Incidence and Outcomes of Central Nervous System Hemophagocytic Lymphohistiocytosis Relapse after Reduced-Intensity Conditioning Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Hemophagocytic lymphohistiocytosis (HLH) is an immune regulatory disorder that commonly presents with central nervous system (CNS) involvement. The only cure for genetic HLH is hematopoietic stem cell transplantation (HSCT), typically treated with reduced-intensity conditioning (RIC) regimens. We sought to estimate the incidence of CNS relapse after RIC HSCT, determine risk factors, and evaluate outcomes. We performed a retrospective chart review of 94 consecutive children and young adults with primary HLH who received RIC HSCT. CNS relapse within 1 year after transplantation was diagnosed by review of clinical symptoms, cerebral spinal fluid (CSF), and radiologic findings. Four (4.25%) patients developed symptoms of possible CNS HLH after HSCT and 3 patients were diagnosed. Eight patients underwent screening lumbar puncture because of history of active CNS disease at the onset of the conditioning regimen and 4 had evidence of continued disease. The overall incidence of CNS relapse and continued CNS disease after RIC HSCT was 8%. All patients with CNS disease after HSCT responded to CNS-directed therapy. Whole blood donor chimerism at the time of CNS relapse was low at 1% to 34%, but it remained high at 88% to 100% for patients with continued CNS disease. Overall survival for patients with CNS relapse was 50%, compared with 75% for patients without CNS disease ($P = .079$). Our data suggest that a low level of donor chimerism or active CNS disease at the time of transplantation increase the risk of CNS HLH after HSCT. Surveillance CSF evaluation after allogeneic RIC HSCT should be considered in patients with risk factors and CNS-directed treatment should be initiated if appropriate.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an immune regulatory disorder that is characterized by fever, organomegaly, and pancytopenia [1]. Initial signs and symptoms can mimic many other common conditions, including sepsis, viral infections, autoimmune disorders, hepatitis, and encephalitis [2]. Primary HLH generally occurs when there is a clear familial inheritance or genetic etiology that leads to a fixed defect in cytotoxic function of natural killer cells and T lymphocytes [1]. There are a variety of genetic defects that lead to impaired cytotoxic function, leading to predisposition to HLH [1]. Central nervous system (CNS) involvement is common at diagnosis and has been reported in 10% to 73% of all HLH patients and examination of the cerebral spinal fluid (CSF) is a key part of the initial work-up of HLH [2]. CNS involvement can be apparent at presentation or occur any time during the course of the disease. Symptoms can be variable between patients. Multiple studies have shown that CNS involvement is associated with poorer prognosis and increased rates of mortality [2-5].

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative therapeutic modality for patients with primary HLH [6]. Historically, outcomes for patients with primary HLH were quite poor, with long-term overall survival ranging from 45% to 65%, when using myeloablative conditioning regimens [7-11].

Over the past decade, multiple studies have looked at outcomes after reduced-intensity conditioning (RIC) regimens; primarily RIC regimens consisting of alemtuzumab, fludarabine, and melphalan. RIC has led to improved overall survival, ranging from 75% to 92%, with decreased incidences of life-threatening toxicities such as veno-occlusive disease of the liver and pulmonary hemorrhage, as well as complications such as acute graft-versus-host disease (GVHD) [12-14]. An increased incidence of mixed whole blood donor and recipient chimerism occurs in patients who have been treated with RIC HSCT compared with those treated with myeloablative conditioning (65% versus 18%) [14]. Despite the increased incidence of mixed donor chimerism, overall survival remained high and chimerism improved in most patients by reduction of immunosuppressive therapy or with donor lymphocyte infusions.

There are no data regarding the risk of CNS relapse after RIC HSCT. It is possible that mixed chimerism may increase risk of CNS relapse after RIC HSCT, and the outcomes of such patients are undocumented. Whole blood mixed donor chimerism is also thought to be a risk factor for systemic HLH relapse; however, a threshold of donor cells is unknown. We sought to estimate the incidence of CNS relapse in children

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and young adults with primary HLH after RIC HSCT, determine predisposing risk factors, and evaluate outcomes.

PATIENTS AND METHODS

Patients and Data Collection

We performed a retrospective chart review of 94 consecutive patients diagnosed with HLH who underwent allogeneic HSCT with a standard RIC regimen containing alemtuzumab, fludarabine, and melphalan between January 2007 and July 2014. The transplantation outcomes of 91 patients have been reported previously [15]. Patient demographics and transplantation information are detailed in Table 1. The median age of patients was 3 years (range, 0 to 25 years). CNS involvement at diagnosis was assessed by evaluation of CSF studies, neuroradiologic findings, and neurologic symptoms. Genetic mutations associated with HLH were found in 74 of the 94 (79%) patients reviewed. Data describing CNS clinical symptoms, CSF findings, radiologic findings within the first year after HSCT, response to CNS-directed therapy, and outcomes were extracted from medical records. Diagnosis of CNS HLH was made if CSF analysis after transplantation showed an elevated WBC count (>5 cells/high power field) or elevated protein (above the normal range), or if there were new or developing CNS radiologic findings without clinical suspicion of posterior reversible encephalopathy syndrome or infection.

Initial HLH treatment included steroids, dexamethasone (n = 81), and methylprednisolone (n = 15), with or without etoposide (n = 75). Thirty-four patients were also treated with cyclosporine, 12 with alemtuzumab, 3 with antithymocyte globulin, 5 with abatacept, 3 with tacrolimus, and 16 with rituximab. Patients with CNS involvement at diagnosis received intrathecal methotrexate (n = 16) and/or hydrocortisone (n = 28) according to treatment schemas based on the HLH-94 or HLH-2004 protocol. Five patients did not receive any therapy directed toward HLH as they did not meet criteria for active hemophagocytosis, but they underwent allogeneic HSCT because of genetic diagnosis of X-linked inhibitor of apoptosis protein deficiency or SLAM-associated protein deficiency.

The RIC regimen consisted of alemtuzumab, fludarabine (150 mg/m^2 for patients >10 kg and 5 mg/kg for patients <10 kg), and melphalan (140 mg/m^2 for patients >10 kg and 4.7 mg/kg for patients <10 kg). The dosing of alemtuzumab changed over time at our institution. Alemtuzumab was administered to 14 patients proximal to HSCT at 48 mg total dose divided over 4 days, from -13 to -10, -12 to -9, -11 to -8, or -9 to -6. Alemtuzumab was administered to 18 patients proximal to HSCT at 1 mg/kg divided over 5 days: -9 to -5 or -8 to -4. Alemtuzumab was administered to 37 patients intermediate to HSCT at 1 mg/kg divided over 5 days from days -14 to -10. Alemtuzumab was administered to 16 patients distal to HSCT at 48 mg or 33 mg total dose divided over 4 days on days -22 to -19. The remaining patients received unique schedules of alemtuzumab [16].

Table 1
Patient (n = 94) and Transplantation Demographic Information

Characteristic	Value
Male/female	68/26
Age, median (range), yr	3 (0-25)
HLH mutation	
PRF1	12
UNC13D	11
SH2D1A	13
STXBP2	15
BIRC4	12
RAB27A	1
UNCD13/PRF1	4
UNC13D/STXBP2	2
RAB27A/PRF1	1
LYST	1
No mutation identified	22
Donor type	
Related	24
Unrelated	70
HLA match	
8/8 or 10/10	72
7/8 or 9/10	21
6/8 or 8/10	1
Stem cell source	
Bone marrow	91
PBSC	2
Cord blood	1

PBSC indicates peripheral blood stem cell.

GVHD prophylaxis consisted of cyclosporine and methylprednisolone for 85 patients, tacrolimus and methylprednisolone for 5 patients, and mycophenolate and methylprednisolone for 4 patients. Ninety-one patients received bone marrow as the stem cell source, 2 received peripheral blood, and 1 received cord blood (Table 1). Seventy-two patients received cells from an 8/8 or 10/10 HLA–matched donor, 21 from a 7/8 or 9/10 HLA–mismatched donor, and 1 from an 8/10 HLA–mismatched donor (Table 1). Antimicrobial prophylaxis, intravenous immunoglobulin replacement, and nutritional support were given per institutional standard-of-care practices. *Mixed chimerism* was defined as having less than 95% donor chimerism detected on peripheral blood analyses on 2 or more consecutive measurements and were performed using XY fluorescence in situ hybridization in the case of opposite sex donor and short tandem repeat sequences in the case of same-sex donors. Chimerism studies were performed in the clinical genetics laboratory at Cincinnati Children's Hospital; methodologies are available upon request.

Statistical Analysis

We generated Kaplan-Meier curves to analyze the survival of patients with and without development of CNS HLH disease after HSCT using XLSTAT (Addinsoft, Paris, France). Groups were compared using the log-rank test.

RESULTS

Ninety-four patients with primary HLH underwent allogeneic RIC HSCT. Twenty-eight patients had findings of CNS disease and were treated with CNS-directed therapy before HSCT. Four patients developed symptoms concerning for CNS HLH after transplantation, a median of 63 days after stem cell infusion (range, 30 to 150 days) (Table 2). Symptoms included irritability (n = 1), seizures (n = 1), neurologic deficits (n = 1), and bulging fontanelle (n = 1). CSF leukocytosis and elevated protein were observed in 3 patients, with 2 of the patients also having active hemophagocytosis in the CSF, confirming the diagnosis of CNS HLH in these 3 patients. One patient had no CSF abnormalities or magnetic imaging resonance findings to suggest active CNS HLH.

Eight additional patients with active CNS HLH at time of transplantation underwent screening lumbar punctures after HSCT. Four patients had evidence of continued CNS disease after transplantation with CSF abnormalities (Table 2). One of these patients also developed symptoms concerning for CNS HLH flare, including headache, seizure, and altered mental status with worsening of CSF findings at the time of evaluation. No other etiology was found, including infection or posterior reversible encephalopathy syndrome. The other 3 patients were asymptomatic at the time of continued abnormal CSF findings.

All patients with CNS HLH after HSCT received CNS-directed therapy with intrathecal hydrocortisone and methotrexate (n = 7) and/or intravenous dexamethasone (n = 4). All patients responded to treatment with normalization of CSF at a median of 38 days (range, 14 to 108 days) after initiation of CNS-directed therapy.

All 3 patients with CNS relapse had low levels of whole blood donor chimerism at the time of relapse. Whole blood donor chimerism was 1%, 29%, and 34% at the time of relapse. One patient additionally developed systemic relapse of HLH concurrent with CNS HLH and underwent a second HSCT (Table 2, patient 21). One patient developed systemic relapse 4 months after CNS relapse and was eventually treated with multiple donor lymphocyte infusions as well as a stem cell boost (Table 2, patient 38). This patient later developed GHVD and died from infectious complications of immunosuppressive therapy. Of note, 20 patients (21.2%) possessed whole blood donor chimerism of less than 30% at 1 year or at the time of death and had not developed CNS or other HLH relapse. A total of 5 patients (5.1%) developed systemic HLH relapse in the first year after allogeneic HSCT. Two of these patients also had CNS relapse.