The Role of Hematopoietic Stem Cell Transplantation in Treatment of Hemophagocytic Lymphohistiocytosis

Sarah Nikiforow, MD, PhD

KEYWORDS

• Hemophagocytic lymphohistiocytosis • Stem cell transplantation • Alemtuzumab • Chimerism • Treatment

KEY POINTS

- In cases of familial or relapsed/refractory HLH, hematopoietic stem cell transplant (HSCT) is indicated for optimal survival.
- Seventy-one percent of patients with pediatric/familial HLH for whom transplant is indicated are able to undergo HSCT. Long-term survival of children who undergo transplant is 66%.
- Use of alemtuzumab before conditioning favorably impacts donor chimerism and is becoming standard peritransplant therapy.
- Adult-onset HLH is increasingly recognized, and patients often bear classical familial HLH-associated genetic variants.
- The role of HSCT in adults, particularly older adults, is unclear, but overall outcomes after HSCT are encouraging.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) was initially described as an inflammatory condition affecting young children with an abysmal prognosis. Early introduction of chemotherapeutic and immunomodulatory agents to suppress the unbridled yet ineffective phagocytic, natural killer (NK), and T-cell activity of HLH through the HLH-94 protocol had a dramatic impact on survival. To consolidate disease remission, children with familial, genetically based HLH and those with relapsed or primary refractory HLH require allogeneic hematopoietic stem cell transplantation (HSCT).

Stem Cell Transplantation Program, Cell Manipulation Core Facility, Dana-Farber Cancer Institute, Dana 168, 450 Brookline Avenue, Boston, MA 02215, USA
E-mail address: Sarah_Nikiforow@DFCI.HARVARD.EDU

Hematol Oncol Clin N Am 29 (2015) 943–959
http://dx.doi.org/10.1016/j.hoc.2015.06.011 **hemonc.theclinics.com**
0889-8588/15/$ – see front matter

Introduction of alemtuzumab into the peritransplant regimen is under investigation to improve chimerism and other clinical outcomes. Unfortunately, the role of stem cell transplantation in adults with HLH is not as clear-cut. HLH often presents in adults in concert with an underlying malignancy and may shift the decision to pursue allogeneic HSCT sooner in the cancer treatment algorithm. When adults present with HLH without an accompanying lymphoma or leukemia, decisions to pursue HSCT are individualized and, unfortunately, not informed by adequate published data. At our institution, this decision is made based on the constellation of underlying mutations/genetic variants, aspects of the HLH remission after therapy, and donor availability.

ACHIEVING REMISSION IN PEDIATRIC HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Familial HLH was initially described by Farquhar and Claireaux[1] in two infant siblings who both had a rapidly fatal clinical course. Over the succeeding decades, genetic underpinnings of the disease in familial cases were described, namely autosomal-recessive mutations at 9q21.3-locus 6 and in perforin, MUNC 13–4, Syntaxin 11, and Syntaxin Binding Protein 2/MUNC 18 to two genes. These mutations affect cytotoxic granule composition, transport, and release. They result in impaired apoptosis and a vicious cytokine-driven, cell-mediated inflammatory response.[2] Provoking infectious agents, particularly those of the herpes virus family, were identified. Lymphocyte-directed chemotherapy and immunotherapy were noted to have some efficacy in small studies, but children with familial HLH all experienced relapse.

The Histiocyte Society's prospective international therapeutic study, HLH-94, represented the first large effort to systematically define the disease and implement a standardized therapeutic strategy.[3] On this study, children younger than 15 years of age were treated with 8 weeks of induction therapy consisting of tapering dexamethasone doses, etoposide, and intrathecal methotrexate. Patients with no evidence of familial disease who showed disease resolution after the 8-week induction period were followed but did not continue to further therapy unless reactivation occurred. For patients with familial, clinically persistent, or relapsing disease, continuation therapy consisting of dexamethasone pulses, etoposide doses every 2 weeks, and cyclosporine was recommended. Allogeneic HSCT was pursued in those patients for whom a suitable donor was available.

Long-term results of this study, representing a cohort of 227 patients with greater than or equal to 5 years follow-up, demonstrated that 86% of patients were alive after the 8-week induction course; 59% of these had no signs of active disease.[4] Children who did not survive the induction period were more likely to have presented with hyperbilirubinemia, renal failure, and abnormal findings on brain imaging. Notable characteristics of patients in this study included a median age of 8 months; 76% were younger than 2 years of age. Neurologic symptoms were present in 33% before therapy, and 46% had a history of recent infection. Familial disease was documented in 24%. Poor prognoses were associated with neurologic symptoms and central nervous system (CNS) pleocytosis at presentation and age less than 6 months. In this and subsequent studies, thrombocytopenia, initial or persistent ferritin levels greater than 2000 ng/mL, degree of soluble interleukin-2 receptor (sIL-2R) elevation, and the rate of decline of ferritin had prognostic implications. A ferritin decrease of less than 50% imparts an odds ratio for death of 17 when compared with a ferritin decrease of greater than 95% during therapy.[5] Therapeutic guidelines and diagnostic criteria were further updated in the HLH-2004 treatment protocol, with primary changes being initiation of