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ARTICLE

Hematopoietic Stem Cell Transplantation in Hemophagocytic Lymphohistiocytosis: A Single-Center Report of 48 Patients

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ABSTRACT

OBJECTIVES. Familial hemophagocytic lymphohistiocytosis (FHLH) is a genetically determined disorder characterized by the early onset of fever, hepatosplenomegaly, central nervous system disease, thrombocytopenia, coagulation disorders, and hemophagocytosis. It is caused by genetic defects that impair T cell–mediated and natural cytotoxicity. Chemotherapy- or immunotherapy-based treatments can achieve remission. Hematopoietic stem cell transplantation (HSCT), however, is the only curative option, but optimal modalities and long-term outcome are not yet well known.

METHODS. We retrospectively analyzed the outcome of HSCT that was performed in 48 consecutive patients who had FHLH and were treated in a single center between 1982 and 2004.

RESULTS. The overall survival was 58.5% with a median follow-up of 5.8 years and extending to 20 years. A combination of active disease and haploidentical HSCT had a poor prognosis because in this situation, HLH disease is more frequently associated with graft failure. Twelve patients received 2 transplants because of graft failure ($n = 7$) or secondary graft loss that led to HLH relapse ($n = 5$). Transplant-related toxicity essentially consisted in veno-occlusive disease, which occurred in 28% of transplants and was associated with young age, haploidentical transplantation, and the use of antithymocyte globulin (ATG) in the conditioning regimen. A sustained remission was achieved in all patients with a donor chimerism ≥20% of leukocytes. Long-term sequelae were limited, because only 2 (7%) of 28 patients experienced a mild neurologic disorder.

CONCLUSIONS . This survey demonstrates the long-term efficacy of HSCT as a cure of FHLH. HSCT preserves quality of life. It shows that HSCT should be performed as early as a complete remission has been achieved. Additional studies are required to improve the procedure and reduce its toxic effects.

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Key Words
hemophagocytic lymphohistiocytosis, allogeneic hematopoietic stem cell transplantation, chimerism, veno-occlusive disease

Abbreviations
HLH— hemophagocytosis lymphohistiocytosis
FHLH—familial HLH
CNS— central nervous system
ATG—antithymocyte globulins
HSCT— hematopoietic stem cell transplantation
CR— complete remission
URD— unrelated donor
PR—partial remission
AD—active disease
MSD—matched sibling donor
TCD—T cell depleted
GVHD— graft-versus-host disease
VOD—veno-occlusive disease
PHTN—pulmonary hypertension
TRM—transplant-related mortality

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HEMOPHAGOCYTOSIS LYMPHOHISTIOCYTOSIS (HLH) is a rare disorder that can be genetically determined.[1,2] Mutations in perforin-, Munc 13-4–, and more recently Syntaxin-11–encoding genes have been shown to result in HLH.[3–5] X-linked proliferative syndrome can also result in HLH.[6] Familial HLH (FHLH) is an unremitting disease with a usually early onset.[1,2] It is characterized by the infiltration of various organs, including the central nervous system (CNS), by activated polyclonal CD8 T lymphocytes and activated macrophages.[7,8] Hypercytokinemia is a hallmark of the disease.[9,10] The recent description of an animal model of HLH in perforin knockout mice that were infected with the lymphocytic choriomeningitis virus has clearly determined the central role of CD8 T cell activation, γ-interferon production, and secondary macrophage activation in the disease pathogenesis.[11] All genetic disorders that are associated with FHLH lead to a profound impairment of lymphocyte cytolytic activity.[3–5,7,12,13] It is thought, therefore, that persisting CD8 T-cell activation is either directly or indirectly a consequence of the cytolytic activity deficiency.[7]

FHLH is fatal in the absence of therapy. Remission can be achieved by using a chemotherapy-based regimen with etoposide (VP-16)[14–17] combined with corticosteroids and intrathecal methotrexate. In light of the pathophysiology of FHLH, a immunotherapy that consists of antithymocyte globulins (ATG) combined with corticosteroids and cyclosporin A for maintenance therapy (plus intrathecal methotrexate) also has been proposed.[18] However, the disease eventually relapses in all patients, ultimately leading to death. This is why allogeneic hematopoietic stem cell transplantation (HSCT) has been attempted to cure the condition. Several reports from individual centers[19–28] as well as an international study group[17,29] have shown that HSCT can lead to a control of FHLH manifestations. It is still unclear, however, what is the best regimen to treat patients with FHLH; questions such as the optimal interval between initial therapy and HSCT, conditioning regimen, whether to achieve a complete remission (CR) at HSCT, influence of type of genetic disease, and long-term outcome have not been addressed. Given the rarity of the disease, any advances will still require long and careful assessment of the patients who receive a transplant. In this report, we present the results of the outcome of HSCT for a cohort of 48 patients who were treated in the same center during a 22-year period.

MATERIALS

Patients

Between May 1982 and March 2004, 67 patients received a diagnosis of HLH at Necker-Enfants Malades Hospital, Paris. Forty-eight of these 67 patients received an HSCT from a related donor or an unrelated donor (URD; Table 1). Seventeen of the 19 other patients died; 2 were alive with active HLH at time of this report. Criteria that were used for HLH diagnosis were those of the Histiocyte Society.[30] CNS involvement was determined by clinical examination, cerebrospinal fluid analysis (pleocytosis), and neuroradiologic studies.[31] A retrospective analysis of the outcome of HSCT was performed. Endpoint for analysis was November 1, 2004.

In 27 (56%) of 48 patients, a comprehensive study of the known genetic defects that are associated with FHLH was performed. Biallelic mutations of the perforin gene[3] were found in 7 children, mutations of the Munc 13-4 gene[4] were found in 11, and mutations of the syntaxin-11[5] gene were found in 1; no mutations in these genes were found in 8 cases. Mutations in the SH2D1A/SAP gene[6] associated with X-linked lymphoproliferative syndrome were excluded in boys. In 14 additional children, a diagnosis of FHLH was made on the basis of a positive family history and/or the presence of parental consanguinity. Altogether, FHLH was diagnosed in 33 (69%) children. An inherited defect was suggested in the 15 (31%) other children because of disease severity and

TABLE 1 Patients Characteristics

Gender ratio (F/M)	18/30
Median age at diagnosis, mo (range)	3 (1 d–18 y)
Consanguinity, *n* (%)	15 (31)
Family history, *n* (%)	17 (35)
Genetic studies, *n* (%)	27 (56)
Perforin	7
Munc 13-4	11
Syntaxin-11	1
No mutations found	8
Incomplete genetic studies, %	21 (44)
Proven familial HLH, %	33 (69)
Neurologic involvement at diagnosis, *n* (%)	30 (62)
Neurologic involvement before HSCT, *n* (%)	38 (80)
Median age at HSCT, mo (range), y	6 (1–19.5)
Median time from diagnosis to HSCT, mo (range), y	3.5 (1–11)
Pre-HSCT therapy *n* (%)	
Chemotherapy	15 (31)
Immunotherapy with ATG	26 (54)
Immunotherapy without ATG	7 (15)
Status at HSCT, *n* (%)	
CR	27 (56)
PR	16 (34)
AD	5 (10)
Conditioning regimen, *n* (%)	
VP 16 + Bu + Cy	19 (40)
ATG + Bu + Cy	26 (54)
Others	3 (6)
Donor type, *n* (%)	
MSD	14 (30)
Haploidentical	29 (60)
URD	5 (10)
Year of HSCT (%)	
1982–1989	9 (19)
1990–1997	17 (35)
1998–2004	22 (46)

Bu indicates busulfan; Cy, cyclophosphamide.

occurrence of relapses without evidence of secondary HLH disease.

Primary treatment of HLH differed in time. Between 1982 and 1991, 15 (31%) children received a chemotherapy regimen before HSCT based on VP-16 combined with corticosteroids, cyclosporin A, and intrathecal methotrexate.[15] From 1991 to 2004, 33 (69%) children received an immunotherapy regimen that consisted of corticosteroids and cyclosporin A associated with (n = 26) ATG[18] or not (n = 7), according to disease severity. All patients received intrathecal methotrexate.

A CR was defined by a complete disappearance of clinical and biological manifestations of HLH; a partial remission (PR) was defined by a significant improvement but with persisting clinical and/or biological manifestations. Clinical manifestations included fever, hepatosplenomegaly, neurologic symptoms, biological manifestations, and bleedings. Biological manifestations included cytopenia, hypertriglyceridemia, hypofibrinogenemia, hypoferritinemia, high liver enzymes, detection of HLADR+/CD8+ T cells in blood, and an excess of cells in cerebrospinal fluid. As shown in Table 1, pre-HSCT therapy at time of HSCT led to a CR in 27 (56%) patients and a PR in 16 (34%), whereas a fully active disease (AD) was present in 5. Indications for HSCT were either diagnosis of FHLH (n = 33) or disease recurrence under maintenance therapy or refractory HLH (n = 15).

HSCT Procedures

Fourteen (30%) patients received an HSCT from a matched sibling donor (MSD). In 1 case, it was later recognized that the donor also had FHLH. Four patients received a transplant from a fully matched URD, 1 from a 2-antigen-mismatched URD and 29 (60%) from a family haploidentical donor (Table 1). The decision to perform a haploidentical HSCT was made when a suitable URD was not made available within a 3-month search period. A total of 60 transplants were performed. Twelve (25%) children received a second HSCT because of primary graft failure (n = 7) or secondary graft rejection (n = 5). These 5 patients received an additional course of immunotherapy before undergoing a second HSCT.

The conditioning regimen for the first HSCT was VP-16 (900 mg/m^2 total dose), busulfan (20 mg/kg or 16 mg/kg total dose according to age), and cyclophosphamide (200 mg/kg total dose) in 19 (40%) patients. Twenty-six (54%) patients received a combination of rabbit ATG (IMTIX-Sangstat, Lyon, France; 50 mg/kg), busulfan (16 or 20 mg/kg according to age), and cyclophosphamide (200 mg/kg). Three (6%) patients received another conditioning regimen,[19] attenuated in 2 because of a critical condition. Ten of 12 patients who received a second HSCT were given a conditioning regimen that consisted in VP16, busulfan, and cyclophosphamide in 1 and ATG, busulfan, and cyclophosphamide in 8 and attenuated in 1. Bone marrow was the source of hematopoietic stem cells in 53 (88%) transplants and peripheral blood stem cells were the source in 7.

All patients with an MSD received T-repleted grafts, cyclosporin A for 6 months, and a short course of methotrexate (10 mg/m^2 on days 1, 3, 6, and 11). Transplants from a URD or a haploidentical donor were T-cell depleted (TCD) by E-rosetting (n = 8) or monoclonal anti–T cell antibodies (n = 3) up to 1996, then by positive CD34(+) selection using the Clinimacs system (n = 22). Between 1990 and 1996, 11 recipients (15 transplants) of URD or haploidentical HSCT received injections of anti–LFA-1 and anti-CD2 antibodies in an attempt to prevent graft failure.[24] Eleven second transplants were TCD by E-rosetting (n = 2), monoclonal antibodies (n = 2), or CD34 cell selection (n = 7).

The median number of nucleated cells that were injected in non-TCD HSCT procedures was 6×10^8/kg (range: 0.3–17.9). The median number of nucleated cells that were injected in TCD HSCT (after E-rosetting or use of anti–T cell antibody) was 1.4×10^8/kg (range: 0.4–9.0). The median number of CD34(+) cells that were injected in CD34 selected HSCT procedures was 8.5×10^6/kg (range: 1.9–54.0).

Antimicrobial prophylaxis during the transplantation period consisted of gut decontamination with nonabsorbable antibiotics, acyclovir (750 mg/m^2 or 1500 mg/m^2) for herpes simplex virus, or cytomegalovirus prophylaxis from day −1 to day 60. All patients received intravenous immunoglobin and were placed in a sterile isolator. All patients received parental nutrition through a central line. They received appropriate anti-infectious therapy.

Myeloid engraftment was confirmed on the finding of 3 consecutive days of absolute neutrophil counts $>0.5 \times 10^9$/L. Platelet recovery was defined by the day at which platelet counts were $>20 \times 10^9$/L without transfusion for 5 days. Patients who died in the first 4 weeks of HSCT were considered as nonassessable for engraftment (n = 4). Chimerism was assessed on whole blood and, in case of mixed chimerism, on positively selected CD3(+) T cells, negatively selected CD3(−) mononuclear cells, and buffy-coat isolated cells by using variable nucleotides tandem repeats markers analysis and additionally X and Y chromosome–specific probes in fluorescence in situ hybridization in case of gender mismatch combination. Mixed chimerism was defined by the presence of at least 5% host-derived cells in blood leukocytes.

Graft-versus-host disease (GVHD) grading was performed according to a published method[32] and confirmed whenever possible by appropriate histologic studies. The diagnosis of hepatic veno-occlusive disease (VOD) and pulmonary hypertension (PHTN) was defined according to published criteria.[33,34] After HSCT, patients were investigated on a yearly basis at the outpatient department. Clinical examination, biological tests of HLH activity, and chimerism analysis were per-

formed. Neuroradiologic studies were repeated at least once after HSCT, more often when appropriate. Neuropsychological performances and school attendance were recorded.

Statistical Analyses

All statistical analyses were performed using R software package.[35] The relationships between categorical variables were tested using the χ^2 test or Fisher's exact test, when appropriate. The relationships between continuous and categorical variables were tested using the Student's *t* test or the Wilcoxon's signed rank test, when appropriate. Follow-up time was measured from the date of transplantation to the date of death or, if the latter was unknown, the time of last follow-up. Patients who were alive at last follow-up were censored. Survival curves were derived from Kaplan-Meier estimates.[36] The log-rank test was used to compare survival distributions between the subgroups. Statistical significance was considered at $P < .05$, and all tests were 2 tailed.

RESULTS

Engraftment

The 48 patients received a total of 60 transplants. Engraftment occurred in 42 of the attempts, failed in 14, and was not assessable in 4 because of early death after HSCT. As shown in Table 2, the first HSCT attempt led to engraftment in 35 (78%) of 45 assessable patients. Seven of 10 patients with primary failure received a second transplant. Engraftment was achieved in 2 of 6 assessable patients. Secondary loss of engraftment occurred in 5. All 5 received successful second transplants. HLH activity at time of HSCT ($P = .003$) and older age at HSCT ($P = .003$) were associated with primary graft failure (Table 2). Nevertheless, a nonsignificant trend was found, suggesting a possible role in graft failure of a longer interval between diagnosis and HSCT, pre-HSCT treatment of HLH by chemotherapy regimen, and haploincompatibility with donor.

It is interesting that when the possible influence of donor incompatibility was examined in the subgroup of patients in who were CR at first HSCT, it was found that donor incompatibility had no influence because engraftment occurred in 10 (91%) of 11 assessable recipients of HSCT from MSD or URD and in 12 (92%) of 13 assessable recipients of HSCT from haploidentical donors. In contrast, when patients were not in CR at time of HSCT ($n = 21$), incompatibility was possibly influential because engraftment occurred in 7 (88%) of 8 recipients of HSCT from MSD or URD versus 6 (46%) of 13 recipients of HSCT from haploidentical donors. A confirmed, as opposed to suspected, diagnosis of FHLH did not influence engraftment rate (Table 2).

Secondary graft loss occurred in 5 patients 8 to 15 months after HSCT. Four had a transplant from a haploidentical donor and 1 had a transplant from a partially mismatched URD. Graft loss was associated with relapses of HLH manifestations. Immunotherapy with ATG led to a CR in 3 and PR in 2. Remarkably, engraftment occurred in all 5 after a second HSCT. HSCT was performed 8 to 44 months after the first (median: 13 months) using either another haploidentical donor ($n = 4$) or a matched URD ($n = 1$). No clear-cut associations between secondary graft failure and pre-HSCT or HSCT characteristics could be found, apart from donor incompatibility.

HSCT-Related Toxicity

The complications of HSCT are listed in Table 3. VOD was a significant complication; it occurred on 17 occa-

TABLE 2 **Engraftment**

	First HSCT ($N = 48$)		Second HSCT ($N = 12$)	
	n	(%)	*n*	(%)
Assessable for engraftment	45	35 (78)	11	7 (64)
Age at diagnosis, mo				
<3	19	17 (90)	2	2 (100)
3–12	12	9 (75)	5	3 (60)
>12	14	9 (64)	4	2 (50)
FHLH proved	31	23 (74)	9	6 (67)
FHLH not proved	14	12 (86)	2	1 (50)
Time from diagnosis to HSCT, mo				
<3	17	16 (89)	0	
3–6	13	10 (77)	1	1 (100)
>6	15	9 (60)	10	6 (60)
Age at HSCT, mo				
<6	21	19 (90)	0	
6–12	5	5 (100)	1	1 (100)
>12	19	11 (58)	10	6 (60)
Pre-HSCT treatment				
Immunotherapy	32	27 (84)	8	5 (63)
Chemotherapy	13	8 (61)	3	2 (67)
Status at HSCT				
CR	24	22 (92)	5	4 (80)
PR + AD	21	13 (62)	6	3 (50)
HSCT donor				
MSD	13	11 (85)	1	0 (0)
URD	5	5 (100)	1	1 (100)
Haploidentical	27	19 (70)	9	6 (67)

Twelve patients underwent a second HSCT, 7 after primary failure of the graft.

TABLE 3 **Transplant-Related Complications**

	All HSCT ($n = 60$)	First HSCT ($n = 48$)	Second HSCT ($n = 12$)
VOD, *n* (%)	17 (28)	14 (29)	3 (25)
PHTN, *n* (%)	3 (5)	1 (2)	2 (17)
Significant infections, *n* (%)	36 (60)	29 (60)	7 (58)
Virus	19 (32)	16 (33)	3 (25)
Fungus	9 (15)	8 (17)	1 (8)
Bacterium	8 (13)	5 (11)	3 (25)
Acute GVHD ≥ II%	$n = 42$ 7 (17)	$n = 35$ 6 (17)	$n = 7$ 1 (14)
Chronic GVHD, %	$n = 33$ 3 (9)	$n = 31$ 2 (6)	$n = 7$ 1 (14)

sions (28% of transplants), causing the death in 3 of 15 affected patients. Of note, VOD occurred more frequently after haploidentical HSCT (45%) than after MSD or URD transplants (10%; $P = .024$). Age at HSCT also had an influence; 13 (44%) of 29 patients who were younger than 12 months at first HSCT developed a VOD compared with 2 (10%) of 19 who were older than 1 year ($P = .034$). VOD occurred more frequently in patients who received ATG in the conditioning regimen: 50% as opposed to 10% in those who did not ($P = .008$). The independence of these risk factors could not be assessed because of the size of the study populations. No association of VOD with disease status at HSCT could be found. PHTN occurred in 3 cases, being fatal in 1. Significant infections occurred in 36 (60%) cases. Viral infections were found in 19 of 60 transplants, including 8 cytomegalovirus infections. Infections were the primary cause of death in 5 patients. A remarkable observation was the low frequency of GVHD (Table 3). Acute GVHD, grade 2 or higher, occurred in only 7 (17%) cases, with 2 cases of grade 3 GVHD. Chronic GVHD occurred in only 3 (9%) cases, a particularly low incidence.

Survival

The overall event-free survival rate was 58.5%, with a median follow-up of 5.8 years (Fig 1A). It extends to 20 years in the first successfully treated patient.[19] As shown in Fig 1, donor compatibility had no significant impact on survival (Fig 1B), whereas disease control at HSCT probably had an influence ($P = .053$; Fig 1C). By combining compatibility and disease control status, it was found that HSCT from MSD or URD had a better prognosis than HSCT from a haploidentical donor only when HLH disease was active at HSCT ($P = .03$; Fig 1D). There is a trend toward improvement: the survival of patients who were treated in 1992 and after was 62% versus 41% in those who were treated before that year ($P = .2$). Age at diagnosis, interval between diagnosis and HSCT, and confirmed diagnosis of FHLH had no significant influence on survival (data not shown). The presence of CNS disease had no influence. There was, however, a trend toward a poorer prognosis of HSCT for patients with clinical neurologic manifestations and abnormal neuroimagery features before HSCT: 5 (36%) of 14 survived compared with 15 (62%) of 24 with pleocytosis in the cerebrospinal fluid only.

The causes of death were mostly related to HLH disease; it was the primary cause in 10 (50%) of 20 cases. This reflects the influence of HLH disease control on engraftment at HSCT. AD impairs engraftment and may be fatal. Transplant-related mortality (TRM) was more frequent in HSCT that was performed in CR (5 of 7 deaths) and accounted for 5 of 13 deaths of those who received a transplant during AD, suggesting that AD at HSCT does not predispose to a higher TRM.

HLH Disease Control and Sequelae

HSCT resulted in a sustained full chimerism in 14 of the long-term survivors and a mixed chimerism in 14.

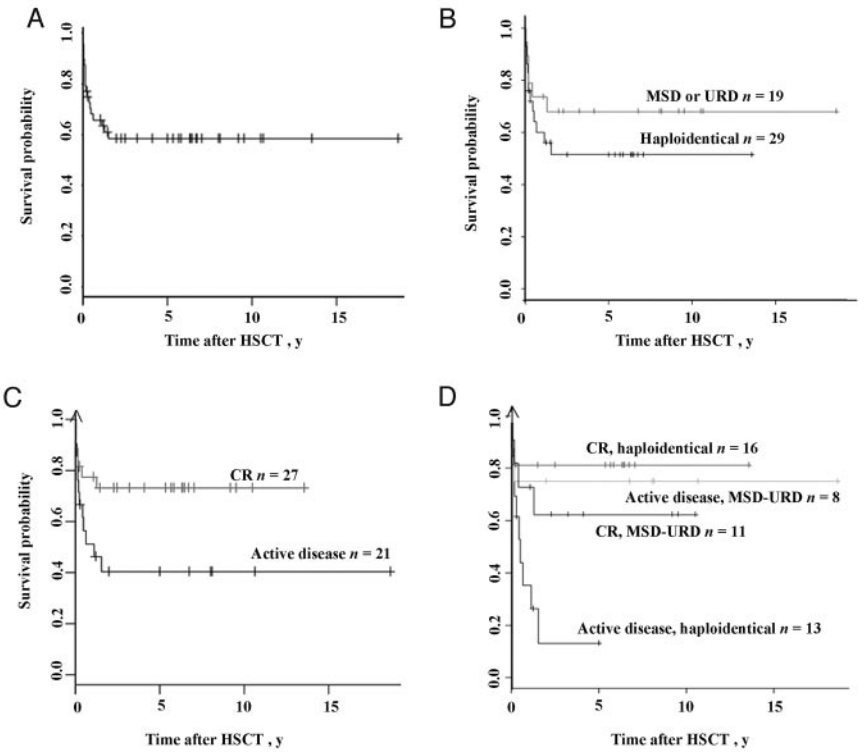

FIGURE 1
Survival of patients with HLH after HSCT. A, Overall survival ($n = 48$) calculated from the time of the first attempts at HSCT. B, Survival according to donor origin. Because of low numbers and similar data, patients who received a transplant with an MSD and a URD have been grouped together ($P = .3$, log-rank test). C, Survival related to status of HLH at HSCT (CR versus AD; $P = .053$ log-rank test). D, Survival according to a combination of donor compatibility and disease activity (for patients with AD, MSD-URD versus haploidentical HSCT $P = .03$ log-rank test, for patients in CR $P = .39$ log-rank test).

Mixed chimerism ≥50% was detected in 6 (43%), between 20% and 50% in 7 (50%), and <20% in 1 (6%). Chimerism was found to be stable over time in these 28 patients (data not shown). It thus turned out that a mixed chimerism >10% to 20% was associated with stable CR in the absence of treatment for up to 20 years. Below this threshold, as observed in the 5 secondary graft rejection cases, HLH symptoms reappeared. Mild HLH-related sequelae were noted in 2 patients with severe CNS disease. They consisted of a mild spastic diplegia in 1 and a slight delay in cognitive development in the other. Altogether, it is remarkable that only 2 (10%) of 21 patients with neurologic HLH disease detected before HSCT had sequelae. In all others, a normal cognitive development has been observed with normal school performances. No other sequelae have been observed within a follow-up now reaching 20 years.

DISCUSSION

We report herein on the largest cohort of patients who had HLH and underwent HSCT treatment in a single center. A long follow-up, over a 20-year period after HSCT, enabled us to determine that HSCT is a curative treatment of FHLH, because donor chimerism >20% was always associated with a stable and complete remission. The overall survival was 58.5%, very comparable to the results of the HLH 94 protocol with a 3-year survival rate of 62% ($n = 65$) for patients who received a transplant between 1994 and 2001[17] and 64% ($n = 86$) in patients who received a transplant between 1995 and 2000.[29] As previously suggested, the major risk factor for HSCT failure and death is AD at HSCT.[23,29] This factor is more important than donor compatibility, although, remarkably, a combination of disease activity at HSCT with haploincompatibility led to a very poor prognosis (Fig 1D). It is conceivable that AD hampers donor cell engraftment because cytokines, such as γ-interferon, which is markedly produced in HLH,[9] exerts an inhibitory effect on hematopoiesis.[37] Other cytokines, such as tumor necrosis factor-α and hemophagocytosis by activated macrophages, could also play a role, as well as bone marrow infiltration by activated T lymphocytes and macrophages. It is also possible that the survival advantage of abnormal T (+/− NK) cells may result sometimes in secondary graft rejection. No other factor apart from donor incompatibility has been identified in secondary graft rejection. As previously suggested in reports of smaller series,[23–28] these results firmly establish that HSCT should be performed as early as feasible, whatever donors are available, provided that a CR has been achieved. All efforts therefore should be made to obtain CR in patients who lack an HLA identical donor. Aggressive immunotherapy with anti–T cell antibodies and chemotherapy with VP-16 are the currently recognized options to achieve remission.

TRM is a significant issue, because VOD and, to a lesser extent, PHTN were frequently observed. A young age seems to be a significant risk factor. This observation confirms what has been observed in patients who receive a transplant early in life for malignant osteopetrosis.[38] It is interesting that disease activity that is associated with hypercytokinemia does not influence the risk for VOD. In contrast, the use of high-dose ATG in the conditioning regimen seems to predispose to VOD. It was used preferentially, however, in haploidentical transplants, for which VOD was more frequently observed. These factors cannot also be distinguished from age. Additional studies therefore are warranted to analyze their respective contributions.

Another observation was the uncommon character of GVHD, which had not been noticed in previous reports.[17,19,28,29] It could be related to the high rate of observed mixed chimerism and perhaps the persisting post-HSCT immunosuppression caused by intensive use of ATG after HSCT combined with the ATG's somewhat long half-life. It may be that the high incidence of viral infections observed in this study reflects the immunosuppression status.

There are at present 2 approaches to first-line therapy of HLH: 1 based on chemotherapy (VP-16), the HLH international protocol, and 1 entirely consisting of immunotherapy.[7,11] It is beyond the scope of this work to assess the respective merits of these approaches. As far as HSCT outcome is concerned, there was a trend in our series for a better prognosis for patients who received immunotherapy, but this was possibly because the immunotherapy was used later than the chemotherapy. Additional studies will be needed, possibly a comparative randomized trial, to define the best strategy. It should be noted that occurrence of acute myeloblastic leukemia/myelodysplastic syndrome in 3 patients of the HLH 94 cohort[17] has not been observed so far in patients who were treated only by a combination of immunotherapy and HSCT.

This study confirms with long-term observation that HSCT cures FHLH, despite the potentially selective survival advantage of T/NK cells, as discussed above. As long as donor T cells persist, it seems that FHLH disease is controlled, probably because the restored T/NK cytolytic activity exerts a transregulatory effect on host T cell expansion driven by an infection.[7,39] The rare occurrence of neurologic sequelae clearly indicates that once HLH is controlled, there is no additional progression of CNS lesions, thus preserving cognitive function. Given the frequency, the early onset, and the potential severity of CNS disease associated with FHLH, these findings emphasize that HSCT should be performed as soon as possible in patients with FHLH, once a remission has been achieved, when there is no matched donor.

CONCLUSION

This analysis confirms that HSCT, whatever the donor compatibility, is the treatment of choice for FHLH. It prevents relapses and CNS disease progression. However, not all the aspects of treatment strategy have been optimized. The most appropriate means to achieving the required HLH remission remains to be defined, as well as a sufficiently immunosuppressive conditioning regimen to prevent graft rejection while reducing toxicity to avoid VOD.

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