Treatment of Familial Hemophagocytic Lymphohistiocytosis With Bone Marrow Transplantation From HLA Genetically Nonidentical Donors

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Familial hemophagocytic lymphohistiocytosis (FHL) is a rare genetic disorder associated with the onset early in life of overwhelming activation of T lymphocytes and macrophages invariably leading to death. Allogeneic bone marrow transplantation (BMT) from an HLA-identical related donor is the treatment of choice in patients with this disease. However, fewer than 20% of patients have a disease-free HLA-identical sibling. BMT from HLA-nonidentical related donors has previously met with poor results, with graft rejection a major obstacle in all cases. We describe BMTs from HLA-nonidentical related donors (n = 13) and from a matched unrelated donor (n = 1) performed in two centers in 14 consecutive cases of FHL. Remission of disease was achieved before BMT in 10 patients. Marrow was T-cell–depleted to minimize graft-versus-host disease (GVHD). Antiadhesion antibodies specific for the α chain of the leukocyte function–associated antigen-1 (LFA-1, CD11a) and the CD2 molecules were infused pre-BMT and post-BMT to help prevent graft rejection, in addition to a conditioning regimen of busulfan (BU), cyclophosphamide (CP), and etoposide (VP16) or antithymocyte globulin (ATG). Sustained engraftment was obtained in 11 of 17 transplants (3 patients had 2 transplants) and disease-free survival in 9 patients with a follow-up period of 8 to 69 months (mean, 33). Acute GVHD greater than stage I was not observed, and 1 patient had mild cutaneous chronic GVHD that resolved. Toxicity due to the BMT procedure was low. Results obtained using this protocol are promising in terms of engraftment and event-free survival within the limitations of the small sample. We conclude that an immunologic approach in terms of drugs used to obtain disease remission and a conditioning regimen that includes antiadhesion molecules in T-cell–depleted BMT from HLA genetically nonidentical donors is an alternative treatment that warrants further study in FHL patients who lack a suitable HLA genetically identical donor.

FAMILIAL HEMOPHAGOCYTIC lymphohistiocytosis (FHL) is a rare inherited disorder with an unknown genetic basis. A recent study has shown an annual childhood incidence of FHL in Sweden of 1.2 cases per 100,000.[1] The disease occurs during infancy or early childhood and is associated with fever, edema, and hepatosplenomegaly accompanied by pancytopenia, hypertriglyceridemia, and hypofibrinogenemia with histologic evidence of hemophagocytosis.[2-4] Central nervous system (CNS) involvement is frequent, with symptoms ranging from confusion to severe seizures and neurologic impairment.[5-7] Both sporadic and familial forms are reported, and an autosomal recessive mode of transmission is suggested.[8]

The use of cytotoxic therapy with etoposide (VP16) or other chemotherapeutic drugs has achieved remissions in this invariably fatal disease.[9-11] Steroid treatment and the use of intrathecal methotrexate injections also help transiently to treat and/or prevent the frequent neurocerebral involvement.[6] However, chemotherapy is sometimes ineffective in treatment of the primary disease and frequently fails to control relapses.[12] It is also toxic and may be fatal.[13] On the basis of evidence that T cells play a key role in the disease, an alternative primary and maintenance therapy using immunosuppressive agents was proposed.[4,14] The use of antithymocyte globulins (ATGs) and steroids followed by Cyclosporin A (CsA) maintenance therapy combined with intrathecal methotrexate has led to disease remission for up to 2 years. However, frequent neurocerebral relapses were observed, possibly due to the poor availability of CsA within the CNS.[6] Ultimately, all patients treated with this protocol only have relapsed and died.

Allogeneic HLA-identical bone marrow transplantation (BMT) remains the only curative treatment in this disease, providing long-term remissions of up to 10 years.[13,15-17] The probability of finding a matched related disease-free sibling is low, estimated at less than 20%.[18] BMT from an unrelated donor offers another valuable therapeutic option as recently reported, given the present probability of finding a suitable donor.[19] In Necker Hospital in Paris, 40 children with the diagnosis of FHL, excluding the patients in this protocol, have been investigated. Twelve had an HLA-identical related donor and were treated with BMT. Seven of these patients are alive and well with a follow-up period of 2 to 10 years. Twenty-three children seen before 1988 had no suitable HLA-identical donor, and in the absence of BMT, they died of disease progression and/or drug toxicity within a mean of 18 months of diagnosis. Five consecutive children with no HLA-identical donor were treated with BMT from an HLA-nonidentical related donor before 1991. Conditioning consisted of busulfan (BU), cyclophosphamide (CP), and VP16 in all cases. Marrow was T-cell–depleted to prevent graft-versus-host disease (GVHD). All five children died of graft failure and subsequent disease progression within 3 months of BMT.

Experience with mismatched donors is limited and has often met with graft failure and fatal disease progression. This therapy has thus seldom been proposed as an alternative treatment in FHL. We report herein the experience of two European centers where BMT from HLA-nonidentical related donors or MUD was performed in 14 consecutive chil-

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Table 1. Clinical and Biologic Characteristics of 14 Children With FHL at Diagnosis

Characteristic	Value
Sex ratio (female/male)	5/9
Mean age at diagnosis, mo (range)	16 (2-48)
Consanguinity (n)	2
Family history (n)	5
Initial clinical presentation (n)	
Hepatosplenomegaly	14
High fever	14
Skin rash	9
Neurologic symptoms	8
Initial biologic presentation (n)	
Pancytopenia	14
Low fibrinogen level	14
Hypertriglyceridemia	14
Hyponatremia	14
Hemophagocytosis on bone marrow aspirate (n)	12
Activated peripheral T lymphocytes (HLA-$DR^+/CD3^+$)	11/11

dren with ascertained cases of FHL. To prevent graft rejection, immunotherapy with ATG, corticosteroids, and CsA was used in most cases to achieve clinical and biologic remission. In addition, on the basis of previous studies,[20-23] two monoclonal antibodies (MoAbs) directed against the leukocyte function–associated antigen-1 (LFA-1, CD11a) and CD2 adhesion molecules were used to prevent graft rejection in combination with the standard conditioning regimen.

MATERIALS AND METHODS

Fourteen consecutive patients were treated with BMT from HLA-nonidentical related donors (n = 13) or one matched unrelated donor between 1991 and 1996. BMT was performed in two European centers: 10 patients were treated at Hôpital Necker-Enfants Malades, Paris, France, and 4 patients at Wilhelmina Hospital for Sick Children, Utrecht, The Netherlands. The age at diagnosis varied from 2 months to 4 years (Table 1). In the absence of a specific marker for the disease, the diagnosis of FHL was based, as described elsewhere,[13] on (1) a positive family history in 7 cases; (2) the absence of virus-induced hemophagocytic syndrome (serum and cells from blood and/or bone marrow and/or cerebrospinal fluid were tested for cytomegalovirus and Epstein-Barr virus by serology, viral culture, or polymerase chain reaction); and (3) clinical and biologic manifestations (Table 1). Clinical or cytologic evidence of CNS involvement was found in 8 patients. Activated circulating T cells with membrane expression of HLA class II molecules were present in 11 patients studied.

Treatment of FHL before BMT consisted of several courses of VP16 and corticosteroids in patients no. 1, 3, 4, 5, 7, 9, 10, and 11 (Table 2) and ATG, corticosteroids, and CsA maintenance therapy in patients no. 2, 6, 8, 12, 13, and 14 (Table 2) as previously described.[13] Patients no. 1 and 11 had clinical and biologic signs of active disease under VP16 and corticosteroid treatment. They received a course of ATG, corticosteroids, and CsA before BMT, which resulted in disease remission in both patients. In all cases, intrathecal methotrexate was administered (6 mg for <2 years of age and 12 mg for >2 years of age) for a period determined by the severity of CNS disease (mean, six injections). Ten children were in complete remission (CR) at the time of BMT as defined by the absence for at least 1 month of clinical, biologic, and cytologic symptoms of disease activity as already described. Seven patients were in first CR, patients no. 3 and 7 were in second CR, and patient no. 1 was in third CR. Patients no. 11 to 14 had active clinical and/or biologic signs of disease including hepatosplenomegaly (patients no. 12 to 14), CNS involvement consisting of hypotonia in patient no. 11 and ataxia in patient no. 13 with bilateral cerebellar necrotic lesions visible on brain imaging in both patients, and thrombopenia and low fibrinogen levels (patients no. 12 to 14).

BMT

Donors. HLA class I typing was performed using serologic reagents and class II using serologic and molecular biology methods, as described elsewhere.[21] Donors were related HLA-nonidentical in 13 cases. A full-haplotype mismatch between donor and recipient was present in 10 cases (Table 3). In 2 cases, there was a two-antigen disparity (patients no. 4 and 5) and in one case a one-antigen disparity (patient no. 3). One patient received a transplant from a MUD (patient no. 13).

Conditioning. Eleven patients were conditioned with VP16 300 mg/m^2 on days -12, -11, and -10, BU 5 mg/kg on days -9, -8, -7, and -6, and CP 50 mg/kg on days -5, -4, -3, and -2. The 3 second transplants (Table 3, patients no. 1, 8, and 11) and 3 first transplants were performed with the same conditioning regimen except for replacement of VP16 by a 5-day course of rabbit ATG 10 mg/kg/d. BU was administered at 16 mg/kg instead of 20 mg/kg in second transplants. To further prevent graft rejection, all patients received an anti-LFA-1 antibody (25-3; Imtix, Lyon, France) administered daily from day -3 to day $+10$ after BMT and an anti-CD2 antibody (BE-2; Diaclone, Besançon, France) from day -2 to day $+11$. Both were infused at a dose of 0.2 mg/kg/d.[20-24] Seven patients who received both antibodies have already been briefly reported elsewhere[21] (patients no. 1 to 7). Both antibodies are available for use as investigational drugs only in Europe.

Prevention of GVHD

Marrow samples were T-cell–depleted using E-rosetting in 9 patients, anti-CD2 and anti-CD7 antibodies plus autologous complement in 4 patients (patients no. 6 and 11 to 13), or Campath 1-M plus autologous complement (C-1M) in one patient, as previously described[21] (Table 3). The number of T cells infused with marrow samples varied between 0.5 and 5.2×10^5/kg (mean, 1.65×10^5/kg). The total number of mononuclear cells infused per kilogram varied between 0.15 and 3.72×10^8 (mean, 0.65×10^8). All patients except for the recipient of the C-1M–depleted marrow received an additional 60-day course of CsA.

Supportive Care

Patients were placed in a sterile isolator or under laminar air flow. They received intravenous Igs weekly, gut decontamination by means of nonabsorbable antibiotics, and acyclovir if the donor or recipient was positive for cytomegalovirus.

Chimerism

HLA class I and II typing were performed on mononuclear peripheral cells as previously described.[21] In cases of sex mismatch, Y chromosome–specific probe in Southern blot analysis was additionally used.

GVHD

GVHD grading was performed according to the method of Glucksberg et al[25] and confirmed whenever possible by appropriate histologic studies.

Table 2. Patient Characteristics and Treatment Before BMT

Patient No.	Age at Onset/Sex	CNS Involvement	Treatment Before BMT	Clinical Status at BMT	Interval Between Diagnosis and BMT (mo)	Interval Between Last Remission and BMT (mo)
1	4 yr/F	+	VP16/ATG/Cs/CsA/IT MTX	CR	24	1
2	2 mo/M	+	ATG/Cs/CsA/IT MTX	CR	1	0.5
3	15 mo/M	−	VP16/Cs/CsA/IT MTX	CR	10	1
4	1 yr/F	+	VP16/Cs/CsA/IT MTX	CR	2	1.5
5	2 yr/M	−	VP16/Cs/CsA/IT MTX	CR	2	1
6	13 mo/M	+	ATG/Cs/CsA/IT MTX	CR	1	0.5
7	29 mo/M	+	ATG/Cs/CsA/IT MTX	CR	3	2
8	7 mo/F	−	ATG/Cs/CsA/IT MTX	CR	1	0.5
9	1 yr/F	−	VP16/Cs/CsA/IT MTX	CR	2	1
10	2 yr/M	+	VP16/Cs/CsA/IT MTX	CR	8	1
11	2 yr/M	+	VP16/ATG/Cs/CsA/IT MTX	CNS/low platelet count	24	1
12	4 mo/M	−	ATG/Cs/CsA/IT MTX	HSM/low platelet count	1	0.5
13	3 mo/M	+	ATG/Cs/CsA/IT MTX	HSM/CNS/low platelet count	2	1
14	4 mo/F	−	ATG/Cs/CsA/IT MTX	HSM/low platelet count	6	4

Abbreviations: HSM, hepatosplenomegaly; Cs, corticosteroids; IT MTX, intrathecal methotrexate; CsA, cyclosporine A; ATG, antithimoglobulins.

Immunologic Analysis

T-cell phenotyping was studied by immunofluorescence using the MoAbs Leu4, Leu3, Leu2, anti-CD25, and anti-DR (Becton Dickinson, Mountain View, CA) as described elsewhere.[26] Lymphocyte populations were identified by immunofluorescence staining with T- and B-cell–specific MoAbs. Mitogen, antigen (*Candida albicans*, tetanus toxin, and influenza virus), and allogeneic cell-induced lymphocyte proliferation were tested as previously described.[20] Serum Ig levels and specific antibody titers to poliovirus, tetanus, and diphtheria toxins were measured using standard serologic techniques. Natural killer activity was measured using K562 cells as targets in a ^{51}Cr-release assay.[26]

Informed Consent

The treatment protocol was approved by the institutional review board and ethics committee of both centers, and was sponsored by INSERM. The investigational nature of the treatment was explained in detail to the parents, who provided written informed consent. The end point for analysis was March 1, 1997.

RESULTS

Engraftment

Donor-cell engraftment was achieved in 11 of 17 cases (Table 3), requiring two transplants in three cases (patients no. 1, 8, and 11). For these three patients, the first BMT resulted in graft failure. Autologous reconstitution as ascertained by HLA typing of mononuclear peripheral cells on days 40 and 55, respectively, occurred in patients no. 1 and 8. Acute graft rejection was detected in patient no. 11 1 month posttransplant. All three patients had a second BMT within 45 to 80 days after the first transplant. The same

Table 3. Main Characteristics of BMTs

Patient No.	HLA Incompatibility	T-Cell Depletion Method	Conditioning Regimen	Engraftment*	GVHD	Outcome
1 First BMT	A-B-DR	E-rosetting	VP16/CP/BU	0%		
Second BMT	A-B-DR	E-rosetting	ATG/CP/BU*	Full	I	Died 3 mo, disease progression
2	A-B-DR	E-rosetting	VP16/CP/BU	Full	0	Alive and well, 69 mo+
3	B	C-1M+C	VP16/CP/BU	0%	—	Died 10 mo, disease progression
4	A-B	E-rosetting	VP16/CP/BU	Full	Mild c-GVHD	Alive and well, 57 mo+
5	A	E-rosetting	VP16/CP/BU	0%	—	Died 3 mo, aplasia
6	A-B-DR	Anti-CD2/CD7+C	VP16/CP/BU	Full	0	Alive and well, 46 mo+
7	A-B-DR	E-rosetting	VP16/CP/BU	0%	—	Died 10 mo, disease progression
8 First BMT	A-DR	E-rosetting	VP16/CP/BU	0%		
Second BMT	A-B-DR	E-rosetting	ATG/CP/BU	Full	0	Alive and well, 45 mo+
9	A-B-DR	E-rosetting	VP16/CP/BU	Full	0	Alive and well, 31 mo+
10	A-B-DR	E-rosetting	VP16/CP/BU	Full	0	Died 31 d, liver failure
11 First BMT	A-B-DR	Anti-CD2/CD7+C	VP16/CP/BU	0%		
Second BMT	A-B-DR	Anti-CD2/CD7+C	ATG/CP/BU	85%	0	Alive and well, 13 mo+
12	A-B-DR	Anti-CD2/CD7+C	ATG/CP/BU	56%	0	Alive and well, 14 mo+
13	MUD	Anti-CD2/CD7+C	ATG/CP/BU	80%	0	Alive and well, 8 mo+
14	A-B-DR	E-rosetting	ATG/CP/BU	90%	0	Alive and well, 9 mo+

Abbreviation: C, autologous complement.

* Engraftment assessed on mononuclear cells by HLA typing or Y-specific probe.

donor was used in 2 cases and the other parent in the third. No late graft rejection was reported in any of the patients who engrafted. It is noteworthy that 8 BMTs performed following the use of an immunosuppressive regimen of ATG and CsA to control or reduce disease activity all successfully engrafted (patients no. 1, 2, 6, 8, 11, 12, 13, and 14). In patients no. 3 and 7, autologous reconstitution was observed, and the patients died of progressive disease 1 year and 10 months post-BMT, respectively. A second BMT was not proposed because of the poor general clinical status of these children. Patient no. 5 died with persistent aplasia and progressive disease 3 months post-BMT.

BMT Complications

Transient acute GVHD grade I (skin rash) was observed in only one patient. Mild chronic resolutive skin GVHD was also observed in only one patient. Veno-occlusive disease was reported in patient no. 12 and spontaneously resolved. However, in another patient, it was the cause of death at day 31 (patient no. 10). Epstein-Barr virus–associated lymphoproliferative disease occurred in one case (patient no. 11). Cerebral aspergillosis was the cause of death in patient no. 1 at day 99 post-BMT. In 2 cases, interstitial pneumonia occurred at day 30 and day 37 post-BMT, respectively, resolving without identification of the etiologic agent.

Chimerism and Hematopoietic and Immune Reconstitution

Chimerism on mononuclear peripheral cells (as ascertained by HLA typing or use of the Y chromosome–specific probe) was full in 7 cases and mixed in 4 cases, varying between 56% and 90% (Table 3). Neutrophil counts greater than 500 μL were observed after a mean of 21 days, and platelet counts greater than 50,000/μL after a mean of 30 days. Normal blood cell counts were steadily observed thereafter. Lymphocyte counts above 500/μL were achieved after a mean of 70 days in 7 patients evaluated. Mitogen-induced responses were obtained in these patients after a mean of 103 days (range, 86 to 125). Antigen-specific proliferative responses developed after a mean of 6 months (range, 4 to 8) and B-cell function after a mean of 12 months in 6 assessable patients. Natural killer cell activity was tested before and after BMT in 7 children. It was profoundly decreased in all cases before BMT, and was normal within 12 months after BMT in all cases with engraftment (patients no. 2, 4, 8, 9, 11, 12, and 13).

Disease Correction and Outcome

Nine patients are alive and well with a mean follow-up period of 32 months post-BMT (range, 8 to 69; Table 3). Disease correction was observed in all patients with normal clinical and biologic status on regular evaluation. Both patients with CNS involvement had a normal physical examination at 9 months post-BMT, with normal brain magnetic resonance imaging in patient no. 11 and residual necrotic cerebellar lesions in patient no. 13. All children can probably be considered free of disease, since no late rejection or late relapses have been noted. Engraftment prevented further CNS involvement and thus irreversible neurologic sequelae. In one patient (no. 10), severe anorexia was observed post-BMT, requiring enteral nutrition for 24 months. All patients are currently alive and well with neither detectable sequelae of FHL nor toxicity related to BMT.

DISCUSSION

The results reported herein suggest that BMT from HLA genetically nonidentical donors with the proposed regimen that uses both conditioning (VP16 or ATG, CP, and BU) and MoAbs (blocking of LFA-1 and CD2 lymphocyte adhesion pathways) may yield acceptable results in the treatment of FHL patients who lack a matched related donor. Nine of 14 patients are alive and well with no evidence of disease following this procedure.

Engraftment was obtained in 11 of 14 patients after 17 transplants. This result shows that graft failure remains a significant problem. However, it can be overcome in a majority of cases without unacceptable toxicity. It is worth noting that in the three cases requiring a second transplant, no additional toxicity was observed, engraftment was obtained in all cases, and a positive outcome was observed in 2 of 3.

Severe GVHD was not observed, and the low incidence of severe infections post-BMT in a setting of slow immune reconstitution associated with T-cell depletion of marrow grafts was remarkable. However, this observation could reflect the small sample size. Long-term follow-up study showed complete correction of the disease with disappearance of clinical and/or biologic manifestations. Preexisting neurologic signs were stabilized, and no new lesions were reported.[6] In BMT from HLA-identical related donors, correction of the disease could be observed even in the presence of a small amount of donor leukocytes (as low as 10% of donor cells).[13,17] In this study, complete chimerism on mononuclear cells was obtained in 7 transplants and mixed chimerism in 4 transplants with no late graft loss. The persistence of donor cells is likely responsible for the long-term disease remission we observed.

Among this small series of patients, an examination of factors potentially associated with success of the marrow procedure indicated that the degree of HLA incompatibility between donor and recipient, method of T-cell depletion, conditioning regimen and previous treatments used to induce remission of the disease, interval between the last remission and BMT, and clinical status at BMT had no detectable influence on engraftment and survival. In contrast, it is possible that the age at onset (7 months [range, 2 to 24] in the survivor group *v* 24 months [range, 15 to 48] in the group of patients who died) and the interval between diagnosis and BMT (2 months [range, 1 to 24] in the survivor group *v* 4 months [range, 3 to 24] in the group of patients who died) may be prognostic factors. These parameters should be prospectively analyzed in further studies.

FHL in the absence of BMT is ultimately fatal.[11,12,27] All 23 patients treated exclusively with chemotherapy or immunotherapy at Necker Hospital died of toxicity and disease progression. The use of unrelated donors is still limited.[16-19,28,29] A recent report describes the efficient use of unrelated donors (matched or closely matched) as an alternative to HLA-identical siblings as donors for BMT in patients with FHL.[19]

A 44% probability of event-free survival was reported for 16 patients treated. In another report, two patients who received BMT from an unrelated donor died of grade IV GVHD and chronic bronchiolitis.[16] Although few data regarding mismatched BMT for the treatment of FHL are available, single-case reports, excluding one recently reported successful transplant infusing a high dose of $CD34^+$ cells,[30] suggest a very high incidence of graft failure, including 5 cases in our past experience. Thus, this alternative is generally not considered a suitable option. The present series indicate that BMT from partially mismatched related donors can also be an alternative treatment, since long-term disease correction has been achieved in surviving patients. It is possible that the use of ATG and CsA to obtain remission of the disease could have reduced the overwhelming lymphocyte activation[13,31] and also could have helped reduce graft rejection. Also, the use of antiadhesion molecules to prevent graft rejection (anti-LFA-1 and anti-CD2) could have further improved engraftment,[21] although it is difficult to conclude given the small number of patients studied and the relative heterogeneity of the treatments used.

Progress with all forms of alternative donor transplants for FHL is occurring.[19] We suggest that in patients with an ascertained diagnosis of FHL, following disease remission induced by ATG, CsA, and Cs exclusively and avoiding chemotherapeutic drugs, a BMT should be proposed. In the absence of a disease-free matched related sibling, BMT using an unrelated donor, if available, or a partially mismatched related donor should be considered to avoid disease progression and neurologic sequelae. It will be important to further assess the results of these alternative sources of BMT in more FHL patients.

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