Bone Marrow Transplantation (2008) 42, 175–180

www.nature.com/bmt

ORIGINAL ARTICLE

Unrelated donor hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis

KS Baker[1], AH Filipovich[2], TG Gross[3], WJ Grossman[4], GA Hale[5], RJ Hayashi[6], NR Kamani[7], S Kurian[8], N Kapoor[9], O Ringdén[10] and M Eapen[11]

[1]*University of Minnesota Medical Center, Minneapolis, MN, USA;* [2]*Cincinnati's Children's Hospital Medical Center, Cincinnati, OH, USA;* [3]*Columbus Children's Hospital, Columbus, Ohio, USA;* [4]*Children's Hospital of Wisconsin, Milwaukee, WI, USA;* [5]*St Jude Children's Research Hospital, Memphis, TN, USA;* [6]*St Louis Children's Hospital, St Louis, Missouri, USA;* [7]*Children's National Medical Center, Washington, DC, USA;* [8]*City of Hope National Medical Center, Duarte, CA, USA;* [9]*Children's Hospital of Los Angeles, Los Angeles, CA, USA;* [10]*Karolinska University Hospital, Stockholm, Sweden and* [11]*Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI, USA*

We report outcomes after unrelated donor hematopoietic cell transplantation (HCT) for 91 patients with hemophagocytic lymphohistiocytosis (HLH) transplanted in the US in 1989–2005. Fifty-one percent were <1 year at HCT and 29% had Lansky performance scores <90%. Most (80%) were conditioned with BU, CY, and etoposide (VP16) with or without anti-thymocyte globulin. Bone marrow was the predominant graft source. Neutrophil recovery was 91% at day-42. The probabilities of grades 2–4 acute GVHD at day-100 and chronic GVHD at 5 years were 41 and 23%, respectively. The overall mortality rate was higher in patients who did not receive BU/CY/VP16-conditioning regimen (RR 1.95, $P = 0.035$). The 5-year probability of overall survival was 53% in patients who received BU/CY/VP16 compared to 24% in those who received other regimens. In the subset of patients with known disease-specific characteristics, only one of five patients with active disease at HCT is alive. For those in clinical remission at HCT ($n = 46$), the 5-year probability of overall survival was 49%. Early mortality rates after HCT were high, 35% at day-100. These data demonstrate that a BU/CY/VP16-conditioning regimen provides cure in approximately 50% of patients and future studies should explore strategies to lower early mortality.
Bone Marrow Transplantation (2008) **42,** 175–180; doi:10.1038/bmt.2008.133; published online 5 May 2008
Keywords: hemophagocytic lymphohistiocytosis; unrelated donor transplant; conditioning regimen; mortality; bone marrow graft

Correspondence: Dr M Eapen, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI 53211, USA.
E-mail: meapen@mcw.edu
Received 4 January 2008; revised 11 March 2008; accepted 13 March 2008; published online 5 May 2008

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare immunoregulatory disorder characterized by defective lymphocyte cytotoxic activity that results in uncontrolled proliferation of macrophages, lymphocytes, and overproduction of inflammatory cytokines. Because of this dysregulation, there is an infiltration of various organs including the spleen, liver, bone marrow and central nervous system (CNS) by activated macrophages and lymphocytes that leads to the typical clinical findings of the disease including hepatosplenomegaly, hemophagocytosis, cytopenias, and in some cases neurologic changes and seizures from CNS involvement. Additional disease characteristics that result from the pro-inflammatory state include fevers, hypertriglyceridemia, coagulopathy, hyperferritinemia, and high levels of soluble interleukin-2 receptor α-chain levels (sCD25). The Histiocyte Society has recently published the clinical and pathological features of HLH.[1] HLH is classified as primary (familial) or secondary. To date, there have been several genetic mutations identified, all of which produce alterations in the perforin/granzyme cellular cytotoxic pathways utilized by T lymphocytes and natural killer cells and subsequently lead to HLH.[2] The first mutation described was in the gene encoding perforin (PRF1), at chromosome10q21–22.[3] PRF1 mutations account for approximately 20–30% of cases of primary HLH. An additional 20–25% of cases are associated with a mutation in the *MUNC13-4* gene at chromosome 17q25.[4] The third mutation identified on chromosome 6q24 encodes for the protein syntaxin 11 (*STX11*), and thus far has only been found to account for a small percentage of cases.[5] Other genetic mutations associated with primary HLH include: *SAP*/*SH2D1A* (x-linked lymphoproliferative disease), *RAB27A* (Griscelli syndrome), *CHS1* (Chediak-Higashi syndrome), and WASP (Wiskott–Aldrich syndrome). However, for nearly half of patients with HLH, specific genetic mutations have yet to be determined.

For patients with either primary or secondary HLH, prompt recognition and treatment with cytotoxic chemotherapy (etoposide) and immunosuppression with agents such as steroids, cyclosporine, and/or anti-thymocyte globulin are necessary to prevent an otherwise rapidly fatal course. The HLH-94 protocol developed by the Histiocyte Society in the mid 1990s provided a uniform treatment approach that improved survival from less than 10%,[6] to a 3-year probability of survival of 55%.[7] Nevertheless, for patients with primary HLH, this treatment will not provide permanent remission and for those with secondary HLH who fail chemotherapy and immunosuppression, hematopoietic cell transplant (HCT) provides the only curative option. The purpose of the analysis presented herein is to describe the outcome after URD HCT in the US facilitated by the National Marrow Donor Program (NMDP) and to examine the impact of preparative regimen and disease characteristics on long-term survival in this group of patients.

Patients and methods

Data collection

A formal affiliation of the research division of the NMDP (established in 1986) and the International Bone Marrow Transplant Registry (established in 1972) led to the establishment of the Center for International Blood and Marrow Transplant Research (CIBMTR) in 2004. The CIBMTR is a working group of over 500 transplant centers worldwide that voluntarily contribute detailed patient-, disease- and, transplant-characteristics and outcome data on allogeneic HSCT recipients to a Statistical Center at the Medical College of Wisconsin. Participating centers register consecutive transplantations. Detailed demographic, disease and transplant characteristics and, outcome data are collected on a representative sample of registered patients and all unrelated donor transplantations facilitated by the NMDP in the United States. All patients are followed longitudinally. Computerized error checks, physician review of submitted data and on-site audits of participating centers ensure data quality.

Inclusion criteria

The study population consists of 91 patients with HLH who received unrelated donor HCT facilitated by the NMDP in the United States in 1989–2005. The diagnosis of HLH was determined by transplant centers.[1] Genetic testing was not used as a criterion for diagnosis. The NMDP retrospectively obtained consent for data submission and study participation from surviving patients or their parent/legal guardian for transplantations it facilitated in the United States during the study period; the NMDP Institutional Review Board waived consent for patients who had died prior to soliciting consent. To address bias introduced by inclusion of only a proportion of surviving patients (those consenting) but all deceased patients, a sample of deceased patients was selected using a weighted randomized scheme that adjusts for over-representation of deceased patients in the consented cohort. This weighted randomized scheme was developed based on all survivors in the NMDP database. A logistic regression model was fitted to identify factors that predicted whether patients had consented or not consented to use of data collected by the NMDP. This analysis found the following factors were associated with the likelihood of a patient consenting: age, disease type, race, sex, cytomegalovirus serologic status and country of transplantation (US vs non-US). Using estimated consenting probabilities from this model based on the characteristics of dead patients, the biased coin method of randomization was performed to determine which of the likely deceased patients would have consented to participate had they been alive. Approximately 13% of surviving patients failed to consent and 12% of dead patients were deleted by the weighted randomized method. The above described method was tested several times and on every occasion the proportion of deleted dead patients was similar. Thus, this procedure ensures that the pre-consented dead patients are included in the sample with the same probability as the survivors who actually consented to participate in the study.[8] One hundred and one patients met the eligibility criteria and 12 deceased patients were excluded by the weighted randomized method; the current analysis includes 91 patients.

End points

The primary outcomes studied were neutrophil recovery, acute and chronic GVHD and overall mortality. Neutrophil recovery was defined as achieving an absolute neutrophil count of $\geqslant 0.5 \times 10^9$/l for three consecutive days and platelets $\geqslant 20 \times 10^9$/l for 7 days, unsupported. Incidence of grades 2–4 acute GVHD and chronic GVHD was determined in all patients. The diagnosis of acute and chronic GVHD was based on local institutional criteria, with overall grade of acute GVHD assigned retrospectively by the CIBMTR based on the stage of involvement reported for each individual organ.[9] Surviving patients were censored at last follow-up.

Statistical analysis

The probability of overall survival was calculated using the Kaplan–Meier estimator.[10] For analysis of survival rates, death from any cause was considered an event and data on patients alive at last follow-up were censored. The probabilities of neutrophil recovery, and acute and chronic GVHD were calculated using the cumulative-incidence-function method.[10] For neutrophil and GVHD, death without an event (neutrophil recovery or GVHD) was the competing event. Data on patients without an event were censored at last follow-up. Confidence intervals were calculated using log-transformation. Cox regression models were built for analysis of risk factors for overall mortality.[11] Multivariate models were built with the use of stepwise forward selection, with a *P*-value of 0.05 or less considered to indicate statistical significance. All variables met the proportional-hazards assumptions and there were no first order interactions. Variables considered in multi-variate model building are shown in Table 1. *P*-values are two-sided. Analyses were completed with the use of SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Table 1 Characteristics of patients with HLH who received an unrelated donor HCT

Variable	*Number (%)*
Total	91
Sex, male	45 (49)
Age at transplantation	
<1 year	46 (51)
⩾1 year	45 (49)
Performance score	
90–100	61 (67)
⩽80	26 (29)
Unknown	4 (4)
Year of transplant	
1989–1994	12 (13)
1995–1999	30 (33)
2000–2005	49 (54)
Time from diagnosis to transplantation	
⩽6 months	40 (44)
>6 months	36 (40)
Unknown	15 (16)
Conditioning regimen	
Bu + Cy + etoposide + ATG	61 (67)
Bu + Cy + etoposide	12 (13)
Bu + Cy + ATG	6 (7)
Cy + ATG	4 (4)
Cy + etoposide	1 (1)
Cy + cytosine arabinoside	2 (2)
Melphalan + fludarabine + ATG	2 (2)
Cy alone	3 (3)
Graft-versus-host disease prophylaxis	
Cyclosporine + steroids	19 (21)
Cyclosporine + methotrexate ± steroids	56 (62)
Tacrolimus ± other	6 (7)
T-cell depletion	10 (11)
Graft source[a]	
Bone marrow	78 (86)
Peripheral blood	4 (4)
Cord blood	9 (10)
Donor-recipient HLA match or mismatch at HLA A, B (low resolution) DRB1 (allele-level)[a,b]	
Matched	54 (59)
1-locus mismatch	32 (35)
2-loci mismatch	4 (4)
Donor-recipient CMV status	
Donor (−)/recipient (−)	23 (25)
Donor (−)/recipient (+)	20 (22)
Donor (+)/recipient (−)	12 (13)
Donor (+)/recipient (+)	16 (18)
Unknown	20 (22)
Donor-recipient sex match	
Male → male	25 (27)
Male → female	20 (22)
Female → male	20 (22)
Female → female	26 (29)
Follow-up, median (range), months	59 (12–160)

Abbreviations: ATG = anti-thymocyte globulin; Bu = busulfan; Cy = cyclophosphamide.
[a]Donor-recipient HLA-match by graft type: bone marrow: 49 matched at HLA A, B (low resolution) DRB1 (allele-level), 27 mismatched at 1-locus and one mismatched at 2-loci; peripheral blood: two matched and two mismatched at 1-locus; umbilical cord blood: 3 matched, three mismatched at 1-locus and three mismatched at 2-loci.
[b]Allele-level HLA typing at HLA A, B, C and DRB1 were available for 59 of 91 patients (65%). Twenty-seven were matched at 8-loci; 20 mismatched at 1-locus and 10 mismatched at 2-loci and two mismatched at 3-loci. By graft type: bone marrow: 23 matched at HLA A, B, C, DRB1, 19 mismatched at 1-locus, eight mismatched at 2-loci and one mismatched at 3-loci; peripheral blood: two matched, one mismatched at 1-locus and one mismatched at 2-loci; umbilical cord blood: 2 matched, one mismatched at 2-loci and one mismatched at 3-loci.

Results

Patients

Patient, disease and transplant characteristics are shown in Table 1. Approximately half of patients undergoing HCT were younger than a year at transplantation. A third of patients reported a poor performance score (Lansky score <90) at HCT. Over half of transplantations occurred after 1999 and bone marrow was the predominant graft type used. Most (86%) received BU, CY and etoposide with or without antithymocyte globulin as transplant conditioning regimen. The majority (89%) received calcineurin-inhibitor containing GVHD prophylaxis. As transplantations spanned over a decade, donor-recipient HLA compatibility was available for all patients at HLA-A and -B by low resolution (antigen-level) typing and allele-level typing at DRB1. HLA-antigen mismatch was defined as the presence of a mismatch between donor and recipient at the antigen level for HLA-A and HLA-B and the allele-level for HLA-DRB1. Sixty five percent (59 of 91) of donor-recipient pairs had allele-level HLA typing available at HLA A, B, C and DRB1. Disease-specific characteristics were available in a subset of 51 of 91 (56%) patients. Twenty-one of 51 (41%) of patients had central nervous system (CNS) involvement at diagnosis. Definitions of disease status at time of HCT were the same as those previously published as utilized in the HLH-94 and HLH-2004 protocols.[1,12]

Neutrophil and platelet recovery

Eighty-three of 91 patients achieved neutrophil recovery. The probabilities of recovery were 85% (95% CI 75–91) and 91% (95% CI 83–96) at days 28 and 42, respectively. Fifty-four of 91 achieved platelet recovery at a median of 33 days after transplantation. The probabilities of platelet recovery were 54% (95% CI 43–63) and 58% (95% CI 47–67) at day-100 and 6 months, respectively.

GVHD

Thirty-six of 88 evaluable patients developed grades 2–4 acute GVHD. Fifteen of 36 patients developed grade 2, 14 patients developed grade 3 and seven patients, grade 4 acute GVHD. The day-100 probability of grade 2–4 acute GVHD was 41% (95% CI 31–51). The corresponding probability of grade 3–4 acute GVHD was 24% (95% CI 16–33). Twenty of 88 evaluable patients developed chronic GVHD. The 5-year probability of chronic GVHD was 25% (95% CI 16–36). Twelve developed extensive chronic GVHD, seven limited chronic GVHD and the grade was not reported for one patient.

Overall mortality

Forty-one of 91 patients are alive at a median of 5 years after transplantation with follow-up extending to 13 years. The 1- and 5-year probabilities of overall survival for the entire cohort were 52% (95% CI 41–62) and 45% (95% CI 34–55), respectively. The use of a conditioning regimen other than BU, CY and etoposide with or without anti-thymocyte globulin was associated with higher mortality (RR 1.95, 95% CI 1.05–3.63, $P = 0.035$). The 5-year probability of overall survival after BU, CY and etoposide

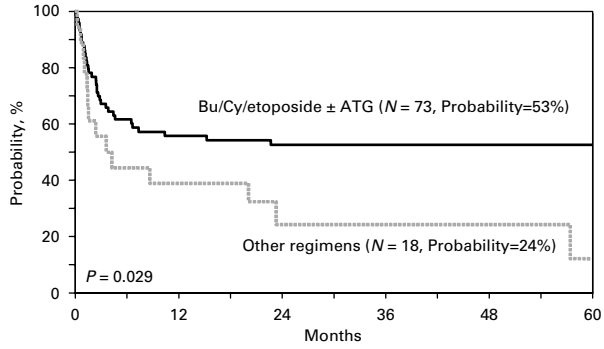

Figure 1 Probabilities of overall survival by transplant conditioning regimen: BU, CY, etoposide with or without antithymocyte globulin (ATG) versus other regimens.

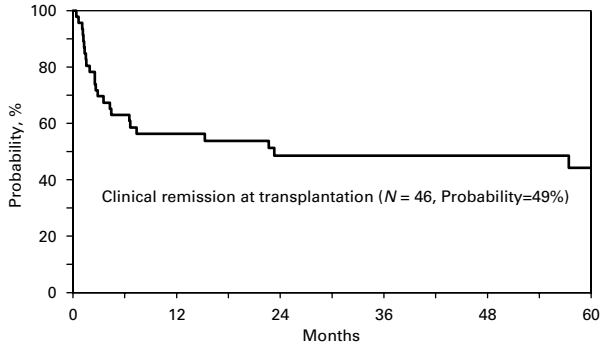

Figure 2 The probability of overall survival in patients transplanted in clinical systemic remission.

with or without anti-thymocyte globulin-containing conditioning regimen was 52% (95% CI 40–63) compared to 19% (95% CI 4–41) with other regimens (Figure 1). We were unable to examine whether use of anti-thymocyte globulin was associated with mortality as too few patients (12 of 73) did not receive anti-thymocyte globulin with the BU, CY and etoposide-conditioning regimen.

In univariate analysis survival was not influenced by age at diagnosis, interval from diagnosis to transplantation, gender, year of HCT, Lansky performance score, GVHD prophylaxis, donor-recipient CMV status, donor-recipient HLA disparity or donor-recipient sex match. However, in the subset of patients for whom allele-level HLA typing was available, the risk of mortality was higher with mismatched transplants (RR 2.16, 95% CI 0.98–4.75, $P=0.056$) even though the level of significance is marginal; the 5-year probabilities of overall survival after allele-level mismatched and matched transplants were 35% (95% CI 19–52) and 66% (95% CI 45–81), respectively. Though only nine patients received umbilical cord blood grafts it is noteworthy that all achieved neutrophil recovery and six achieved platelet recovery and six of these nine patients are alive at last follow-up. All recipients of peripheral blood grafts died ($n=4$); recurrent disease ($n=1$), GVHD ($n=1$) and infection ($n=2$). Among surviving patients, donor-recipient chimerism data is available for 30 of 41 recipients; 27 patients have full donor chimerism (three recipients of umbilical cord blood and 24 bone marrow) and the remaining three patients have 83, 84 and 95% donor chimerism at 4.5, 8 and 3 years, respectively after transplantation. These patients with mixed donor-recipient chimerism have no clinical features of HLH; one received umbilical cord blood and the others, bone marrow.

In the subset of patients ($n=51$) for whom disease-specific data were available, disease status at transplantation were as follows: 43 patients were in clinical systemic and CNS remission, three patients were in clinical systemic remission but had active CNS disease, four patients had active systemic disease without CNS involvement, and one patient had active systemic and CNS disease. The 5-year probability of overall survival of patients in systemic remission at time of transplantation was 49% (95% CI 33–62) (Figure 2). Only one of the five patients with active systemic disease at transplantation is alive. The presence of CNS disease at diagnosis was not associated with an increased risk of mortality after transplantation (RR 1.10, $P=0.806$). As only four patients had active CNS disease at transplantation we are unable to comment on whether persistent CNS involvement at transplantation affects mortality.

Early mortality was high with 32 deaths occurring within the first 100 days after HCT. The day-100 probability of overall mortality was 35% (95% CI 26–45). Most deaths (30 of 32) were from complications associated with transplantation. Causes include infections ($n=8$), interstitial pneumonitis ($n=8$), organ failure ($n=6$), hemorrhage ($n=3$), GVHD ($n=5$) and persistent disease ($n=2$). Veno-occlusive disease was reported in 16 patients; 11 of these patients are dead (early death) and veno-occlusive disease was a contributing cause of death in three patients with organ failure and one patient whose primary cause of death was infection. Though not reported by the transplant centers as a contributing cause of death, it is likely that veno-occlusive disease may have also been a contributing cause of death in the remaining seven patients who died from infection or interstitial pneumonitis. Eighteen deaths occurred after day-100. Causes of late mortality include infection ($n=6$), GVHD ($n=3$), recurrent or persistent disease ($n=5$), organ failure ($n=2$), interstitial pneumonitis ($n=1$) and hemorrhage ($n=1$).

Discussion

We report outcome data on the largest number of unrelated donor HCT for HLH to date with median follow-ups over 5 years, and provide information on some of the unique challenges encountered with this disease during transplantation. The current report confirms and extends the findings others have previously described, the impact of pre-transplant disease status at the time of HCT (active vs quiescent) as an adverse prognostic factor for patients with HLH undergoing matched related or unrelated HCT.[13–15] Although single case reports do support the fact that HCT can be successful in some cases with active disease,[16,17] there is clearly a need for novel improved salvage therapies for patients who fail first line treatment. Consistent with others,[15] we did not find CNS disease activity at diagnosis,

to have an impact on overall survival. Thus transplantation does appear to be effective in controlling active CNS HLH but not clinically active systemic disease. We observed 5-year overall survival rates of approximately 50% after matched or mismatched URD HCT and when limited to transplants matched at HLA A, B, C and DRB1 (allele-level typing) overall survival rates were 66% at 5-years. The overall survival rates reported in the current study are consistent with rates reported after matched sibling, mismatched related and matched or mismatched unrelated donor transplants though the number of patients undergoing unrelated donor transplantation were considerably fewer in those reports ($n = 35$) compared to ours.[7,15] Rates of acute and chronic GVHD observed in the current analysis are consistent with that reported by others.[18,19]

Thus far, there have been no studies comparing transplant-conditioning regimens on the outcome after transplantation for HLH. We show here that the regimen of busulfan, cyclophosphamide, etoposide with or without anti-thymocyte globulin provided superior outcomes compared to the other regimens that were utilized. This however, must be interpreted with caution as we do not have any information available to determine as to why some of the alternative regimens may have been chosen, a limitation when using an observational database. These data here suggest patient, disease and transplant characteristics of those who received busulfan, cyclophosphamide, etoposide with or without anti-thymocyte globulin are similar to those who received other regimens except, T-cell depleted bone marrow grafts were more frequent with the later regimens. Despite the apparent activity for busulfan, cyclophosphamide, etoposide with or without anti-thymocyte globulin regimen in controlling disease we found transplant-related mortality rates to be extraordinarily high at 35% with most events occurring early after transplantation (within the first 100 days). The high transplant-related mortality rate associated with transplantation for this disease has been reported by others and has been reported after standard and reduced intensity-conditioning regimens.[7,15,16,20] The reason for higher transplant-related mortality is unclear, but may be explained in part by factors related to the disease itself. VOD was reported in 18% of cases, a higher incidence than reported for most other diseases. At the onset of the disease, the majority of HLH patients have hepatic involvement with evidence of lymphohistiocytic infiltrates in the portal regions and endothelial cell abnormalities.[21] Whether any of these abnormalities persist and/or predispose these patients to VOD is unknown since liver biopsies are rarely undertaken in these patients as part of their evaluation prior to HCT. The other causes of TRM in these patients are not unusual after URD HCT, but may occur more frequently. Whether this is related to the underlying pro-inflammatory state associated with HLH is unknown, particularly in patients whose diseases are in a quiescent state at the time of HCT.

As transplantations occurred over a decade earlier changes in donor-selection and supportive care practices occurred even though we were not able to show a difference in mortality rate over time. This is most likely due to limited patient numbers even though this is the largest series undergoing unrelated donor transplantation to date for this disease.

The use of a reduced intensity-conditioning regimen for this disease may be a potential way to reduce the high early transplant-related mortality. The first report of a small case series utilizing this approach was published recently.[20] Twelve patients with significant pre-existing co-morbidity received a regimen of fludarabine, melphalan and alemtuzumab or antithymocyte globulin. Nine out of 12 patients (75%) were alive in complete remission at a median of 30 months. Though no patient rejected their graft or had recurrent symptoms of HLH, three of nine patients show mixed donor-recipient chimerism leading to concerns regarding the level of stable donor chimerism that can be achieved with this approach and whether mixed chimerism will ultimately result in recurrent disease. With longer follow-up, others have reported recurrence of disease warranting a second allogeneic HCT when donor chimerism levels are less than 10–20%.[14] In this report, donor chimerism was 100% in the majority of patients with extended follow-up for whom this data was available.

The majority of patients with HLH will require an alternative donor source of hematopoietic stem cells for transplantation. In this series donor-recipient HLA match as determined by allele-level typing resulted in higher overall survival rates though the level of statistical significance was marginal. Our numbers are small and may have limited our ability to detect a statistically significant difference. However, larger studies in unrelated donor transplantation clearly demonstrate the negative effect of HLA mismatch on overall survival.[22] Therefore, matching between recipient and donor using allele-level HLA typing at HLA A, B, C and DRB1 represents the current standard of care and donor selection should be determined by the results of these larger studies.[22] Further, the current standards used for donor selection may lower the high rates acute and chronic GVHD and consequently lower morbidity and mortality secondary to GVHD-related complications.

The current report while subject to the limitations of utilizing data available through a large observational database, nevertheless highlight the challenges of URD transplantation for this disease as well as a modest success in long-term survival rates for an otherwise fatal disease in patients who lack an HLA-matched sibling. The successful utilization of mismatched umbilical cord blood grafts increases access to HCT for patients who lack a matched related or matched unrelated donor. Disease status at HCT appears to be the most important disease-specific prognostic indicator and larger studies will be required to examine the impact of other disease-specific markers such as ferritin or sIL-2R levels or of specific genetic subtypes of HLH. In similar fashion, such studies should collect lineage-specific chimerism data as it will be important to determine the impact of T cell engraftment as compared to whole blood or bone marrow particularly as the use of reduced intensity conditioning regimens are increasingly considered in this disease.

Acknowledgements

The CIBMTR is supported by Public Health Service Grant U24-CA76518 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute; Office of Naval Research; Health Resources and Services Administration (DHHS); and grants from AABB; Aetna; American International Group Inc.; American Society for Blood and Marrow Transplantation; Amgen Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US Inc.; Baxter International Inc.; Bayer HealthCare Pharmaceuticals; BioOne Corporation; BloodCenter of Wisconsin; Blue Cross and Blue Shield Association; Bone Marrow Foundation; Bristol-Myers Squibb Company; Cangene Corporation; Celgene Corporation; CellGenix, GmbH; Cerus Corporation; Cubist Pharmaceuticals; Cylex Inc.; CytoTherm; DOR BioPharma Inc.; Dynal Biotech, an Invitrogen Company; EKR Therapeutics; Enzon Pharmaceuticals Inc.; Gambro BCT Inc.; Gamida Cell, Ltd.; Genzyme Corporation; Gift of Life Bone Marrow Foundation; GlaxoSmithKline Inc.; Histogenetics Inc.; HKS Medical Information Systems; Hospira Inc.; Infectious Diseases Society of America; Kiadis Pharma; Kirin Brewery Co., Ltd.; Merck & Company; The Medical College of Wisconsin; MGI Pharma Inc.; Millennium Pharmaceuticals Inc.; Miller Pharmacal Group; Milliman USA Inc.; Miltenyi Biotec Inc.; MultiPlan Inc.; National Marrow Donor Program; Nature Publishing Group; Oncology Nursing Society; Osiris Therapeutics Inc.; Pall Life Sciences; PDL BioPharma Inc; Pfizer Inc; Pharmion Corporation; Roche Laboratories; Schering Plough Corporation; Society for Healthcare Epidemiology of America; StemCyte, Inc.; StemSoft Software, Inc.; SuperGen, Inc.; Sysmex; Teva Pharmaceutical Industries; The Marrow Foundation; THERAKOS Inc.; University of Colorado Cord Blood Bank; ViaCell Inc.; Vidacare Corporation; ViraCor Laboratories; ViroPharma Inc.; and Wellpoint Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, or any other agency of the US Government.

References

1 Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; **48**: 124–131.
2 Ueda I, Ishii E, Morimoto A, Ohga S, Sako M, Imashuku S. Correlation between phenotypic heterogeneity and gene mutational characteristics in familial hemophagocytic lymphohistiocytosis (FHL). *Pediatr Blood Cancer* 2006; **46**: 482–488.
3 Stepp SE, Dufourcq-Lagelouse R, Le Deist F, Bhawan S, Certain S, Mathew PA *et al*. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. *Science* 1999; **286**: 1957–1959.
4 Feldmann J, Callebaut I, Raposo G, Certain S, Bacq D, Dumont C *et al*. Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). *Cell* 2003; **115**: 461–473.
5 Rudd E, Goransdotter Ericson K, Zheng C, Uysal Z, Ozkan A, Gurgey A *et al*. Spectrum and clinical implications of syntaxin 11 gene mutations in familial haemophagocytic lymphohistiocytosis: association with disease-free remissions and haematopoietic malignancies. *J Med Genet* 2006; **43**: e14.
6 Arico M, Janka G, Fischer A, Henter JI, Blanche S, Elinder G *et al*. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. *Leukemia* 1996; **10**: 197–203.
7 Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, Filipovich AH *et al*. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002; **100**: 2367–2373.
8 Farag SS, Bacigalupo A, Eapen M, Hurley C, Dupont B, Caligiuri MA *et al*. The effect of KIR ligand incompatibility on the outcome of unrelated donor transplantation: a report from the center for international blood and marrow transplant research, the European blood and marrow transplant registry, and the Dutch registry. *Biol Blood Marrow Transplant* 2006; **12**: 876–884.
9 Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J *et al*. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995; **15**: 825–828.
10 Klein J, Moeschberger M. *Survival Analysis: Techniques of Censored and Truncated Data*, 2nd edn. Springer Verlag: New York, NY, 2003.
11 Cox DR. Regression models and life-tables. *J Royal Stat Soc* 1972; **34**: 187–202.
12 Henter JI, Arico M, Egeler RM, Elinder G, Favara BE, Filipovich AH *et al*. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. *Med Pediatr Oncol* 1997; **28**: 342–347.
13 Baker KS, DeLaat CA, Steinbuch M, Gross TG, Shapiro RS, Loechelt B *et al*. Successful correction of hemophagocytic lymphohistiocytosis with related or unrelated bone marrow transplantation. *Blood* 1997; **89**: 3857–3863.
14 Ouachee-Chardin M, Elie C, de Saint Basile G, Le Deist F, Mahlaoui N, Picard C *et al*. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. *Pediatrics* 2006; **117**: e743–e750.
15 Blanche S, Caniglia M, Girault D, Landman J, Griscelli C, Fischer A. Treatment of hemophagocytic lymphohistiocytosis with chemotherapy and bone marrow transplantation: a single-center study of 22 cases. *Blood* 1991; **78**: 51–54.
16 Adachi S, Kubota M, Akiyama Y, Kato T, Kitoh T, Furusho K. Successful bone marrow transplantation from an HLA-identical unrelated donor in a patient with hemophagocytic lymphohistiocytosis. *Bone Marrow Transplant* 1997; **19**: 183–185.
17 Chan KW, Mullen CA, Korbling M. Allogeneic peripheral blood stem cell transplantation for active hemophagocytic lymphohistiocytosis. *Bone Marrow Transplant* 1998; **22**: 301–302.
18 Jacobsohn DA. Acute graft-versus-host disease in children. *Bone Marrow Transplant* 2008; **41**: 215–221.
19 Zecca M, Prete A, Rondelli R, Lanino E, Balduzzi A, Messina C *et al*. Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. *Blood* 2002; **100**: 1192–1200.
20 Cooper N, Rao K, Gilmour K, Hadad L, Adams S, Cale C *et al*. Stem cell transplantation with reduced-intensity conditioning for hemophagocytic lymphohistiocytosis. *Blood* 2006; **107**: 1233–1236.
21 Favara BE. Hemophagocytic lymphohistiocytosis: a hemophagocytic syndrome. *Semin Diagn Pathol* 1992; **9**: 63–74.
22 Lee SJ, Klein J, Haagenson M, Baxter-Lowe LA, Confer DL, Eapen M *et al*. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood* 2007; **110**: 4576–4583.