Role of Hematopoietic Cell Transplantation in Pediatric and Adult Hemophagocytic Lymphohistiocytosis—Remaining Unknowns and Challenges

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KEYWORDS

• Stem cell transplant • Donor • Conditioning • Chimerism • HLH • Immunodeficiency

KEY POINTS

- The main indication for allogeneic hematopoietic stem cell transplantation (HSCT) in children is primary/familial hemophagocytic lymphohistiocytosis (HLH), but indications in adults are more diverse.
- Matched related donors remain the preferred stem cell source, if there are no shared predisposing genetics.
- Myeloablative and reduced-intensity conditioning regimens trade off early toxicity for poor initial engraftment and chimerism.
- Allogeneic HSCT for HLH is most successful when primary disease is under control.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only currently available curative therapy for primary/familial and high-risk/refractory cases of secondary hemophagocytic lymphohistiocytosis (HLH).[1–3] The first transplant for HLH was performed in 1986, and while the number of transplants has grown since then, toxicity remains great and survival suboptimal.[4] Introduction of recommendations for induction therapy along with guidance on transplant care in the HLH-94 protocol significantly improved long-term survival to 54%.[5,6] The international HLH-2004 study

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Abbreviations	
Alem	alemtuzumab
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ATG	antithymocyte globulin
Bu/Cy	busulfan/cyclophosphamide
Bu/Flu	busulfan/fludarabine
DLI	donor lymphocyte infusion
EBMT	European BMT
Flu/Alem/Mel	fludarabine, alemtuzumab, and melphalan
Flu/Mel	fludarabine/melphalan
Flu/Mel/TT	fludarabine/melphalan/thiotepa
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
IL	Interleukin
MAC	myeloablative conditioning
MA-HLH	HLH cases associated with an underlying malignancy
NK	natural killer
RIC	reduced-intensity conditioning
TRM	transplant-related mortality
UCB	umbilical cord blood
VOD	veno-occlusive disease

demonstrated continued improvement with an overall survival of 66% in the entire cohort and 71% in genetically confirmed HLH.[7] The HLH-94 and HLH-2004 studies reflect results in pediatric patients aged under 18 years, so less is known about indications for and outcomes after HSCT in adults. The decision to proceed and choice of transplant regimen is further complicated by the myriad etiologies of HLH in adults, particularly malignancy, and potential predisposing genetic factors. There remain unanswered questions, particularly about the optimal conditioning regimen and management of posttransplant mixed chimerism, for HLH patients of all ages.

APPROACH TO TRANSPLANT: PEDIATRIC POPULATION

Indications

Transplantation in children with HLH is almost exclusively performed in those with primary/familial disease, which typically presents in early childhood with known genetic mutations (PRF1, UNC13D, STX11, and STXBP2). Additionally, there are multiple genetic diagnoses with predisposition to HLH that need to be considered including XLP-1 and 2, Griscelli syndrome, Chediak–Higashi syndrome, and Epstein Barr Virus (EBV)-susceptibility disorders.[1] Ideal diagnosis and induction care includes a multidisciplinary team, with remote support if the relevant pediatric specialists are not available at the treating center. All patients should have genetic testing and comprehensive evaluation for infectious diseases performed, particularly viruses, as both may impact donor selection. It is often helpful for transplant providers to participate early in the patient's course so that HLA-typing and transplant donor identification can be done in parallel with the diagnostic evaluation when appropriate.

Donor Selection

The selection of a transplant donor is similar to the algorithm in other pediatric inherited diseases. Bone marrow stem cells from an HLA-matched sibling are preferred. It is vitally important that any HLA-matched sibling is tested before being selected as a potential donor to ensure that they do not carry the same genetic

diagnosis. Siblings who have the same genetic mutations may have different presentations of HLH; lack of clinical symptoms is insufficient to rule out disease. If an unaffected HLA-matched sibling is not available, then alternative donor sources are pursued. In those who presented with EBV or other viral illness, the potential donor should have antibody testing to determine prior exposure as prior donor immune response to the involved virus is preferred.

Unrelated bone marrow and peripheral blood stem cell donors have been used with success when a matched related donor is unavailable. Historically, there has been reluctance to use umbilical cord blood (UCB) as a stem cell source due to concerns about engraftment, availability of additional cells if needed for mixed chimerism, and limited ability of the transplanted cells to mount proper responses to viral infection. In the HLH-2004 study, the event-free and overall survival (OS) of patients who received UCB transplant was lower than matched related and matched unrelated transplant, though the difference was not statistically significant.[7] However, case series have shown results following UCB transplantation similar to those using other sources, and UCB may be considered when other donors are unavailable.[8,9] Haploidentical transplantation is an additional option for those without a fully matched related donor.[10,11]

Asymptomatic Carriers

There is no consensus on whether asymptomatic children who have biallelic HLH-mutations should undergo HSCT. An attempt is made to balance the risks of allo-HSCT with that of an inflammatory HLH flare. Factors affecting treatment recommendations are the age of the child, donor availability, presentation of the sibling's disease, and specific genetic mutation, though studies show a lack of concordance in age of presentation of relatives who have the same genetic mutation.[12] For example, there is likely greater acceptance and precedent for the transplant of a young sibling of a child with perforin-driven HLH with systemic presentation than for HSCT in an older sibling of a child with Central Nervous System (CNS)-restricted HLH. This issue was addressed in an international study of sibling pairs in which one child had symptomatic HLH and the other child was an asymptomatic carrier of the same pathogenic biallelic mutations.[13] Of the 32 asymptomatic patients, 26 received allogeneic transplant (10 after developing symptoms while being observed and 16 while asymptomatic) and 6 remained asymptomatic without therapy. The 8 year probability of OS of those who received pre-emptive transplant while asymptomatic (93%) was greater than both the symptomatic index cases (45%) and the patients who developed symptoms while being observed (64%). The authors concluded that pre-emptive transplant for asymptomatic individuals who have pathogenic, biallelic HLH mutations is safe and should be considered. Additionally, an expert consensus panel stated that transplant should be strongly considered in asymptomatic carriers of biallelic HLH-associated mutations, if HLH was manifested in infancy by a sibling. They further recommended that discussion about the timing of transplant in those with biallelic mutations without symptomatic family history is conducted at an HLH-experienced center.[14]

PRETRANSPLANT DISEASE CONTROL

HLH treatment before transplantation has been discussed in prior sections of this issue including combinations of corticosteroid, etoposide, cyclosporine, and antithymocyte globulin (ATG).[5,7,14–19] Antibody therapy targeting different components of the hyperinflammatory response has shown promising effect in recent years and include

emapalumab, an anti-interferon gamma antibody, anakinra, a recombinant interleukin (IL)-1 receptor antagonist, ruxolitinib, a Janus kinase (JAK) inhibitor, and tocilizumab, an IL-6 antagonist.[15,20–23]

The best transplant outcomes occur when complete remission is attained prior to the start of the transplant conditioning regimen. Data from 187 pediatric patients transplanted on HLH-2004 showed superior OS in confirmed familial HLH when complete remission was attained compared to partial remission.[7] Transplant should occur as quickly as possible once a patient is in complete remission given the risk of disease flare. Consensus recommendations support tapering HLH-directed therapy once disease control is achieved, followed by continuation at a lower level of therapy as a bridge to transplant.[14] There is not international agreement on specific continuation regimens. As complete remission prior to transplant is not always possible, proceeding in a partial remission is acceptable with the understanding that this course is associated with lower survival after allo-HSCT.

APPROACH TO TRANSPLANT: ADULT POPULATION

As with pediatric patients, the workup for any adult presenting with severe inflammatory symptoms is multidisciplinary and includes a rigorous workup for an oncologic diagnosis, thorough infectious disease workup, and a rheumatologic workup, with grading of inflammation based on ferritin, soluble IL-2 receptor (sIL-2R) and, increasingly utilized, CXCL9 levels, if not full cytokine profiling.[24] Distinguishing HLH from sepsis and other reasons for increased ferritin and fever, which is often what brings the patient to medical attention, has occurred by the time of referral for transplantation, but these inflammatory markers can still be used to track disease activity and readiness for transplantation. Control of inflammation is as important in adults as it is in children: active status versus inactive status yielded 88% versus 18% transplant-related mortality (TRM), respectively, in one study of adolescents and adults. This was similar to an odds ratio for mortality of 1.8 for children with active versus controlled disease at time of allo-HSCT.[25,26] We recommend early involvement of a transplant physician specializing in HLH to tailor disease-directed therapy to synchronize with transplant timing in order to not miss an optimal window of inflammatory control.

Unclear Genetic Contributions

Although the data remain murky regarding the genetic underpinnings of HLH in adults, our institutional practice is to sequence HLH-related inflammatory and immunodeficiency syndrome genes. Retrospective reviews suggest that hypomorphic mutations in PRF1, MUNC13-4 and STXBP2 are enriched to 14% in adult samples sent for HLH-related sequencing, that 50% of adults with secondary HLH have a monoallelic variant in a lymphocyte cytotoxicity gene (especially the A91V PRF1 variant), and that 42.9% of 112 adult HLH cases in an East Asian population had a mutation or rare variant in an HLH-associated gene.[27–29] However, on sequencing of 17 HLH-related or inherited immune disorder genes and identification of 7 putatively disrupted variants (including A91V PRF1) in a US-based cohort, these variants were not enriched for in adult HLH populations versus a control healthy population, although clonal hematopoiesis was more prevalent in the HLH population.[30,31] Compound heterozygosity of mutations/variants such as STXBP2/lysosomal trafficking regulator protein (LYST), PRF1/PRF1, STXBP2/STX11, LYST/MUNC 13-4, or GATA2 and 3 deficiencies have been present at diagnoses of HLH in adulthood in case reports and in our practice, typically with years of preceding nonspecific inflammatory flares. Patients with late onset/diagnosis of HLH and this type of genetic background are strongly considered for

allo-HSCT, but heterozygosity for potentially predisposing variants is not a priori considered a transplant indication.

Indications for Transplant

Whether and when to pursue allogeneic HSCT in adults with HLH is quite complex, driven largely by the presence of an underlying malignancy and the response of inflammation to initial therapy. Between 31% and 50% of adult HLH cases are associated with an underlying malignancy (MA-HLH), primarily B or T/natural killer (NK)-cell lymphomas, with survival of less than 40% at 1 year.[32–37] Initial therapy should be anchored on cytotoxic chemotherapy targeting the underlying malignancy, with consideration for introducing etoposide and steroids, particularly if inflammatory symptoms are not controlled. In practice, inflammatory symptoms are unlikely to be controlled unless the malignancy responds to therapy. Allo-HSCT is typically pursued only when both aspects are under control, even if on continued immunosuppressive therapy. There are no prospective studies utilizing consolidative transplant for MA-HLH. However, expert consensus favors allo-HSCT in the primary refractory or relapsed setting and potentially as primary consolidation after initial response, particularly in the setting of the more aggressive NK- and T-cell lymphomas.[38] Notably, some patients who are started on HLH therapy without a full oncologic workup can have their malignancy temporarily masked by etoposide and steroids. Any flare of HLH while on treatment in an adult should prompt consideration of a repeat workup for malignancy before escalating therapy, with higher soluble IL-2R/ferritin ratios raising suspicion for MA-HLH.[39] Allo-HSCT data in lymphoma, regardless of the presence of HLH, have favored reduced-intensity conditioning (RIC) regimens for survival, so the presence of malignancy does not commonly dictate conditioning intensity. However, a peripheral blood stem cell source is typically preferred over bone marrow in MA-HLH to exploit any graft-versus-lymphoma effect.

In contrast, most cases of HLH induced by infectious organisms, with the potential exception of EBV-HLH, and autoimmune inflammatory disease/macrophage activation syndrome, often respond to initial trigger-directed therapy.[40] In only the refractory cases of infection-associated, autoimmune-associated, or idiopathic HLH without a trigger is allo-HSCT pursued. Adults have met criteria for HLH after receiving checkpoint inhibitors for malignancies; these cases often respond to short-term steroid therapy alone.[41] The poorly understood phenomenon of HLH following allo-HSCT and immune effector cell-associated HLH-like syndrome is typically treated with anticytokine agents and steroids, rarely etoposide, and is not considered to require allo-HSCT for cure.[42]

Our practice is to follow inflammatory responses closely during initial therapy. Slow or incomplete normalization of inflammatory markers (even as early as 7 days into therapy) and organ function, even without florid relapse, will prompt the search for a potential HSCT donor.[43] All patients with severe HLH or any MA-HLH should undergo upfront human leukocyte antigen (HLA) typing to minimize delays if HSCT is needed. EBV-HLH is difficult to treat, with literature supporting initial treatment with multiagent chemotherapy and a recommendation for transplant in partial responders, potentially even after complete response.[44,45] Exact time to move to transplant is dependent on the morbidity of the patient's flares, how quickly they failed their last therapy, and prior lines of immunosuppressive therapy received (**Fig. 1**).

Donor Source

Optimal donor stem cell source has not been prospectively evaluated in the adult HLH setting. The preference has historically been for matched related donors, who can be

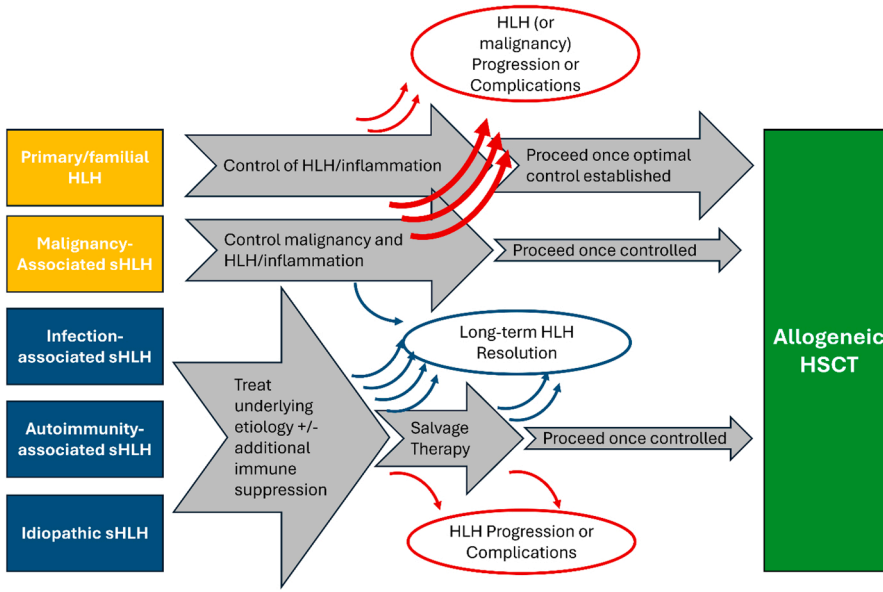

Fig. 1. This stylized diagram depicts the relative role of allo-HSCT in HLH related to various underlying etiologies. In genetically driven primary/familial HLH, allogeneic transplant is the goal as soon as HLH control can be established: ideally complete remission but partial remission is also acceptable. There will be some drop off/death secondary to uncontrolled inflammation or infectious complications, for example, but the goal is to proceed to curative allo-HSCT. In malignancy-associated secondary HLH (sHLH), both the underlying malignancy and the inflammatory syndrome must be controlled simultaneously. The extremely poor overall survival of MA-HLH is largely related to death in this initial period with primary refractory disease or rapid and aggressive relapses. Few patients survive to initiate the allo-HSCT process. Some patients with very early and complete control over both malignancy and HLH can be monitored instead of proceeding to transplant, but that is the minority of patients with MA-HLH. Patients with HLH of other etiologies are much more likely to achieve long-resolution with trigger-directed therapy plus additional immune suppression. Typically, only a portion of those who require salvage therapy and remain in a perpetually inflamed state require allo-HSCT. Some may be successfully maintained on chronic immune suppression including steroids or JAK inhibitors. The widths of the gray arrows reflect the relative proportion of HLH patients of different etiologies advancing toward allo-HSCT at each step. Small blue and red arrows represent other outcomes: long-term disease resolution or death 2/2 progression or complications, respectively.

available for collection of additional lymphocytes or stem cells if needed, with fully matched unrelated donors a close second. European Group for Bloodand Marrow Transplantation (EBMT) registry review of 87 adult allo-HSCTs for HLH logged 36% related and 58% unrelated donors.[46] In that study, only 4 patients received haploidentical transplant. However, studies out of Asia have been dominated by haploidentical donors with similar survival outcomes.[26] Peripheral blood stem cells are the preferred source over bone marrow (EBMT registry 78% vs 21%, without impact on survival), perhaps driven by desire to harness a graft-versus-lymphoma effect for MA-HLH and to optimize engraftment and donor chimerism, which are persistent challenges. Data on utilization of related donors with shared potentially HLH-predisposing variants such as A91V are sparse. Anecdotally, we have utilized one donor who shared the recipient's STXBP2 variant without issue, but if time and availability allow, we

preferentially target unrelated donors in those situations. Umbilical cord graft sources are rarely used, and in one study, they were associated with inferior OSI for adult HLH.[47]

CONDITIONING

Intensity

The choice of appropriate conditioning regimen for patients with HLH is challenging as practitioners attempt to balance acute treatment-related toxicity with long-term donor engraftment. Data have primarily been derived from pediatric cohorts. Traditional busulfan-based myeloablative conditioning (MAC) regimens are associated with high levels of donor engraftment but accompanied by significant rates of veno-occlusive disease (VOD), acute morbidity, and early mortality ranging between 30% and 54%.[7] The acute toxicities of busulfan-based MAC regimens led to the emergence of lower intensity regimens that yielded low mortality rates. Lower intensity regimens are extremely well tolerated in the acute period but complicated by excessive risk of mixed donor chimerism and graft failure.[48,49] A comparison of 40 patients treated with either a busulfan-based MAC regimen or a RIC regimen of fludarabine, alemtuzumab, and melphalan (Flu/Alem/Mel) demonstrated posttransplant mixed chimerism in 18% of patients who received a MAC regimen and 65% of RIC recipients. Intermediate dosing and timing of regimens using largely Flu/Alem/Mel were developed in an attempt to mitigate the shortfalls of the myeloablative and reduced-intensity approaches.[49] The initial response was promising with outstanding overall survival. The enthusiasm was later tempered due to excessive rates of mixed chimerism and secondary graft failure (Fig. 2).

Regimen Choice

The preferred conditioning regimen for patients with HLH remains under investigation. A multicenter, primarily pediatric comparison of 4 common conditioning regimens: MAC busulfan/cyclophosphamide (Bu/Cy), RIC busulfan/fludarabine (Bu/Flu), RIC fludarabine/melphalan (Flu/Mel), and RIC fludarabine/melphalan/thiotepa (Flu/Mel/TT), typically with accompanying alemtuzumab (Alem) or ATG was performed to evaluate

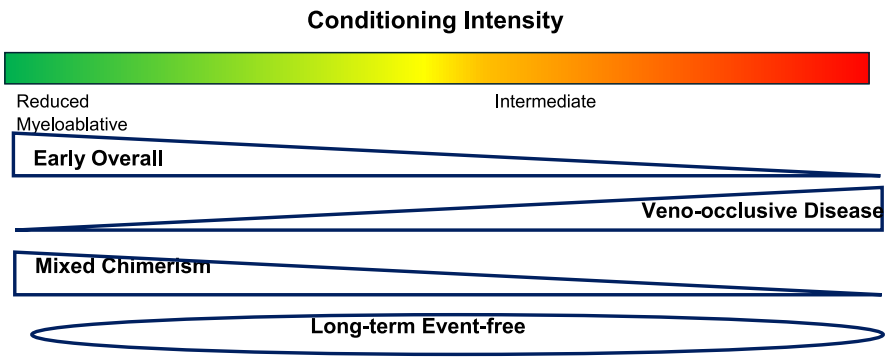

Fig. 2. The relationship between conditioning intensity and survival, veno-occlusive disease, and mixed chimerism. Greater intensity of conditioning is associated with acute toxicity including veno-occlusive disease in the first 100 days after transplant leading to decreased overall survival. Reduced-intensity conditioning regimens are associated with greater risk of mixed chimerism and graft failure requiring subsequent therapy. The balance of these factors leads to comparable event-free survival at the extremes of intensity.

various conditioning regimens.[19] The analysis showed a significant difference in the event-free survival (EFS) between the regimens (Bu/Cy 38%, Bu/Flu 79%, Flu/Mel 44%, and Flu/Mel/TT 70%). Some difference was attributed to a 42% graft failure rate in subjects who received Flu/Mel. The day 100 incidence of VOD was greatest in those who received busulfan-containing regimens (Bu/Cy 22%, Bu/Flu 14%, Flu/Mel 4%, and Flu/Mel/TT 0%). The incidence of VOD did not differ between those who received PK-based busulfan dosing and those who did not. The authors concluded that Flu/Mel/TT may be favored over the other regimens due to lower risk of graft failure and VOD.

Treosulfan-based regimens have demonstrated favorable toxicity profiles with high-rates of EFS and OS in multiple pediatric reports. A single center comparison of traditional myeloablative conditioning, reduced-intensity conditioning, and a treosulfan-based reduced-intensity regimen showed greater mixed chimerism in the non-treosulfan reduced-intensity cohort.[50] Not surprisingly, the traditional myeloablative cohort had the greatest incidence of need for critical care support and VOD. The cohort who received the treosulfan-containing regimen had favorable EFS. Evidence from this and other reports supports treosulfan-based regimens as an appropriate, often preferred, alternative to traditional myeloablative and reduced-intensity strategies.[50–53]

Limited Adult Conditioning Experience

In the more limited adult HLH literature, there is significant heterogeneity in intensity and choice of conditioning agents. In the EBMT HLH registry of 87 adults, 61% of allo-HSCT were MAC, with no survival difference seen between MAC and RIC (3 year OS 44%); of note, this cohort contained no patients with MA-HLH.[46] The most commonly used regimens were Flu/Bu/ATG and Flu/Mel/Alem at 17% and 12%, but 48% were “other.” An Asian-based study showed inferior outcomes for MAC in a population dominated by EBV-HLH (HR 2.45) driven largely by non-relapse mortality (NRM), whereas 2 other studies employed a MAC haploidentical regimen both achieving 2 and 3 year OS of 63%.[26,54,55] An extensive review of HSCT for allo-HLH up thru 2019 found studies ranging in size from case reports to 36 patients, some with a few patients with MA-HLH, others all EBV-HLH, and some all late-onset familial HLH.[56] Survival varied widely from mean OS 8 months to 100% survival at 32 months. NRM, relapse, and incidence of mixed chimerism were sporadically reported. While timing of alemtuzumab prior to conditioning has been explored in the pediatric setting, no such data exist in the adult HLH allo-HSCT setting.[17] Across all studies, older recipient age was a negative prognostic factor.

Extrapolating on excellent 1 year OS of 80% and 18 month OS of 67% in the Blood and Marrow Transplant - Clinical Trials Network (BMT-CTN) 1204 study, our institution has pursued a similar platform for adults.[2,49] Specifically, prior to a RIC backbone of primarily Flu/Bu and tacrolimus/methotrexate graft versus host disease (GvHD) prophylaxis, 21 recipients received 4 days of subcutaneous alemtuzumab ending 3 to 4 weeks prior to stem cell infusion. This regimen achieved 75% OS at 3 years. No isolated HLH relapses were seen without relapse of malignancy. NRM was 15% at 3 years. Only 5 patients had MA-HLH, primarily because those with MA-HLH experienced mortality before allo-HSCT could be delivered.

CNS-RESTRICTED HLH

CNS-restricted disease is an uncommon presentation of familial HLH in which neurologic symptoms are present in the absence of evidence of systemic disease.[1,3] It has been described in patients with pathogenic mutations in PRF1, UNC13D, LYST,

RAB27A, and STXBP2.[57] In pediatric patients, familial CNS-restricted disease is typically diagnosed in patients older than those presenting with systemic findings. While acute-onset seizure and gait disturbance are common presenting symptoms of CNS-restricted HLH, a case series of pediatric patients described 4 patients with chronic neuroinflammatory symptoms lasting years before diagnosis in some cases.[58] It is unknown why some patients with the same pathogenic mutations present with CNS-restricted disease while others have systemic involvement. HSCT has been used in patients with CNS-HLH with generally positive results. In the aforementioned case series, 3 of 4 patients achieved disease control with allogeneic transplant. The fourth patient required a second transplant for relapsed disease. All patients showed improvement in neurologic symptoms. In other case series of patients with CNS-restricted HLH, 58% showed neurologic improvement, 21% had stable disease, one patient had relapsed disease, and 16% died.[59] Available data support the use of allogeneic transplant in familial HLH patients with CNS-restricted disease. Commonly, patients are symptomatic at the time of transplant due to neurologic injury and/or chronic neuroinflammation. In those cases, it is important to try to distinguish active, uncontrolled disease versus residual symptoms of chronic illness, as controlling active disease may lead to improved transplant outcomes. In adults, the presentation of HLH can be accompanied by delirium of critical illness, particularly when febrile, and some patients may exhibit microhemorrhages on MRI. However, cases of adult primary neurology presentation are rare enough to be reportable.[60] Neurologic manifestations, in general, resolve in synchrony with systemic inflammation and do not drive treatment or allo-HSCT decisions in adults.

GRAFT FAILURE AND MIXED CHIMERISM

Primary or secondary graft failure, graft exhaustion, and mixed donor chimerism are known complications after any reduced-intensity allo-HSCT. In HLH, given the highly activated immune milieu of the recipient and use of ATG and alemtuzumab prior to stem cell infusion, these complications are significantly more common (**Table 1**). Mixed chimerism defined as 5% to 95% of leukocytes being of donor origin occurred in 65% of recipients after RIC Flu/Mel/Alem versus 18% following MAC Bu/Cy/ATG ± Etoposide in one study and in 42% to 100% of HLH recipients following RIC allo-HSCT in other studies. In the BMT-CTN 1204 Phase 2 study, which enrolled 34 primarily pediatric patients with HLH and 12 with other primary immune deficiencies to receive RIC dosing of Flu/Mel preceded by "intermediate dosing" of alemtuzumab days −14 through −10, there were 4 graft failures and only 39% of patients (n = 18) were alive with sustained donor chimerism greater than 5% without a second cell therapy intervention.[17,49,61] Risk of poor donor chimerism has been linked to use of an HLA-mismatched donor and timing of alemtuzumab, with in some studies "distal" alemtuzumab administered days −22 to −19 resulting in less mixed chimerism.[17,62] Our adult study utilizing primarily Flu/Bu RIC conditioning and "distal" alemtuzumab dosing showed 30% of patients with total leukocyte donor chimerism less than 90%.[2]

The question of what level of donor chimerism is clinically relevant, that is, required to prevent late reactivation of primary HLH after allo-HLH, was addressed in a retrospective analysis of 103 allo-HSCT recipients whose donor chimerism was permanently or transiently less than 75%. This study concluded that donor chimerism greater than 20% to 30% post-HSCT is protective, although lower levels do not necessary result in recurrences. In murine models, 10% to 20% perforin expression seems to restore immune regulation.[63] It is unclear what thresholds are being used for intervention in practice, but studies in **Table 1** indicate 32% to 71% of pediatric patients with HLH after

Table 1
Incidence of graft failure and mixed chimerism in representative pediatric and adult studies of allogeneic hematopoietic stem cell transplantation for hemophagocytic lymphohistiocytosis

Population	Conditioning Intensity	Graft Source	Graft Type	Graft Failure	Mixed Donor Chimerism (5%–95% Unless Otherwise Indicated)	# Patients Receiving 2nd Cell Therapy Interventions	Survival
Pediatrics (HLH) n = 40[48]	1. MAC: Bu/Cy/ATG ± Etop 2. RIC: Flu/Mel/Alem	Matched or single antigen mismatched related and unrelated donors	90% bone marrow	1. None 2. None	1. 18% (2 of 11) 2. 65% (17 of 26)	1. 1 received DLI 2. CD34+ boost: 3 DLI: 12 (8 received ≥3)	1. MAC: 3 y OS 43% 2. RIC: 3 y OS 92%
Pediatrics (HLH and XLP)[17] n = 71	RIC: Flu/Mel/Alem (proximal, intermediate, and distal Alem timing)	Sibling or unrelated donors	97% bone marrow	Not stated	42% entire group 1. Proximal: 70% (23 of 33) 2. Intermed: 29% (7 of 23) 3. Distal: 0% (0 of 7)	2nd allo HSCT: 4 CD34+ boost: 4 DLI: 18 (9 received ≥3)	1 y OS 80%–91%
Pediatrics[61] (HLH and non-malignant disease) n = 31 (HLH n = 7)	RIC: Flu/Mel/Alem or Flu/Bu/Alem (variable Alem timing)	Sibling or unrelated donors	100% bone marrow	Graft loss/relapse 22% (6 of 27 evaluable) 43% HLH vs 15% non-HLH	66% entire group (44% with DC ≤ 80%) 100% HLH (71% with DC ≤ 80%) Distal alemtuzumab - lowest rates of MC	CD34+ boost: 3 DLI: 3 (71% of HLH pts had intervention vs 5% non-HLH)	3 y OS 85% (HLH 3 y OS 70%)
Pediatrics[49] (HLH and primary immune deficiencies) n = 46 (HLH n = 34)	RIC: Flu/Mel/Alem (intermediate Alem timing)	Matched or single antigen mismatched related and unrelated donors	100% bone marrow	8% graft failure	Sustained DC >5% to 57% (range, 23%–100% donor)	2nd HSCT: 10 DLI: 7	1 y OS 80%

Pediatrics[62] (HLH) n = 60	RIC: Flu/Treo or Flu/Mel based plus Alem or ATG, (mostly proximal Alem timing)	84% matched or single antigen mismatched related and unrelated	66% bone marrow	1 post haplo HSCT	48% DC <95%. (18% with DC <25%)	2nd HSCT: 12 DLI: 7 (median 3; range 1–10)	5 y OS 75%
Adults[2] (HLH) n = 21	RIC: Primarily Flu/ Bu/Alem (distal Alem timing)	90% matched or single antigen mismatched related and unrelated donors (10% haploidentical)	52% PBSC	None	At 30 d, median DC 92% (1 pt <50%) At 1 y, median 99% (30% pts had <90%)	CD34+ boost: 2 DLI: 2 (for donor T-cell chimerism $\leq$20%)	3 y OS 75%

Abbreviations: Alem, alemtuzumab; ATG, anti-thymocyte globulin; Bu, busulfan; Cy, cyclophosphamide; DC, donor chimerism; Etop, etoposide; Flu, fludarabine; Haplo, haploidentical; HLH, hemophagocytic lymphohistiocytosis; MAC, myeloablative conditioning; MC, mixed chimerism; Mel, melphalan; OS, overall survival; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning; Treo, treosulfan.

allo-HSCT and 19% of adults receive either a second HSCT, a CD34-selected stem cell boost for poor graft function, or donor lymphocyte infusion (DLI) to help restore T-cell chimerism, in addition to undergoing a decrease in post-HSCT immune suppression. Donor chimerism may frequently be restored by DLI or stem cell boosts, but DLIs carry a significant risk of graft versus host disease and stem cell boosts are quite resource intensive. Both reflect additional donor commitment and potential risk. Emapalumab, the anti-interferon gamma antibody, has recently been shown in a retrospective review of pediatric patients with HLH to reduce the incidence of donor chimerism less than 95% to 48% versus 77% in the control cohort and to reduce donor chimerism less than 25% to 5% versus 38%.[23] Ruxolitinib has been used both as HLH treatment and as steroid-free bridging therapy to keep HLH quiescent prior to allo-HSCT and might be investigated in place of ATG or alemtuzumab in RIC regimens to avoid in vivo T-cell depletion of the graft, likely a contributing factor to mixed chimerism. In our adult allo-HSCT cohort, at least, chimerism was not associated with OS or PFS.[2] En masse, these data suggest a need for modification of existing RIC regimens to decrease cases of severe mixed/poor donor chimerism and for definition of relevant thresholds triggering a second cell therapy.

SUMMARY

Allogeneic HSCT is still regarded as the only curative therapy for primary/familial HLH and for primary-refractory or relapsed secondary HLH, particularly malignancy-associated HLH. While fully matched related donors remain preferable, unrelated donors and haploidentical donors are also of utility. What genetic variants predispose to adult secondary HLH remain unknown, but sequencing of immunodeficiency genes in HLH patients of all ages is standard, with genetic evaluation of related donors as relevant. Guidance on the conditioning intensity and regimen components remains unclear as published approaches typically trade off upfront TRM secondary to toxicity in the myeloablative setting with poor immune reconstitution and frequent use of additional cell therapies such as second transplant, stem cell boosts, and DLIs in the reduced-intensity setting. Further investigations employing novel immunomodulatory agents are required to improve overall survival. However, the biggest challenge is often identifying who requires a transplant before the window to intervene has passed. This involves constant monitoring of the HLH patient's response to primary or salvage therapy and initiating the allo-HSCT process during a period of disease control, before exclusionary infectious complications or organ toxicities arise. Such multidisciplinary engagement and ongoing investigations are critical to improving outcomes after allogeneic HSCT for HLH.

CLINICS CARE POINTS

- HLH patients of all ages should undergo testing to detect predisposing genes, but in adults a rigorous workup for malignancy is also mandatory.
- Involve transplant physicians early in an HLH patient's course to enable HLA-typing and transplant donor identification in parallel with diagnostic evaluation and therapy, as needed.
- Achieving control of inflammation (and any underlying malignancy) prior to allo-HSCT dramatically improves survival.
- In choosing a donor and conditioning regimen for a given HLH patient, transplant-related morbidity and organ toxicity should be balanced against poor donor engraftment and need for additional cell therapies at an experienced clinical center.

DISCLOSURE

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