Crossing Our T's: An Unusual Presentation of Infantile T-cell Leukemia

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Abstract

T-Cell Acute Lymphoblastic Leukemia (T-ALL) is commonly diagnosed in adolescents and is a rare diagnosis in children under 12 months of age. There is little guidance regarding the details of management and outcomes for infantile T-ALL, in particular the use of nelarabine in an infant. Additionally, the genomic landscape of this rare oncologic presentation has not been well documented. We present the unique management, genomics, outcomes, and clinical course of a patient with the diagnosis of infantile T-ALL.

INTRODUCTION

Leukemia is the most common childhood cancer, with T-cell acute lymphoblastic leukemia (T-ALL) comprising 10-15% of pediatric leukemia diagnoses[1,2]. T-ALL is an aggressive malignancy, with a median age of diagnosis of 9 years old[2]. T-ALL is rarely reported in children less than 12 months of age with only 2 cases in the literature, neither of which outlined treatment, and both of which were before routine use of nelarabine as upfront therapy[3,4]. Later presentation in childhood is hypothesized to occur due to genetic changes in T-ALL rarely arising in utero and instead develop over time[2]. From the limited information regarding infantile T-ALL, the genetic mutations of*NOTCH2, NOTCH3, PTEN,* and *KRAS* have been identified[3]. Activation of the ERK5 pathway was also noted; this pathway is regulated by growth factors among other stimuli[3]. The paucity of data regarding clinical presentation, management, genomics, and outcomes of infantile T-ALL results in difficult treatment decisions including potential use of agents such as nelarabine, with overall uncertainty of disease course and treatment toxicity.

CASE PRESENTATION

We present the case of a previously healthy 4-month-old Caucasian female with hepatomegaly at a routine 4-month-old well child visit. She was found to have lab work significant for a leukocytosis of 770 K/mm^3 comprised of 94% peripheral blasts, hemoglobin of 6.3GM/dL, and platelets 43k/mm^3. Physical exam was notable for marked hepatosplenomegaly, and ˜1cm subcutaneous nodule of the right thigh. Initial management consisted of hyperhydration and rasburicase for an elevated uric acid of 12.9mg/dL.

Peripheral flow was obtained and demonstrated dim CD45 expression, CD34+, dim CD38+, CD7+, CD3+, and TDT+, confirming a diagnosis of T-ALL. Lumbar puncture indicated a CNS1 status. Foundation One testing demonstrated non-MLL-rearranged, a LIM-domain-only 2 (*LM02*) rearrangement, and variants of unknown significance, most uniquely Colony Stimulation Factor 3 Receptor (*CSF3R*) R698H mutation.

She received induction therapy per Children's Oncology Group (COG) protocol AALL0631[5]. Induction included Prednisone for the first week followed by Dexamethasone, Vincristine, Daunorubicin, Pegasparaginase, Cytarabine and triple intrathecal chemotherapy. During Induction she had complications includ-

ing bacteremia (*Staphylococcus epidermidis, Staphylococcus Hominis, Streptococcus Viridans, and Klebsiella Pneumoniae*) and mucositis for which she required parenteral nutritional support. End of Induction bone marrow aspirate demonstrated a minimal residual disease (MRD) of 4.1%. She continued AALL0631 and tolerated Induction Intensification without infections, minimal mucositis or nutritional support. Induction Intensification included high dose methotrexate, etoposide, cyclophosphamide, triple intrathecal chemotherapy, with filgrastim until absolute neutrophil count (ANC) > 1500/uL for two days. MRD at end of Induction Intensification was 3.1%.

Considering her continued disease burden, we changed protocols and she received an individualized treatment plan based off AALL0434 with a course of nelarabine followed by Capizzi methotrexate (Figure 1). This included five days of nelarabine, vincristine, Capizzi methotrexate, PEG-asparaginase, and concluded in triple intrathecal methotrexate. Due to continued neutropenia, we were unable to escalate methotrexate beyond the starting dose. Her MRD at the end of this cycle was 0.02% and she was successfully transitioned to stem cell transplant (SCT). Summary of our patient's treatment course can be seen in Figure 1.

She received a 10/10 matched sibling donor SCT and tolerated therapy well with anticipated supportive care and engrafted on day +20. On day +22 she met the European Society for Blood and Marrow Transplantation criteria for veno-occlusive disease and was started on treatment with Defibrotide[6]. Her clinical course declined rapidly, and she developed transplant associated thrombotic microangiopathy on day +23. She required circulatory and ventilator support for multiple days with blood product, dialysis, one dose of tocilizumab for elevated IL-6, and eculizumab. On day +55 she had improvement in her organ function and subsequently was successfully extubated and weaned off vasopressor support.

DISCUSSION

We report a unique case of infantile T-ALL, treated initially per COG protocol AALL0631, and complete remission was not achieved, who subsequently achieved remission following an individualized therapy based on AALL0434.

T-ALL is an aggressive disease with a slower pattern of disease response compared to B-cell ALL[7]. T-ALL prognosis is heavily based on MRD response after a second cycle of chemotherapy. It has been found in UK ALL trials that increased doses of asparaginase improve rates of successful treatment[1]. Initially the pediatric oncology group (POG) trial 9404 had found that the addition of high dose methotrexate (HD-MTX) to T-ALL treatment protocols increased survival[8]. However, results from COG trial AALL0434 found that HD-MTX had lower 5 year disease free survival (DFS) and overall survival (OS) when compared to Capizzi methotrexate (85.3% and 89.4% respectively versus 91.5% and 93.7%[9,10]). The inclusion of nelarabine resulted in significant improvement, with a 4 year DFS of 92.2% +/- 2.8% for Capizzi methotrexate with nelarabine compared to 78% +/- 3.7% for HD-MTX without nelarabine[9,10]. Analysis of 4year DFS for T-ALL patients who received Capizzi methotrexate with nelarabine found 92.2% +/- 2.8% compared to Capizzi methotrexate without nelarabine of 89.8% +/- 3%[10]. Nelarabine is cytotoxic to T-lymphoblasts through accumulation of ara-GTP which is found in high levels in T-cells, and has been found to have a 55% response rate with relapsed/refractory T-ALL[1,11]. This led us to choose Capizzi methotrexate and nelarabine for our patient's individualized therapy, after which she was found to be MRD negative, allowing for progression to SCT.

Nelarabine can result in neurological toxicity, which typically occurs within the first 12 days of infusion; toxicity is cumulative with subsequent dosing[12]. In one study, neurological events were noted in 72% of patients with 50% occurring in children, with a median age of 10-years-old, and 85% in adults, with a median age of 48-years-old[12]. Most neurological symptoms were reversible and included malaise, somnolence, confusion, ataxia, muscle weakness, and peripheral neuropathy[8,12]. Our patient had no identifiable neurological toxicity associated with her nelarabine infusion; however, identifying neurologic toxicity in an infant is difficult, and is a clear limitation of our assessment of the patient's tolerance of this regimen.

A diverse spectrum of genetic and epigenetic mutations of immature thymocytes comprise T-ALL, with several well documented, targetable pathways including Notch, JAK/STAT, P13K/Akt/mTOR, and MAPK[1].

However, how best to decipher these genetic changes to improve our understanding behind the pathogenesis of T-ALL is understudied. In addition, how to utilize this information for further treatment options remains unclear.

Foundation One identified a LMO2 overexpression, which is found in ˜9% of patients with T-ALL[1]. LMO2 overexpression results in an effect similar to that of a T-cell receptor translocation in T-ALL, and is a common driver of T-cell malignancies, but has not previously been reported in infantile T-ALL[2]. Our patient also had a unique *CSF3R*mutation which is associated with promotion of neutrophil differentiation through granulocyte colony-stimulation factor binding[13,14]. *CSF3R* mutation has been identified in chronic neutrophilic leukemia and atypical chronic myeloid leukemia[15]. There is little information available regarding this genetic mutation in T-ALL. The use of GCSF during Induction Intensification was taken into context with our patients CSF3R mutation, as this is a variant of unknown significance it was determined that keeping GCSF in her treatment did not present significant risk of changing the effect of GCSF of her neutrophils.

This case highlights the specialized management, outcome, and unique genomic findings in a rare diagnosis of infantile T-ALL. Future research should focus on reporting rare infantile T-ALL leukemia cases to help guide management and successful remissions for these patients.

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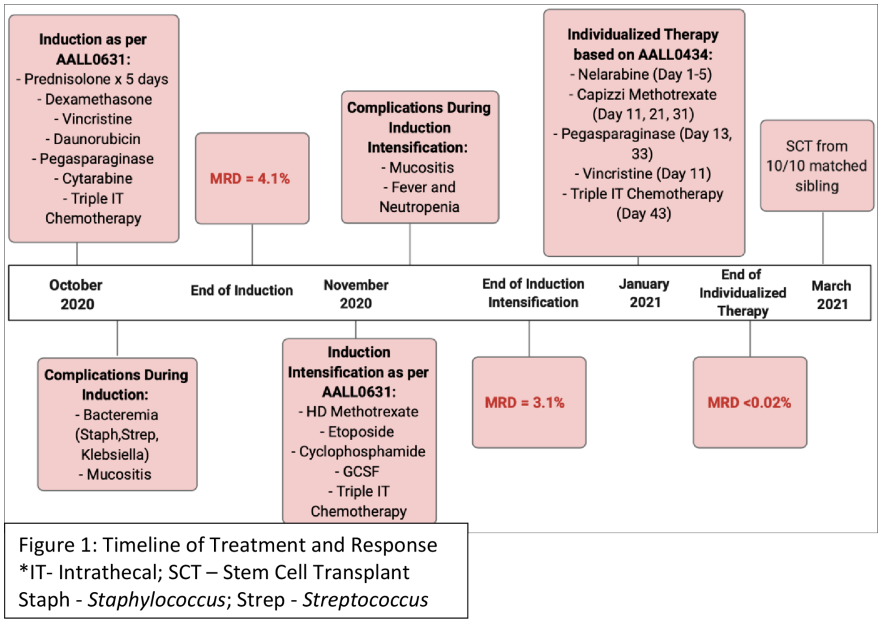

Figure 1: Timeline of Treatment and Response
*IT- Intrathecal; SCT – Stem Cell Transplant
Staph - *Staphylococcus*; Strep - *Streptococcus*