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Pre- and Post-Natal Treatment of Hemophagocytic Lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare autosomal recessive disorder of infancy and childhood that is invariably fatal if not treated. We report on the first patient to receive post-natal HSCT for HLH after receiving *in utero* chemotherapy for disease stabilization

Keywords

Hematopoietic stem cell transplantation; Hemophagocytosis Lymphohistiocytosis; *in utero* chemotherapy

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare autosomal recessive disorder of infancy and childhood that is invariably fatal if not treated. Common findings include fever, hepatosplenomegaly, cytopenias and immune dysregulation (1–4).

Early recognition and treatment of HLH is necessary to prevent disease progression. Remission can be achieved with the use of chemotherapy (Etoposide) and immune modulating medications [Cyclosporin A (CSA), steroids and antithymocyte globulin (ATG)]. However, hematopoietic stem cell transplantation (HSCT) provides the only curative therapy for these patients (4–9). We report on a patient who received post-natal HSCT for HLH after receiving *in utero* chemotherapy for disease stabilization.

Case History

A pregnant female at 24 weeks gestation was referred after a routine prenatal ultrasound showed massive hepatosplenomegaly, ascites, and hydrocephalus in the fetus. The family history was notable for two male siblings having died shortly after birth from HLH. After consent from the family, the fetus was given one dose of Etoposide (150 mg/ m²) and dexamethasone (10 mg/ m²) *in utero* via umbilical vein injection at 27 weeks gestation. The dosages were those recommended from the HLH-94 protocol (10) and calculated based on the estimated *in utero* weight. Following the treatment, the hydrocephalus and ascites resolved and the hepatosplenomegaly improved. Within 2 weeks of the initial chemotherapy, the hydrocephalus and ascites recurred and the hepatosplenomegaly increased. At 30 weeks, the fetus received a second course of the same chemotherapy and was delivered via elective Caesarian section at 32 weeks of gestation. At birth, he had massive hepatosplenomegaly and ascites, but no hydrocephalus. Laboratory evaluation showed Hb 8.2 g/ dL, platelets 133K/ μ L, AST/ ALT: 188/171 U/ L) and absent natural killer cell function. The patient was given one dose of Etoposide at birth, but no additional doses were given since his disease remained stable. A bone marrow aspirate performed on day 3 of life showed evidence of hemophagocytosis. He was maintained on CSA and dexamethasone. A cranial MRI showed patchy areas of white matter disease consistent with HLH. Genetic testing for the *Munc* mutation or perforin mutation was not available at the time. Therefore the diagnosis was based on clinical manifestations of the disease and the strong family history.

At 4 months of age a matched unrelated female bone marrow donor (HLA 5/6 allele matched with a Class 1 mismatch at the A locus) was found through the National Marrow Donor Program (NMDP). High resolution HLA typing was not being performed when the patient received his transplant. He received a pre-transplant conditioning regimen of Busulfan (16 mg/ kg), Cyclophosphamide (100 mg/ kg), Etoposide (60 mg/ kg) and ATG. Graft versus host disease (GVHD) prophylaxis consisted of ATG, CSA and Methotrexate. He received a total cell dose of 6.5×10^8 nucleated cells/ kg. His conditioning regimen was complicated with obstructive hydrocephalus requiring ventriculostomy placement and respiratory failure requiring prolonged ventilatory support. His post-transplant course was complicated with an *Aspergillus terreus* infection of his lungs which was successfully treated with 5-FC and liposomal amphotericin. Six weeks post-HSCT, a fluorescence in situ hybridization test (FISH) showed mixed chimerism with total peripheral blood showing 30% of the cells of donor (XX) origin and the remaining 70% of recipient (XY) origin. Isolation of the T cells showed that they were exclusively of donor origin (100%) and the myeloid cells were primarily of recipient origin (92.6%). At discharge, he had mild GVHD of the skin and GI systems.

One year post HSCT, he presented with pancytopenia. A bone marrow aspiration showed a hypocellular marrow with 20% cellularity. Chromosomal analysis showed a 57% of the cells of host origin and 43% of the cells of donor origin. . He was re-transplanted with bone marrow from the same donor 16 months after the first transplant. His conditioning regimen for the second transplant consisted of TBI 100 cGy (days -6, -5, -4)), cyclophosphamide 100 mg/ kg, and ATG. GVHD prophylaxis consisted of CSA, MTX, and ATG. He developed full donor engraftment and normal NK cell function.

Ten years post transplant, he presented with pancytopenia (platelets 35K, hemoglobin 7 gm/ dL and ANC <1000). A bone marrow aspirate and biopsy revealed myelodysplastic syndrome without blasts. Chromosomal analysis revealed a monosomy 7. Further studies revealed that this chromosomal abnormality was present in the female cells, i.e. donor cells (Figure 1). Cryopreserved specimens from the bone marrow of the donor prior to the first

and second transplants were reanalyzed and did not show the presence of the chromosomal abnormality.

The patient received a third unrelated donor transplant 11 years following his second transplant from a different donor (10/10 HLA matched male donor). The conditioning regimen consisted of Alemtuzumab (52 mg/ m²), busulfan (16 mg/ kg), Fludarabine (140 mg/ m²) and Cyclophosphamide (105 mg/ kg). GVHD prophylaxis consisted of tacrolimus and steroids. He had an uncomplicated course.

He is now 19 months status-post the third HSCT, and has minimal skin GVHD. His long-term follow up performed at 12.7 years of age showed that his height was 122 cm (<5%) and his weight was 22 kg (<5%). He has bilateral cataracts. He has no evidence of seizures by EEG. He has normal cardiac anatomy and a shortening fraction of 36%. He has mild hyperinflated lungs, but no evidence of either restrictive lung disease (Total lung capacity = 92%) or obstructive lung disease (FEV1/ FVC ratio = 88%). His oxygenation saturation is 96% on room air. His kidney function is normal with a creatinine clearance of 110 ml/ min/ 1.73 m². He has osteopenia and has had several fractures. Table 1 shows his neurodevelopmental test scores. He did not receive neurocognitive testing at our institution 6-years and 8-years post HSCT since he received similar tests through regional center. He is currently taking special education classes. Although he is 12 years of age, developmentally, he functions at a 5 year old level.

Discussion

HLH is an autosomal recessive disease that is due to immune dysregulation and defective T lymphocyte cytotoxic activity (1–4). It has been shown that the prompt institution of immunochemotherapy followed by HSCT allows for the best chances of long-term survival. (5–8).

Our case is extremely unusual in that patients are rarely diagnosed and treated *in utero*. We are unaware of any previous patient with HLH receiving therapy *in utero*. The family history of an aggressive form of HLH in two prior siblings alerted the obstetricians to this possibility and diagnostic procedures were consistent with it in this patient. While administration of chemotherapy *in utero* for this condition is unprecedented and certainly fraught with potential toxicities, it is likely that he survived to 32 weeks gestation only because of this intervention. The fact that this child was able to receive therapy as a fetus, allowed for the potential of receiving an HSCT.

In most cases, a fetus is exposed to *in utero* chemotherapy through transplacental passage of chemotherapy given to the mother. From previous studies, we know that exposure of a fetus to *in utero* chemotherapy during the first trimester (when organogenesis occurs) is associated with spontaneous abortions and fetal malformations. Beyond the first trimester, there does not appear to be an increased risk of malformations (11–16). We are unaware of any fetus directly receiving chemotherapy while *in utero* for any condition innate to the fetus. Although this approach may be considered in other aggressive diseases that require early intervention, the side effects of the disease and its early therapy can result in significant long-term complications.

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Figure 1.

Bone marrow aspirate performed at the time of MDS diagnosis. FISH (fluorescence in situ hybridization) analysis using dual color probe for chromosome region 7q11.23 (Spectrum Orange – red color) and chromosome region 7q31 (Spectrum Green – green color) showing 56.5% of the bone marrow cells having one copy of chromosome 7 (arrows). One metaphase and one interphase showing two copies of chromosome 7 representing normal bone marrow cells.

Neurocognitive test scores over time

Age at Examination (*corrected for 32 weeks gestation)	Developmental Age (by testing)	Relation to HSCT	Test Used	Raw Score	Scaled Score
2 months 4 days*	1.5 months	Pre-HSCT #1	Bayley	15	74
13 months 13 days*	9 months	1 year post HSCT #1	Bayley	73	77
2 years 3 months*	11 months	2 years post-HSCT#1 1 year post-HSCT#2	Bayley	86	<50
4 year 7 months*	~3 year old	4 years post-HSCT#1 3 years post-HSCT#2	WPPSI	12	43
11 year 5 months	~4 year old	~11 years post-HSCT#1 -pre-HSCT#3	WISC- III	3	<50
12 years 7 months	~5 year old	~12 years post-HSCT#1 ~1 year post-HSCT #3	WISC -IV	3	<50

Bayley: Bayley Scales of Infant Development-2nd ; WPPSI: Wechsler Preschool and Primary Scale of Intelligence-R; WISC III and IV: Wechsler Intelligence Scales for Children, 3rd and 4th edition respectively.