

Case Report

$\gamma\delta$ T-cell acute lymphoid leukemia after BMT of AML: Case report



Elissandra Machado Arlindo de Mattos ^{*}, Mariela Granero Farias ,
Mariana Monteiro Burin, Ana Paula Alegretti

Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

ARTICLE INFO

Article history:

Received 29 December 2021

Accepted 17 November 2022

Available online 2 December 2022

Introduction

$\gamma\delta$ T-cell neoplasms are rare, including a variety of clinical pathological entities, and characterized by the expression of T-cell antigen receptors (TCRs), distributed in four types: T-cell acute lymphoblastic leukemia/lymphoma (T-ALL), hepatosplenic T-cell lymphoma (HSTCL), skin and mucosal T-cell lymphoma, and T-cells large granular lymphocytic leukemia (T-LGLL).¹

The 2016 World Health Organization (WHO) classification of lymphoid neoplasms recognizes only two distinct entities of $\gamma\delta$ T-cell: hepatosplenic $\gamma\delta$ T-cell lymphoma and the $\gamma\delta$ T-cell lymphoma. These neoplasms belong to a group of biologically distinct diseases, and they are usually clinically aggressive, with unfavorable prognosis. The $\gamma\delta$ T-ALL represents 9 to 12% of T-ALL, including children and adults. Case reports of patients with T-ALL expressing the $\gamma\delta$ TCR suggest that these patients also have a worse prognosis.² $\gamma\delta$ T-ALL is a rare variant of T-ALL and compared to $\alpha\beta$ T-ALL patients, usually present with lower hemoglobin concentrations in children, more

frequent splenomegaly and higher WBC in adults, and higher percentages of the CD45RA[−]/CD45RO⁺ phenotype in all ages.³

We aimed to describe a case of $\gamma\delta$ T-ALL after hematopoietic stem cell transplantation (HSCT) for AML due to the rarity of this diagnosis in adult patients, the difficulty of classification and the peculiarity of the post-transplant onset.

Case presentation

Female patient, 29-year-old, diagnosed with Acute Myeloid Leukemia (AML), in October 2017. Bone marrow aspirate showed infiltration by immature cells (Figures 1 and 3). Immunophenotyping demonstrated 74.0% of immature cells (CD34⁺, CD117⁺, HLADR⁺, CD33⁺ heterogeneous, CD13⁺ strong, CD7⁺ partial).

Despite CD117 expression, which is associated with FLT3-ITD mutation and consequently worse prognosis,⁴ FLT3-ITD analysis of the patient was negative, and the karyotype showed no growth. 7+3 protocol was performed with induction failure, replaced by two IDA-FLAG cycles. She was subjected, in June 2018, to HSCT, non-myeloablative by cardiotoxicity (FluCy + TBI). Evaluations of D+30, D+180 and D+360 post HSCT showed morphological remission, negative bone marrow minimal residual disease (MRD) with a limit of detection of 1×10^{-5}

^{*} Corresponding author at: Hospital de Clínicas de Porto Alegre, Ramiro Barcelos n° 2350, Porto Alegre, RS, CEP 90035903, Brazil.

E-mail address: elissandrakm@gmail.com (E.M.A. de Mattos).

<https://doi.org/10.1016/j.htct.2022.11.004>

2531-1379/© 2022 Published by Elsevier España, S.L.U. on behalf of Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

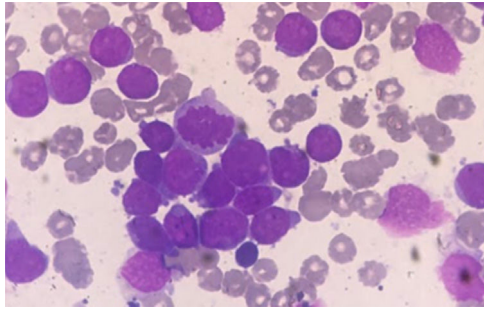


Figure 1 – Bone marrow aspirate smear showing infiltration by morphologically undifferentiated blasts. May-Grumwald-Giemsa, 1000x.

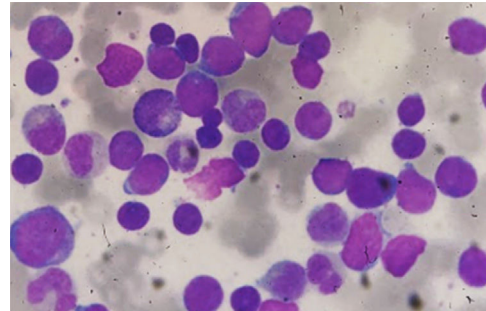


Figure 2 – Bone marrow aspirate smear showing infiltration by pleomorphic blasts. May-Grumwald-Giemsa, 1000x.

events, and complete chimerism. In October 2019, the patient attended the review consultation complaining of tiredness. In physical examination, she presented pallor, without skin lesions, and without palpable visceromegaly or adenomegaly. Blood count showed leukocytes: $308.76 \times 10^9/L$, Hb: 9.8g/dL and platelets: $94 \times 10^9/L$ with presence of immature cells. Myelogram identified hypercellularity, infiltration by pleomorphic blasts with loose chromatin, evident nucleolus, agranular and high nucleus-cytoplasm relationship compatible with Acute Leukemia (Figures 2 and 4). There were no cytogenetic changes in karyotype. Immunophenotyping showed 84.0% of lymphoid T-cells (cCD3+, sCD3+, CD99+weak, CD7+strong, CD5+weak, CD2+weak heterogeneous, CD38+heterogeneous, CD8+weak partial in 20% of population, $\gamma\delta$ TCR and CD45+) with heterogeneous CD117 antigen expression without other stem cell or myeloid markers (CD34, HLA-DR, CD13, CD33). These cells were negative for cMPO, CD19, CD10, nTdT, CD56, CD123, CD1a, CD44, CD45RA, CD4 and $\alpha\beta$ TCR.

Due to positivity to sCD3 and the presentation of $\gamma\delta$ T-cell receptor (TCR), it could be $\gamma\delta$ T lymphoma. However, the absence of hepatosplenomegaly, marked leukocytosis, and the presence of T antigens with CD117 expression corroborates a diagnosis of T-strain Acute Lymphoid Leukemia (T-ALL). The possibility of mixed phenotype was excluded due to the absence of MPO. Expression of sCD3, partial and weak expression of CD8 and lack of other myeloid (CD11b, CD13, CD33) or stem cell (CD34, HLADR) markers excluded the classification of Early T Leukemia. Thus, in this case, according to clinical findings and other laboratory tests, this immunophenotype was suggestive of T-ALL with expression of CD117 and $\gamma\delta$ TCR. The patient was treated with an increased Hyper-CVAD protocol, presenting morphological remission and immunophenotyping with absence of anomalous cells after the first cycle. Due to severe infectious complications (candidemia with systemic involvement requiring surgery for heart valvuloplasty) and worsening of the general state, the patient chose not to follow treatment, presenting a new recurrence in May 2020. The patient underwent palliative treatment, and died in 3 months.

Discussion

We present a case of $\gamma\delta$ T-ALL in an adult female patient, after HSCT with initial diagnosis of AML. The differential diagnosis

of this case includes cutaneous and mucous T-cell lymphoma in the leukemic phase, $\gamma\delta$ -HSTCL, Early T acute lymphoblastic leukemia (ETP-ALL), and $\gamma\delta$ T-cell large granular lymphocytic leukemia ($\gamma\delta$ -TLGLL).

Peripheral T-cell lymphoma can affect skin and mucosal regions, such as the nasopharynx, lung and gastrointestinal tract, different from this case, which had no evidence of mucocutaneous infiltration.⁵

$\gamma\delta$ -HSTCL is a rare type of T-cell lymphoma with extra nodal and systemic involvement. Some studies support that clinical data such as splenomegaly is the most consistent clinical finding, hepatomegaly occurs in about 50% of patients and the majority of patients present with bone marrow involvement.⁶ In this case, there was medullary infiltration, but without evidence of splenomegaly, besides the fact that the immunophenotype evaluation presented markers of immaturity, discarding this diagnostic possibility.

$\gamma\delta$ -TLGLL would be a possible diagnosis due to clonal proliferation of T cells with weak and partial CD8 expression; however, in general this disease, presents with an indolent clinical course, rarely associated with cytopenia, besides the peculiar morphology of cells with large volume and cytoplasmic granulation.⁷

Bone marrow is affected in almost all cases of T-ALL, and the mediastinal or thymic involvement is common. Patients tend to have a high count of leukocytes, lymphadenopathy, and hepatosplenomegaly. Morphologically, lymphoblasts have an intermediate size and with delicate chromatin, small nucleolus and scarce cytoplasm. Immunophenotypically, they are generally positive for CD1a, CD2, CD3, CD5, CD7, CD10 surface and/or cytoplasmic, CD34, CD45, and TdT, and are negative for B-cell and myeloid antigens. In these cases, the expression levels of $\alpha\beta$ TCR or $\gamma\delta$ TCR in association with different stages of differentiation are rarely reported.⁸

ETP-ALL/LBL expresses markers of stem cells or myeloid lineage and is a high-risk T-ALL, with worse outcomes, especially in adults.⁹ Blasts usually express CD7, often weak CD5 (<75% positive cells), in the absence of CD1a and CD8, and positivity for ≥ 1 markers of stem cell or myeloid lineage (i.e., CD34, CD117, HLA-DR, CD13, CD33, CD11b, CD65).² Therefore, this diagnosis was also excluded due to the expression of CD8, as well as the absence of other myeloid markers, despite the expression of CD117.

The $\gamma\delta$ T-ALL is a rare variant of T-line lymphoblastic leukemia/lymphoma, and when compared with $\alpha\beta$ T-ALL, it

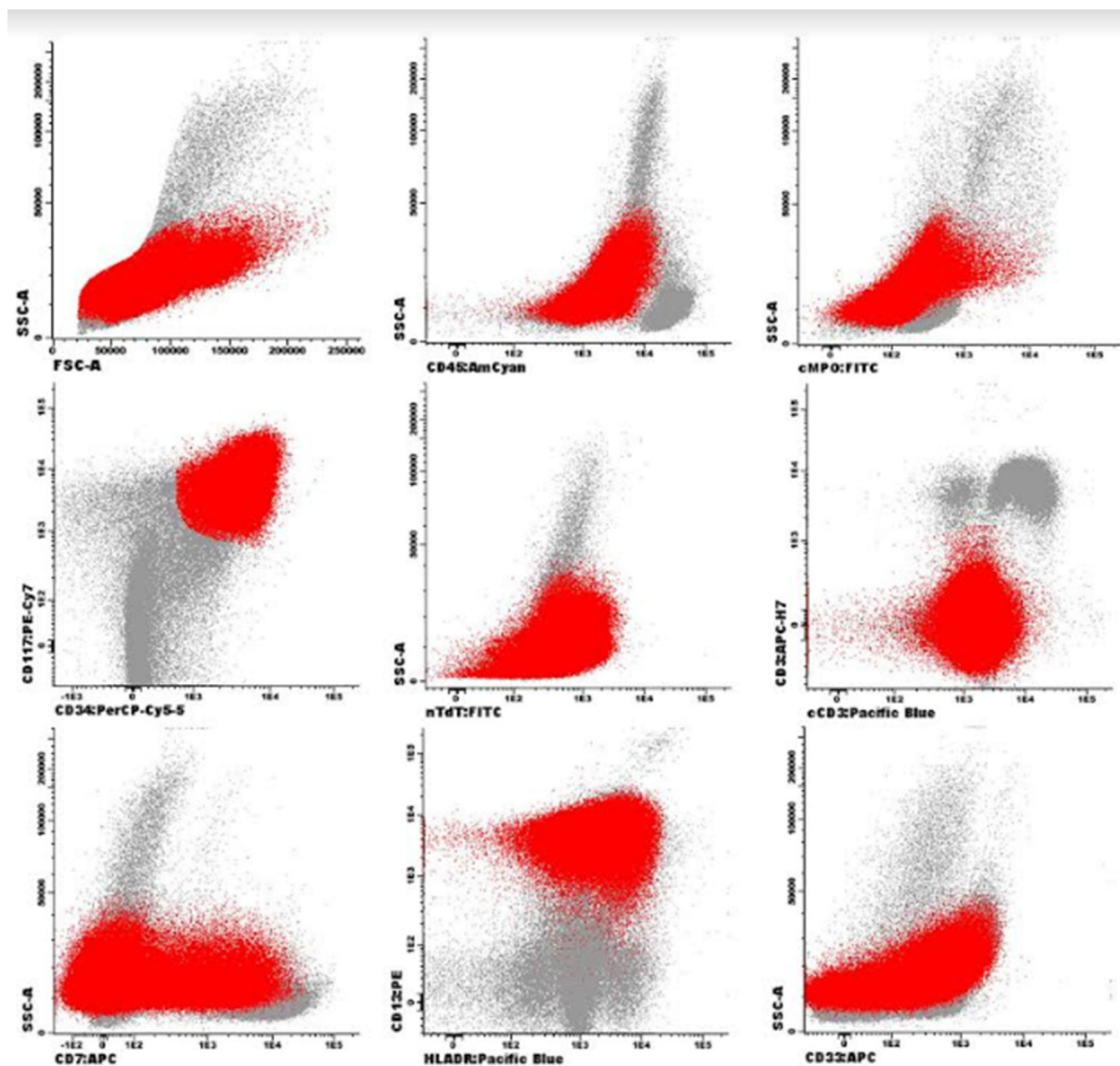


Figure 3 – Representative flow cytometric histograms of bone marrow aspirate expression profile of AML cells in red.

tends to present a more severe anemic picture in children, whereas in adults there is a high leukocyte count and splenomegaly.³

The diagnosis of $\gamma\delta$ T-ALL is based on immunophenotypic features, so we started defining the lineage of the abnormal cells, positive for sCD3, CD7, cCD3 and negative for cMPO and cCD79a. Thus, these were definitely T cells. Then, we clarified the maturation stage based on expression of sCD3 and CD1a (early, thymic or mature T-ALL). T-ALL cells in this case were classified as mature medullary T-ALL (CD1a⁻, sCD3⁺) with $\gamma\delta$ TCR expression.¹⁰ The present case showed clinical and immunophenotyping findings that led to the diagnosis of a “de novo” ALL (dn-ALL). We know that other diagnostic possibilities should be explored, such as therapy-related acute

lymphoblastic leukemia (t-ALL) and lineage switch relapse. Data suggest that t-ALL are associated with deletions of chromosomes 5, 7, 11, 13, 17, and 20, as well as trisomy 8 and higher rates of poor-risk cytogenetic features such as MLL1 rearrangement.^{11,12} The same higher rates of poor-risk cytogenetic features such as MLL1 rearrangement can be seen in lineage switching from B-ALL.¹³ Unfortunately MLLr analysis was not available for the patient at the time. Lineage switching would be possible but there were no cytogenetic signatures to link in the original diagnosis.

The findings in this case suggest that the appropriate diagnosis was $\gamma\delta$ T-ALL, this entity may represent a subcategory of acute lymphoblastic leukemia with slightly distinct clinical and laboratory characteristics with high risk group for

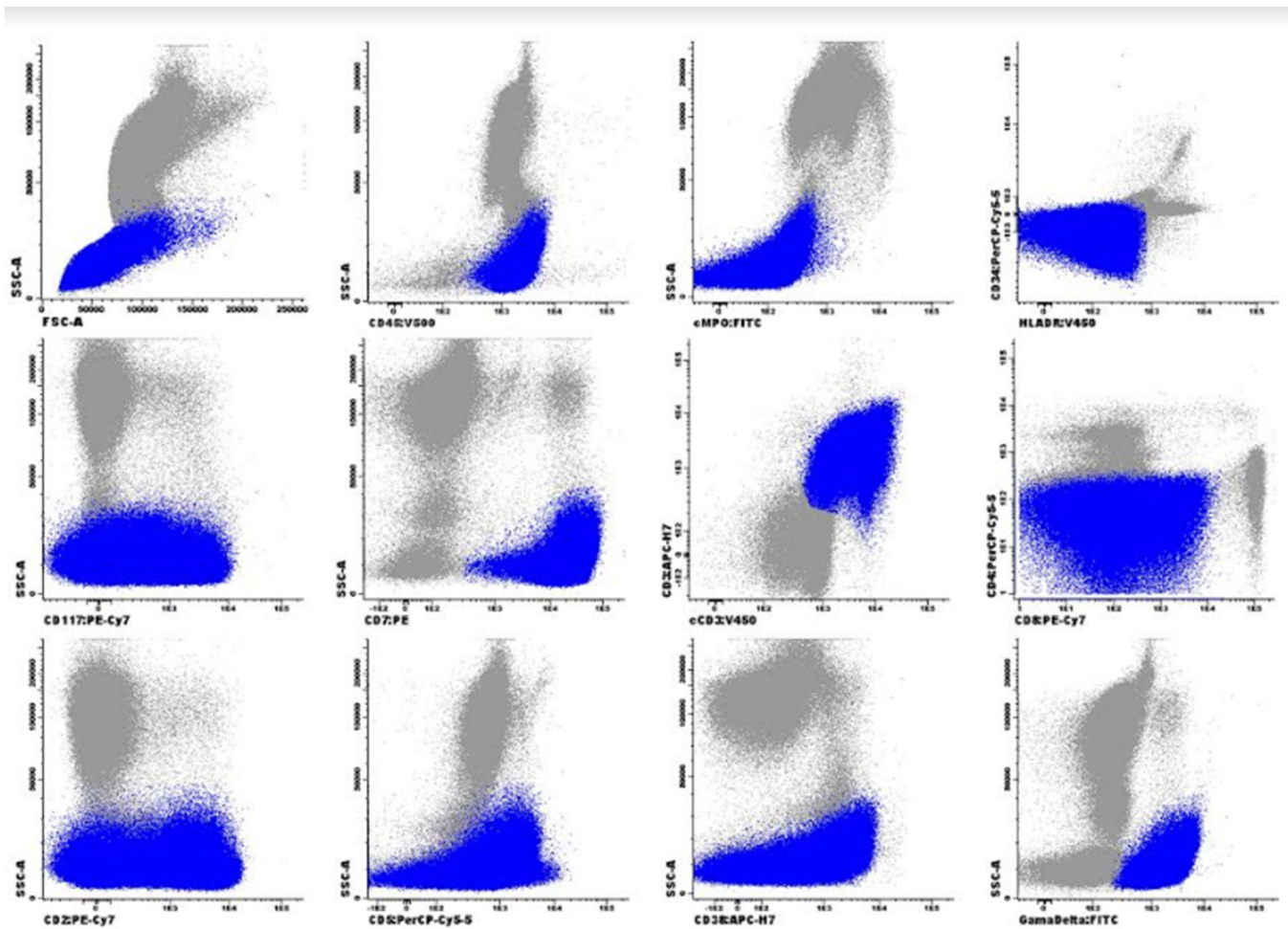


Figure 4 – The expression profile of $\gamma\delta$ T-ALL in blue.

induction failure and decreased survival.^{14,15} Molecular and cytogenetic studies can help in the definition of the diagnosis, but further studies investigating the role of genetics in $\gamma\delta$ T-ALL are needed.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Tripodo C, Iannitto E, Florena AM, Pucillo CE, Piccaluga PP, Franco V, et al. Gamma-delta T-cell lymphomas. *Nat Rev Clin Oncol*. 2009;6(12):707–17.
2. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375–90.
3. Matos DM, Rizzatti EG, Fernandes M, Buccheri V, Falcão RP. Gammadelta and alphabeta T-cell acute lymphoblastic leukemia: comparison of their clinical and immunophenotypic features. *Haematologica*. 2005;90(2):264–6.
4. Tao S, Wang C, Chen Y, Deng Y, Song L, Shi Y, et al. Prognosis and outcome of patients with acute myeloid leukemia based on *FLT3*-ITD mutation with or without additional abnormal cytogenetics. *Oncol Lett*. 2019 Dec;18(6):6766–74.
5. Vega F, Medeiros LJ, Gaulard P. Hepatosplenic and other $\gamma\delta$ T-cell lymphomas. *Am J Clin Pathol*. 2007;127(6):869–80.
6. Yabe M, Medeiros LJ, Tang G, Wang SA, Ahmed S, Nieto Y, et al. Prognostic factors of hepatosplenic T-cell lymphoma clinicopathologic study of 28 cases. *Am J Surg Pathol*. 2016;40(5):676–88.
7. Ahmad E, Kingma DW, Jaffe ES, Schrager JA, Janik J, Wilson W, et al. Flow cytometric immunophenotypic profiles of mature gamma delta T-cell malignancies involving peripheral blood and bone marrow. *Cytometry B Clin Cytom*. 2005;67(1):6–12.
8. Ferreri AJM, Govi S, Pileri SA. Hepatosplenic gamma-delta T-cell lymphoma. *Crit Rev Oncol Hematol*. 2012;83(2):283–92.
9. Jain N, Lamb AV, O'Brien S, Konopleva M, Jabbour E, Zuo Z, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood*. 2016;127(15):1863–9.
10. Bene MC, Castoldi G, Knapp W, Ludwig WD, Matutes E, Orfao A, van't Veer MB. Proposals for the immunological classification

- of acute leukemias. European Group for the Immunological Characterization of Leukemias (EGIL). *Leukemia*. 1995;9(10):1783–6.
11. Saygin C, Kishtagari A, Cassaday RD, Reizine N, Yurkiewicz I, Liedtke M, et al. Therapy-related acute lymphoblastic leukemia is a distinct entity with adverse genetic features and clinical outcomes. *Blood Adv*. 2019;3(24):4228–37.
 12. Meyer C, Burmeister T, Gröger D, Tsau G, Fechina L, Rebbeville A, et al. The MLL recombinome of acute leukemias in 2017. *Leukemia*. 2018(32):273–84.
 13. He RR, Nayer Z, Hogan M, Cuevo RS, Woodward K, Heyer D, 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 Reports in Hematology. 2019.
 14. Pui C, Pei D, Cheng C, Tomchuck SL, Evans SN, et al. Treatment response and outcome of children with T-cell acute lymphoblastic leukemia expressing the gamma-delta T-cell receptor. *OncoImmunology*. 2019;8(8).
 15. Dallas M, Thomas P, Choi J, Evans WE, Inaba H, Jeha S, et al. High incidence of induction failure and poor outcome in patients with gamma delta T cell acute lymphoblastic leukemia. *Blood*. 2015;126(23):1421.