblastic leukemia with persistently positive bone marrow MRD and multiple CNS relapses

Taxiarhia J Arabatzis[2], Biren Desai[2], Sandra Baril[1], Susan Rasul[2], Girmay Tekle-Yohannes[3] and Michal Ann Miller[3*]

Abstract

Here we describe the case of an infant incidentally diagnosed with congenital KMT2A-rearranged (KMT2A-r) B-cell ALL on Day of Life 4. He received the first dose of intrathecal methotrexate on DOL 5, and induction systemic therapy on DOL 6. He demonstrated morphologic remission at the end of induction but had positive bone marrow. Minimal residual disease (MRD) was 1.4%. He experienced isolated CNS disease after consolidation and immunotherapy. At 8 months of age he underwent hematopoietic stem cell transplantation (HSCT). At 14 months of age he had medullary and CNS relapse, and at 16 months of age underwent CD19 CAR-T therapy. At 6 years of age he remains in remission with tolerable developmental delays and a good quality of life.

Keywords B-cell acute lymphoblastic leukemia, KMT2A–r, Neonatology, CD 19 CAR T-cell therapy

Introduction

Neonatal leukemia is a diagnosis made before 1 year of life, with younger age at diagnosis associated with worse outcomes [1]. Presenting clinical features can include leukemia cutis, hepatosplenomegaly, lymphadenopathy, and cardio-respiratory compromise [2]. Infant ALL can carry poor prognostic factors such as KMT2A- gene arrangement (KMT2A-r) [3]. and CNS status at time of initial diagnosis [4]. In a recent phase III randomized trial 6-year event free survival in infants with KMT2A-r ALL was 36.4% [5]. Infants who receive aggressive chemotherapy regimens are at high risk for acute and long-term adverse effects compared to older children [6], and non-chemotherapy agents are greatly needed. Recent research investigating the use of immunotherapeutic agents [7, 8] and CAR-T cell therapy [9–12] as well as new chemotherapy regiments in this population is encouraging. Here we present a case of an asymptomatic newborn who was diagnosed in December of 2017 with congenital KMT2A-rearranged B-cell ALL on day of life (DOL) 4 from incidental CBC showing hyperleukocytosis. He remains in remission with tolerable developmental delays and a good quality of life.

Observations

Our patient is a caucasian male born to a G1P1 30-year-old Caucasian female via elective c-section at 39 weeks and 0/7 days. The pregnancy and delivery were uncomplicated. His weight was appropriate for gestational age

*Correspondence:
Michal Ann Miller
mamiller2@geisinger.edu
[1]Department of Pediatrics, Janet Weis Children's Hospital, Danville, PA, USA
[2]Department of Internal Medicine-Pediatrics, Janet Weis Children's Hospital, Danville, PA, USA
[3]Department of Pediatric Hematology and Oncology, Janet Weis Children's Hospital, 100 N Academy Ave, Danville, PA 17822, USA

Table 1 Treatment timeline

Date of Treatment	Treatment Type	Treatment
12/19/2017-4/2/2018	chemotherapy	Chemotherapy according to AALL15P1 induction and interim maintenance phases
6/4/2018	Immunotherapy	Blinatumomab 5 mcg/kg/day for 21 days (therapy was interrupted for 1 week due to development of seizures)
7/18/2018	immunotherapy	Inotuzumab per AALL1621 protocol
9/1/2018-9/6/2018	Chemotherapy	Conditioned with clofarabine, thiotepa, melphalan, and ATG
9/7/2018	Transplant	Paternal haplo peripheral blood stem cell transplant
3/14/2019	T cell/immunotherapy	T cell collection
3/14/2019	chemotherapy	Reinduction with: Dexamethasone, methotrexate, vincristine per ALL0932 protocol
4/29/2019	Chemotherapy	Cyclophosphamide 500 mg/m^2 given IV twice, Fludarabine 30 mg/m^2 IV for 4 doses
5/7/2019	T cell/immunotherapy	CTL119 (hu CART 19) per 18CT014: humanized CART phase II study

and complete physical examination was normal. In the nursery he remained afebrile, passed meconium < 24 h from birth, and was breast feeding well. Transcutaneous bilirubin levels at 14 h of life (HOL), DOL 2, and DOL 3 was zero, therefore a serum bilirubin and complete blood count (CBC) was collected. Serum bilirubin was within normal limits, but surprisingly CBC was remarkable for white blood cell (WBC) count of 108,000 K/uL with 80% blasts. The patient was subsequently transferred to our neonatal intensive care unit for workup and treatment of presumed infant leukemia.

Additional labs revealed LDH 1,102 U/L (reference range 0-437 U/L) and uric Acid 10.9 mg/dl (reference range 3.4-7.0 mg/dl). Hemoglobin, platelet count, kidney, and liver function were normal. Peripheral blood flow cytometry confirmed B precursors ALL that notably lacked CD10, CD0, surface immunoglobins, and all myeloid antigens. CSF studies were negative for blasts. Cytogenetics showed abnormal karyotype; 46, XY, t(11;19)(q23.2;p13.3)[13]/46,XY[17]. FISH studies showed 11q23 KMT2A gene re-arrangement. There was no evidence of extramedullary involvement at the time of diagnosis.

The patient received intrathecal methotrexate on DOL 5, and induction systemic chemotherapy was initiated on DOL 6. He was enrolled onto Children's Oncology Group (COG) AALL015P1 research protocol (NCT02828358); a pilot study based on Interfant-06 back-bone with addition of the experimental drug azacitidine [11]. While receiving induction chemotherapy, the patient continued to breast feed and gain weight appropriately with limited toxicity. Prednisone response on day 8 showed 0.17 K/μL blasts which was consistent with a poor responder. End of induction bone marrow evaluation showed morphologic remission but minimal residual disease (MRD) of 1.4%. End of consolidation bone marrow evaluation showed MRD of 0.63%. At 3-months of age, at the start of interim maintenance, he was found to have asymptomatic isolated CNS relapse. He continued intensified chemotherapy, including triple therapy with cytarabine, methotrexate and hydrocortisone intrathecal chemotherapy. Bone marrow was MRD negative at the end of interim maintenance. He received supportive therapies including IVIG and palivizumab and experienced no significant infections. Due to being less than 1 year of age at the time, he was deemed ineligible for hematopoietic stem cell transplant (HSCT), and his disease burden was maintained with blinatumomab. He was initially started on blinatumomab with standard 15 mcg/m^2/day dosing, however after day 1 he developed lethargy, hypothermia, and bradycardia, and seizures. He had CT head and MRI brain, and EEG without any abnormalities, and started levetiracetam. His dose of blinatumomab was lowered to 5 mcg/m^2/day, and he finished the cycle without further seizures.

He was treated with inotuzumab ozogamicin per ALL1621 protocol and received 2 cycles (dosed at 0.8 mg /m2 on day 1 and 0.6 mg/m2 on day 8 and 15 of each cycle,). After blinatumomab and inotuzumab he was confirmed CD19- and CD22-. At 8 months of age, he was transferred to an outside institution for HSCT, and was noted to have positive MRD and was his CNS was negative for disease burden. He then underwent conditioning chemotherapy with clofarabine, thiotepa, melphalan, and ATG, 2 days prior to HSCT. Transplant course was complicated by severe mucositis (requiring prolonged TPN), veno-occlusive disease (which required defibrotide), respiratory failure (requiring intubation), epidural hematoma, seizures, and steroid induced adrenal insufficiency. He experienced combined medullary and CNS relapse 6-months post HSCT at 14 months of age, with. a population of blasts that were CD19+, CD22+, and CD10-.

The decision was then made to undergo immunotherapy with CART cell therapy as part of CTL119 (hu CART 19) humanized CART phase II study at an outside institution. He underwent T cell collection, followed shortly after with 3 drug re-induction chemotherapy per ALL0932 protocol with dexamethasone, vincristine, and PEG-asparaginase. Bone marrow after induction chemotherapy was MRD- and he the CNS was negative fordisease. He received cyclophosphamide and fludarabine, then underwent CAR-T cell per 18CT014 protocol which

was a phase II trial at the time Table 1. He developed B cell aplasia and hypogammaglobinemia as expected, and this continues to be replaced with injections of IVIG to this day. He otherwise had limited toxicity from CAR- T cell therapy. He remains in complete remission at 6 years of age at the writing of this manuscript.

During his multiple treatment courses, he had some complications. At 2 years of age during a prolonged PICU course post HSCT he developed iatrogenic adrenal insufficiency and was noted to have elevated TSH. Pediatric endocrinology followed him, and he underwent a prolonged steroid taper for iatrogenic adrenal insufficiency. He later underwent a cosyntropin stimulation test, and growth hormone stimulation testing which was normal. His initial elevated TSH was thought to be due to sick euthyroid syndrome, but it remained elevated after discharge, and he was placed on 25 mcg levothyroxine. His thyroid studies were followed until 2 years of age to prevent long term effects on development. At 4 years of age, his thyroid studies normalized, and he came off levothyroxine. As of this manuscript's writing, he is no longer getting treatment for any endocrine pathology. Late effects of treatment also include a diagnosis of epilepsy at 5 years of age. Neurological exams including mental status, cranial nerves, motor, sensation, gait, coordination, and reflexes have been within normal limits. His linear growth has been consistently tracking in the 5th -10th percentile. Recent neuropsychiatric testing revealed a diagnosis of ADHD and difficulties with memory and synthesizing information together. He is currently in kindergarten and does well academically with an individual education program (IEP) including occupational and speech therapy.

Conclusions

Infant ALL is rare and when associated with KMT2A-Rhas dismal outcomes. Multiple cooperative studies conducted in different parts of the world has failed to improve outcomes due to chemoresistance and increased sensitivity of infants to chemotherapy toxicity. Systemic exposure of chemotherapy drugs in the neonate and young infant is affected by absorption, distribution, metabolism, and elimination which are all influenced by physiological changes that occur during the neonatal and infant period [13]. Here we reported a case of congenital KMT2A-R B cell ALL diagnosed on DOL 4. At the time the physical exam was unremarkable, and he appeared well, unlike. prior cases reports of infants diagnosed within 24 h of life whichhad abnormal physical exam findings [14]. In addition, most neonatal ALL cases present at a later age.

At the time of this writing, the patient is 6 years old, and he is doing well academically with the assistance of an IEP. This is astonishing given previous studies have shown that infants diagnosed with any type of leukemia at 6 months of age or less have many late-term toxicity effects than those older at initial diagnosis [15]. Although he is not the first infant diagnosed with KMT2A-rALL who is alive, he is still a unique case in that his initial diagnosis was incidental. Despite multiple relapses during treatment the patient has had a favorable outcome, perhaps diagnosis before phenotypic disease presentations contributed to his outcome, but this is hard to determine.

Over the past few decades, the treatment of congenital ALL with KMT2A-r has evolved including aggressive multi-agent chemotherapy, selective use of hematopoietic stem cell transplants, immunotherapy, and most recently the introduction of CAR-T cell therapy [16]. Balancing efficacy and toxicity are crucial, as severe adverse drug reactions may lead to treatment failure or reduced adherence.

MRD after induction and consolidation chemotherapy is a prognostic factor in infants with ALL [4, 17, 18]. It is noted that our patient had MRD of 0.63% after consolidation chemotherapy and later experienced multiple relapses as is common in cases of congenital KMT2A-rearranged B-cell ALL with initial elevated MRD [2, 4]. Interestingly at the time of diagnosis he had no CNS involvement, but initial relapse was isolated to the CNS. This is different than prior cases in which relapse in the bone marrow is often without CNS involvement [19]. Our patient is exceptionally unique in that he received multiple immunotherapies' including blinatumumab, inotuzumab ozogamicin, and later CD19 CAR- T cell therapy. Most prior reported cases had received CAR T cell therapy prior to HSCT. However given our patients age of less than 1 year with relapse, at that time he was not a candidate for CAR-T cell therapy and therefore HSCT was done first [9, 11, 12]. Perhaps CAR-T therapy after HSCT led to further survival in our patient, as it has been found to be helpful at clearing CNS disease in prior studies [10]. In addition, our patient was treated with Blinatumomab prior to HSCT which has previously been found to have event free survival to age 3 years old of 47% and overall survival of 81% at 3 years of life [7]. However, our patient developed seizures after treatment with Blinatumomab, which has not been recorded in other more recent trials [7]Since CAR-T cell treatment the patient continues to do well.

After multiple relapses and therapies at such a young age it is surprising how well our patient tolerated them. Although he has developed epilepsy and some developmental delay, he is able to attend school with an IEP and does well academically. His case warrants discussion as he has done well developmentally, which can be referred to with future cases of ALL presenting in the neonatal period. In addition, he received most known current

treatment modalities including chemotherapy, immunotherapy with Blinatumomab and Inotuzumab ozogamicin prior to HSCT, and finally CAR-T cell therapy.

Abbreviations

AGA	Appropriate for gestational age
ALL	Acute Lymphoblastic leukemia
APGAR	Appearance, pulse, Grimace, Activity, and Respiration score
CBC	complete blood count
CART	chimeric antigen receptor T-cell therapy
CD	cluster of differentiation
CMV	Cytomegalovirus
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
FISH	Fluorescence in situ hybridization
HBsAb	Hepatitis B surface antibody
HLA-DR	human leukocyte antigen-DR isotype
HSCT	Hematopoietic stem cell transplantation
MRD	minimal residual disease
NICU	neonatal intensive care unit
Tc Bili	transcutaneous bilirubin

Acknowledgements
Not applicable.

Author contributions
T.A, and B.D wrote the main manuscript and text S.B, S.R, G.T and M.M all contributed as well to the manuscript. All authors reviewed and approved the manuscript.

Funding
Not applicable.

Data availability
Further patient data can be obtained by contacting the corresponding author Dr. Miller.

Declarations

Ethics approval and consent to participate
This study was submitted to the Geisinger Institutional Review Board (IRB #00008345) and was found to be exempt from IRB approval due to it being a case report.

Consent for publication
The patients' parents consented to publication. Informed Consent from the patient's legal guardian(s) for publication of identifying information/images in an online open-access publication was obtained prior to submission.

Competing interests
The authors declare no competing interests.

Received: 8 November 2023 / Accepted: 20 September 2024
Published online: 28 February 2025

References

1. Hunger S, Mcgavran L, Meltesen L, et al. Oncogenesis in utero: fetal death due to acute myelogenous leukemia with an MLL translocation. Br J Haematol. 1998;103(2):539–42.
2. Brown PA. Neonatal Leukemia. *Clin Perinatology*. 2021;48(1):15–33. https://doi.org/10.1016/j.clp.2020.11.002. PMID: 33583502.
3. Ibrahimova A, Pommert L, Breese EH. Acute Leukemia in Infants. Curr Oncol Rep. 2021;23(3):27. https://doi.org/10.1007/s11912-021-01021-1. PMID: 33580326.
4. Popov A, Tsaur G, Permikin Z, et al. Incidence and prognostic value of central nervous system involvement in infants with B-cell precursor acute lymphoblastic leukemia treated according to the MLL-Baby protocol. Pediatr Blood Cancer. 2022;69(9):e29860. Epub. 2022 Jun 30. PMID: 35713168.
5. Pieters R, De Lorenzo P, Ancliffe P, et al. Outcome of infants younger than 1 year with Acute lymphoblastic leukemia treated with the Interfant-06 protocol: results from an International Phase III Randomized Study. J Clin Oncol. 2019;37(25):2246–56. Epub 2019 Jul 8. PMID: 31283407.
6. Leung W, Hudson M, Zhu Y et al. Late effects in survivors of infant leukemia. Leukemia. 2000;14(7):1185-90. https://doi.org/10.1038/sj.leu.2401818. PMID: 10914540.
7. van der Sluis IM, de Lorenzo P, Kotecha RS et al. Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia. N Engl J Med. 2023;388(17):1572–1581. https://doi.org/10.1056/NEJMoa2214171. PMID: 37099340.
8. Clesham K, Rao V, Bartram J, Ancliff P et al. Blinatumomab for infant acute lymphoblastic leukemia. Blood. 2020;135(17):1501–1504. https://doi.org/10.1182/blood.2019004008. PMID: 32043146.
9. Breese EH, Krupski C, Nelson AS, et al. Use of CD19-directed CAR T-Cell Therapy in an Infant With Refractory Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol. 2021;43(4):152–154. https://doi.org/10.1097/MPH.0000000000001857. PMID: 32496443.
10. Leahy AB, Newman H, Li Y, et al. CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukemia: a post-hoc analysis of pooled data from five clinical trials. Lancet Haematology. 2021;8(10):e711–e722. https://doi.org/10.1016/S2352-3026(21)00238-6. Erratum in: Lancet Haematology. 2021;8(11):e789. PMID: 34560014; PMCID: PMC9026766.
11. Guest EM, Kairalla JA, Devidas M, Hibbitts E, Carroll AJ, Heerema NA, Kubaney HR, August MA, Ramesh S, Yoo B, Farooqi MS, Pauly MG, Wechsler DS, Miles RR, Reid JM, Kihei CD, Gore L, Raetz EA, Hunger SP, Loh ML, Brown PA. Azacitidine as epigenetic priming for chemotherapy is safe and well-tolerated in infants with newly diagnosed KMT2A-rearranged acute lymphoblastic leukemia: Children's Oncology Group trial AALL15P1. Haematologica. 2024 Jun;13. https://doi.org/10.3324/haematol.2024.285158. Epub ahead of print. PMID: 38867582.
12. Moskop A, Pommert L, Thakrar P, et al. Chimeric antigen receptor T-cell therapy for marrow and extramedullary relapse of infant acute lymphoblastic leukemia. Pediatric Blood Cancer. 2021;68(1):e28739. https://doi.org/10.1002/pbc.28739. Epub 2020 Oct 3. PMID: 33009894.
13. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology–drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157–67. https://doi.org/10.1056/NEJMra035092. PMID: 13679531.
14. Raj A, Talukdar S, Das S, et al. Congenital leukemia. Indian J Hematol Blood Transfus. 2014;30(Suppl 1):159–61. https://doi.org/10.1007/s12288-013-0307-7. Epub 2013 Dec 6. PMID: 25332567; PMCID: PMC4192207.
15. Gandemer V, Bonneau J, Oudin C, et al. Late effects in survivors of infantile acute leukemia: a study of the L.E.A program. Blood Cancer J. 2017;7:e518. https://doi.org/10.1038/bcj.2016.129
16. Tomizawa D. Evolution and optimization of therapies for acute lymphoblastic leukemia in infants. Int J Hematol. 2023;117(2):162–72. https://doi.org/10.1007/s12185-022-03502-w. Epub 2022 Nov 28. PMID: 36441356.
17. Ishii E, Oda M, Kinugawa N et al. Features and outcome of neonatal leukemia in Japan: experience of the Japan infant leukemia study group. Pediatric Blood Cancer. 2006;47(3):268–72. https://doi.org/10.1002/pbc.20599. PMID: 16333820.
18. Contreras Yametti GP, Ostrow TH, Jasinski S, Raetz EA, Carroll WL, Evensen NA. Minimal Residual Disease in Acute Lymphoblastic Leukemia: Current Practice and Future Directions. Cancers (Basel). 2021;13(8):1847. Published 2021 Apr 13. https://doi.org/10.3390/cancers13081847
19. Van der Linden MH, Valsecchi MG, De Lorenzo P, et al. Outcome of congenital acute lymphoblastic leukemia treated on the Interfant-99 protocol. Blood. 2009;114(18):3764–8. https://doi.org/10.1182/blood-2009-02-204214

Publisher's note