Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993-2002

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CD40 ligand (CD40L) deficiency causes recurrent sinopulmonary infection, *Pneumocystis carinii* pneumonia, and *Cryptosporidium parvum* infection. Approximately 40% to 50% of patients survive to the third decade: long-term survival is unclear. Hematopoietic stem cell transplantation (HSCT) is curative. We present a retrospective analysis of 38 European patients undergoing HSCT for CD40L deficiency in 8 European countries between 1993 and 2002. Donor stem cell source included 14 HLA-identical siblings, 22 unrelated donors, and 2 phenotypically matched parental stem cells (12 T-cell depleted). Of the patients, 34 engrafted and 26 (68%) survived; 3 had autologous reconstitution, 22 (58%) were cured, and 1 engrafted but has poor T-cell immune reconstitution. There were 18 evaluated patients who responded to vaccination. Of the patients, 12 (32%) died from infection-related complications, with severe cryptosporidiosis in 6. Grades 2 to 4 graft-versus-host disease (GvHD) associated with infection occurred in 6 of 12 fatal cases. HSCT cured 58% of patients, 72% of those without hepatic disease. Early T-cell function following whole marrow HSCT may limit cryptosporidial disease, but survival was similar after T-cell–depleted HSCT. Preexisting lung damage was the most important adverse risk factor. Further studies will determine optimal timing and type of HSCT. (Blood. 2004; 103:1152-1157)

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Introduction

CD40 ligand (CD40L) deficiency (X-linked hyper–immunoglobulin M1 [HIGM1]) is a rare X-linked primary T-lymphocyte immunodeficiency caused by mutations in the gene encoding for the CD40L glycoprotein (CD154) expressed on the surface of activated T lymphocytes.[1-2] CD40 ligand interacts with the CD40 surface molecule constitutively expressed on B lymphocytes and cells of the monocyte/macrophage lineage as well as epithelial cells.[3] Interaction between CD40L/CD40 is critical in initiating the immunoglobulin isotype class switch from IgM to IgG, IgA, and IgE in B cells and also has an important role in monocyte/macrophage activation.

Clinical manifestations include recurrent bacterial sinopulmonary infection, as well as pneumonia due to infection with *Pneumocystis carinii.* Susceptibility to gastrointestinal infection with protozoa such as *Cryptosporidium parvum* may lead to sclerosing cholangitis, cirrhosis, and cholangiocarcinoma.[4] Fatal viral infections including cytomegalovirus (CMV) and enteroviral meningoencephalitis are rarely reported complications.[5] Affected patients typically have very low or absent levels of IgG and IgA and normal or high levels of IgM. Neutropenia affects up to 50% of patients[6] and autoimmune disease also occurs. In a recent analysis of 126 patients reported to the European Society for Immunodeficiency (ESID) registry, approximately one sixth developed hepatic disease, associated with cryptosporidial infection in more than 50%.[7] Survival to the fourth decade is 50%,[7] but the number of cases available for analysis in the older age group is very small, and the chances of long-term survival are still unclear.

A significant proportion of affected boys still die in early adult life despite supportive therapy with immunoglobulin replacement and antibiotic prophylaxis.[8] Hematopoietic stem cell transplantation (HSCT) has the potential to cure this T-cell immunodeficiency.[9-17] A particular problem during transplantation is reactivation of cryptosporidial infection resulting in diarrhea and acute cholangiopathy. In a study using molecular techniques to detect asymptomatic carriage of cryptosporidial species in primary immunodeficiency patients, 5 of 12 patients with CD40 ligand deficiency were chronically colonized, of whom only 1 had a known history of infection. Reactivated cryptosporidial disease occurred in all 3 patients who underwent HSCT and was fatal in 1.[18] Indications for HSCT in CD40L deficiency are still not clearly defined. In this retrospective study of patients with CD40L deficiency who underwent HSCT, complications and outcome were analyzed

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Submitted June 25, 2003; accepted September 25, 2003. Prepublished online as *Blood* First Edition Paper, October 2, 2003; DOI 10.1182/blood-2003-06-2014.

A complete list of the members of the European Group for Blood and Bone Marrow Transplantation and the European Society for Immunodeficiencies appears in the "Appendix."

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according to the presence or absence of risk factors at transplantation, and, in particular, source and degree of matching of donor stem cells, evidence of preexisting infection, and hepatic or lung damage.

Patients, materials, and methods

Data collection

European centers known to have performed HSCT for this condition were identified from the Working Party on Inborn Errors of the European Group for Blood and Marrow Transplantation and from the European Society for Immunodeficiency (ESID) database on CD40 ligand deficiency. A retrospective analysis of data from 38 patients with CD40L deficiency who underwent transplantation in 13 centers in 8 European countries between 1993 and 2002 was performed with follow-up between 1.2 to 9.3 years (median, 3.4 years). Data from 15 patients have been previously published.[9,10,12,16,19-22]

Patient characteristics

Patient characteristics are shown in Table 1. All patients showed absence of CD40L on activated mononuclear cells. The detailed methodology varied in different centers but always involved activation with mitogens and/or ionomycin followed by fluorescence-activated cell sorter (FACS) analysis after labeling with anti-CD40L and simultaneous labeling with another T-cell activation marker (CD25 or CD69) as a control for cellular activation. The diagnosis was confirmed by mutation analysis in all but one patient (patient 35).[23] Cryptosporidium detection was performed by standard light microscopy after staining either with a modified Zeihl-Neelsen method or using a fluorescent antibody. In 8 patients (patients 17, 20, 22, 23, 26, 36, 37, and patient 33 after HSCT only) polymerase chain reaction (PCR) techniques were also used.

Clinical characteristics

There were 16 patients who had suffered *Pneumocystis carinii* pneumonia; 6 had bronchiectasis on computed tomography scan prior to transplantation, 4 of whom had had *Pneumocystis carinii* pneumonia (Table 1). One had intrapulmonary calcification. There were 19 patients who had documented previous cryptosporidial infection; in 1 patient (patient 29), *Cryptosporidium parvum* was first detected following chemotherapy conditioning. Of the patients, 13 had normal hepatic function and ultrasound imaging and did not undergo hepatic biopsy; 6 (patients 2, 13, 16, 21, 22, and 33) in whom hepatic biopsy was normal had normal hepatic ultrasound imaging, 2 of whom (patients 21 and 22) also had mildly abnormal hepatic function. The

Table 1. Clinical characteristics of European patients with CD40 ligand deficiency

Case	Age at Tx, y	PCP	Respiratory status	Liver histology	Cryptosporidium infection
1	1	+	Normal	Not evaluated	−
2	1.2	+	Normal	Normal	−
3	2	+	Normal	Not evaluated	−
4	2	+	Normal	Not evaluated	−
5	3	−	Normal	Not evaluated	−
6	3.5	+	Normal	Not evaluated	−
7	3.75	−	Normal	Sclerosing cholangitis	+
8	4	−	Normal	Not evaluated	−
9	4	−	Normal	Not evaluated	−
10	4	−	Normal	Cirrhosis	+
11	4	+	Bronchiectasis	Not evaluated	−
12	4.5	+	Normal	Not evaluated	+
13	4.5	−	Normal	Normal	−
14	4.5	−	Normal	Not evaluated	−
15	7	−	Normal	Sclerosing cholangitis	+
16	7	+	Normal	Normal	−
17	7.3	−	Normal	Sclerosing cholangitis	+
18	8	+	Normal	Sclerosing cholangitis	+
19	8	−	Bronchiectasis	Portal inflammation	+
20	8.7	−	Normal	Sclerosing cholangitis	+
21	9.5	−	Normal	Normal	−
22	9.5	+	Normal	Normal	+*
23	10	+	Normal	Sclerosing cholangitis	−
24	10	−	Normal	Sclerosing cholangitis cirrhosis	+
25	11	+	Normal	Sclerosing cholangitis	+
26	11.5	−	Normal	Sclerosing cholangitis	+
27	11.5	+	Bronchiectasis	Sclerosing cholangitis cirrhosis	+
28	11.5	−	Normal	Not evaluated	−
29	13	+	Bronchiectasis	Portal inflammation	+
30	13	−	Normal	Sclerosing cholangitis	+
31	14	−	Normal	Fibrosis	+
32	14	+	Bronchiectasis	Sclerosing cholangitis	+
33	15	−	Normal	Normal	−
34	15.7	−	Normal	Sclerosing cholangitis	+
35	16	+	Intrapulmonary calcification	Sclerosing cholangitis atypical sarcoma	−
36	16.5	−	Normal	Sclerosing cholangitis	+*
37	18	−	Normal	Sclerosing cholangitis cirrhosis	−
38	19	−	Bronchiectasis	Not evaluated	−

Tx indicates transplantation; PCP, Pneumocystis carinii pneumonia.
*Positive on PCR testing only.

remaining 20 patients who had abnormal hepatic function, ultrasound imaging, or endoscopic retrograde cholangiopancreatography had histologic hepatic disease: sclerosing cholangitis only (12), sclerosing cholangitis and hepatic cirrhosis (3), fibrosis (1), portal inflammation (2), cirrhosis (1), and sarcoma (1). There were 3 patients who underwent elective orthotopic hepatic transplantation at 4, 5, and 26 weeks prior to hematopoietic stem cell transplantation (patients 24, 37,[16] and 27, respectively) because of preexisting cirrhosis and hepatic failure, and 1 patient at 14 weeks prior to hematopoietic stem cell transplantation (patient 35) because of an atypical sarcoma. One patient had inflammatory bowel disease and seronegative polyarthritis (patient 23). There were 6 patients who had severe failure to thrive (patients 16, 23, 30, 32, 35, and 38), of whom 4 required long-term total parenteral nutrition (patients 23, 30, 35, and 38). All patients received immunoglobulin replacement therapy and had normal trough IgG levels prior to transplantation.

Transplantation

Age at transplantation ranged from 1 to 19 years (median, 8.4 years). There were 27 patients who received cytoreductive conditioning with 16 to 20 mg/kg busulphan and 200 mg/kg cyclophosphamide, 3 of whom received additional anti–leukocyte function antigen-1 (LFA-1) and anti-CD2 antibodies and 12 rabbit antithymocyte globulin (ATG). Other regimens included the following: 16 mg/kg busulphan, 200 mg/kg cyclophosphamide, and alemtuzumab (1 patient); fludarabine and melphalan with ATG administered immediately before and after stem cell infusion (resulting in in vivo T-cell depletion; 5 patients, 1 of whom also received total lymphoid irradiation); fludarabine and melphalan with alemtuzumab administered immediately before and after stem cell infusion (2 patients); total body irradiation with partial hepatic shielding and cyclophosphamide (1 patient); 12 mg/kg busulphan, 20 mg/kg thiotepa, 20 mg/m^2 fludarabine, and 60 mg/kg cyclophosphamide (1 patient); and fludarabine and melphalan alone (1 patient). The choice of conditioning regimen was institutionally dependent.

HLA matching of donor and recipient was confirmed by serology and molecular typing. There were 14 patients who received whole marrow from HLA-identical sibling donors; 22 received unrelated donor hematopoietic stem cells, of which 15 were full (10/10) matches and 7 mismatched at one major antigen. Of the patients, 2 received phenotypically matched related hematopoietic stem cells from a parent, and 12 patients received T-cell–depleted grafts (11 unrelated donor and 1 phenotypically matched related donor), 2 by addition of CAMPATH-1M to the marrow in vitro, and 9 by CD34$^+$ stem cell enrichment.

For graft-versus-host disease prophylaxis, 33 patients received cyclosporin A, of whom 10 also received methotrexate, and 1, additional mofotil mycophenolate. Of these 33 patients, 3 additionally received methylprednisolone, 1 of whom also received ATG as graft-versus-host disease (GvHD) prophylaxis. There were 2 patients who received mycophenolate mofetil, and 1 received basiliximab in addition to cyclosporin A; 1 patient received tacrolimus alone, 3 patients given CD34$^+$-enriched stem cells and 1 receiving whole marrow did not receive GvHD prophylaxis. All patients were isolated in Hepar-filtered or laminar flow facilities. Before or during transplantation, 25 received azithromycin alone or azithromycin and paromomycin as anticryptosporidial prophylaxis or treatment. One patient (patient 34) received nitazoxanide treatment for cryptosporidiosis at the time of transplantation.

Statistical analysis

The log-rank test was used to compare cumulative survival between different groups. Statistical analyses were performed using GB-STAT (version 6.5PPC; Dynamic Microsystems, Silver Spring, MD).

Results

Engraftment

As demonstrated by molecular genetic analysis, 34 patients engrafted with full or partial donor chimerism. There were 4 patients who had autologous reconstitution (patients 8, 18, 25, and 34), of whom 3 continue with antibiotic prophylaxis and immunoglobulin replacement. The fourth patient (patient 8) engrafted after a further conditioned transplantation using whole marrow from a different unrelated donor. Patient 33 developed 100% engraftment with grade 2 GvHD but has persistent very low T-cell numbers with a minimal amount of CD40L expression despite a stem cell top up.

Following the initial transplantation, 4 patients received "boost" infusions. One patient (patient 8) received an unconditioned donor stem cell infusion after the second transplantation because of lack of donor T-cell chimerism despite full donor chimerism in other cell lineages. One patient (patient 16) received an unconditioned donor cell infusion, and 2 patients (patients 12 and 33) received an unconditioned donor stem-cell–enriched infusion for failing chimerism. One patient (patient 35) received 3 donor lymphocyte infusions for lack of donor T-cell chimerism despite full donor chimerism in other cell lineages.

Infection

Patient 31 developed probable enteroviral encephalitis, treated with pleconaril, but has residual neurologic impairment. Patient 8 developed disseminated adenovirus type 31 infection during the second transplantation, treated successfully with intravenous ribavarin and cidofovir. Patient 34 developed Epstein-Barr viral infection treated with foscarnet and rituximab. All 12 patients who did not survive died from complications relating to infection, including cryptosporidiosis, CMV, and aspergillus infection.

Adverse events

Despite hepatic disease in 20 patients, veno-occlusive disease (VOD) occurred in only 4 (patients 1, 19, 30, and 32). Significant acute graft-versus-host disease (GvHD) (grades 2-4) occurred in 14 patients and was associated with a fatal outcome in 6 with preexisting infection (adenovirus in 1, cryptosporidiosis in 2, cryptosporidiosis, adenovirus and aspergillosis in 1, aspergillosis in 1, and CMV in 1; Table 2). One patient (patient 36) underwent orthotopic hepatic transplantation following hematopoietic stem cell transplantation, because of fulminant hepatic failure, but died of pulmonary cryptosporidiosis. Of 4 patients who underwent elective orthotopic hepatic transplantation prior to hematopoietic stem cell transplantation, 3 died. One developed hepatic graft rejection following hematopoietic stem cell transplantation and died from ongoing cryptosporidial, adenoviral, and aspergillus infection secondary to immunosuppression (patient 27). One patient failed to engraft donor T lymphocytes, despite full donor chimerism in all other hematopoietic cell lineages and 3 donor lymphocyte infusions following HSCT, and died of aspergillosis (patient 35). The other patient showed no evidence of hepatic growth following HSCT and so underwent a second orthotopic hepatic transplantation but died from overwhelming cryptosporidiosis (patient 24).

Survival

There are 26 patients (68%) who are alive and well with a follow-up of 1.2 to 9.3 years (median, 3.4 years) (Table 3).

Overall, 22 (58%) patients are cured and express CD40L on activated lymphocytes; 20 no longer receive replacement immunoglobulin, 18 (82%) of whom have been assessed and shown to respond to vaccination with *Haemophilus influenzae* type B and tetanus antigens, and 1 of whom is being evaluated.

Table 2. Transplantation characteristics of European patients undergoing hematopoietic stem cell transplantation for CD40 ligand deficiency; nonsurvivors

Case	Age at Tx, y	Donor	T-cell depletion	Conditioning	GvHD	Cause of death
1	1	MUD	Nil	bu/cy/ATG	Nil	CMV
11	4	MUD$^+$	Nil	bu/cy/CIH	3 S, G	Adenovirus/GvHD
15	7	MUD	CD34$^+$	bu/cy/ATG	Nil	Aspergillus
24	10	MSD	Nil	flu/mel	Nil	Cp
27	11.5	MUD	Nil	bu/cy/LFA-1/CD2	2 S, L	Cp/aspergillus/adenovirus
28	11.5	MSD	Nil	bu/cy	Nil	CMV
29	13	MUD$^+$	Campath	bu/cy/ATG	Nil	Cp
30	13	MSD	Nil	bu/cy	3 S, L	Cp
32	14	MSD	Nil	flu/mel/ATG	4 L	Cp/GvHD
35	16	MUD$^+$	CD34$^+$	Flu/mel/ATG/TLI	2 S	Aspergillus
36	16.5	MUD$^+$	CD34$^+$	cy/TBI	1 S	Cp/graft rejection/liver failure, LT
38	19	MSD	Nil	bu/cy	3 S, G, L	CMV/GvHD

GvHD indicates graft versus host disease grades 1 to 4; MUD, matched unrelated donor 10/10; bu, busulphan; cy, cyclophosphamide; ATG, rabbit antithymocyte globulin; CMV, cytomegalovirus; MUD$^+$, matched unrelated donor less than 10 of 10; CIH, alemtuzumab; S, skin; G, gut; MSD, matched sibling donor; flu, fludarabine; mel, melphalan; Cp, *Cryptosporidium parvum;* LFA-1, anti–LFA-1 antibody; CD2, anti-CD2 antibody; L, liver; Campath, CAMPATH-1M; TLI, total lymphoid irradiation; TBI, total body irradiation; and LT, liver transplantation.

All 12 deaths (32%) were associated with infection (Table 2); 6 patients had severe cryptosporidial infection, 1 of whom had coexistent aspergillosis and adenoviral infection. All of these patients had known previous cryptosporidial infection and 5 of 6 received cryptosporidial prophylaxis. Of the remaining 6 patients, 3 had disseminated CMV infection, 1 had overwhelming adenovirus infection, and 2 had disseminated aspergillosis. Of 12 nonsurvivors, 8 had preexisting hepatic disease versus 12 of 26 survivors. Of 14 patients receiving matched sibling donor HSC transplants 5 died, compared with 4 of 12 receiving T-cell–depleted matched unrelated donor HSC transplants. Of the 6 patients with preexisting hepatic disease receiving fludarabine/melphalan (low intensity) conditioning regimens there were 3 survivors, compared with 8 of 12 with preexisting hepatic disease who received busulphan/cyclophosphamide-containing conditioning regimens.

Pre-existing lung damage was significantly associated with a poor outcome ($P = .0002$). Of the 7 patients who received HSC transplants from one antigen-mismatched donor, 4 died and 1 had autologous reconstitution. This was significantly worse than the outcome in the 15 patients receiving fully matched unrelated donors where there were 3 deaths and 2 cases of autologous reconstitution ($P = .02$). There was no statistical difference between survivors and nonsurvivors for other

Table 3. Transplantation characteristics of European patients undergoing hematopoietic stem cell transplantation for CD40 ligand deficiency; survivors

Case	Age at Tx, y	Donor	T-cell depletion	Conditioning	GvHD	Follow-up, y
2	1.2	MSD	Nil	bu/thio/flu/cy	Nil	2
3	2	MUD	CD34$^+$	bu/cy/ATG	Nil	2.8
4	2	MUD	Nil	bu/cy/ATG	1 S	3.3
5	3	MUD	Campath	bu/cy/LFA-1/CD2	Nil	5.8
6	3.5	MSD	Nil	bu/cy	Nil	9.3
7	3.75	MUD	CD34$^+$	bu/cy/ATG	2 S, L	3.3
8	4	MUD	CD34$^+$	flu/mel/C1H	Nil	1.2
9	4	MUD$^+$	CD34$^+$	bu/cy/ATG	2 S	2
10	4	MSD	Nil	bu/cy	Nil	4
12	4.5	MUD	CD34$^+$	bu/cy/ATG	Nil	3.3
13	4.5	MUD	Nil	bu/cy/ATG	2 S	3.8
14	4.5	MSD	Nil	bu/cy	Nil	3.5
16	7	MUD$^+$	CD34$^+$	bu/cy/ATG	Nil	4
17	7.3	MSD	Nil	bu/cy	Nil	1.6
18	8	MRD	CD34$^+$	bu/cy/ATG	Nil	2
19	8	MUD	Nil	bu/cy/ATG	Nil	2.6
20	8.7	MSD	Nil	bu/cy	2 G	1.6
21	9.5	MSD	Nil	bu/cy	Nil	AR, 5.4
22	9.5	MSD	Nil	bu/cy	1 S	5
23	10	MSD	Nil	bu/cy	Nil	6.5
25	11	MUD	Nil	bu/cy/LFA-1/CD2	Nil	AR, 6.3
26	11.5	MUD	Nil	flu/mel/ATG	1 S	4.5
31	14	MRD	Nil	TBI/flu/ATG	2 S	2.5
33	15	MUD	Nil	flu/mel/C1H	2 S, L	3
34	15.7	MUD$^+$	Nil	flu/mel/ATG	1 S, L	AR, 1.7
37	18	MUD	Nil	flu/mel/ATG	2 L	4.5

GvHD indicates graft versus host disease grades 1 to 4; MSD, matched sibling donor; bu, busulphan; thio, thiotepa; flu, fludarabine; cy, cyclophosphamide; MUD, matched unrelated donor 10 of 10; CD34$^+$, CD34$^+$ stem cell selection; ATG, rabbit antithymocyte globulin; Campath, CAMPATH-1M; S, skin; LFA-1, anti–LFA-1 antibody; CD2, anti-CD2 antibody; L, liver; mel, melphalan; C1H, alemtuzumab; MUD$^+$, matched unrelated donor 9 of 10; MRD, phenotypically matched related donor; G, gut; AR, autologous reconstitution patient failed to engraft and remains well on IVIG; and TBI, total body irradiation.

parameters examined, including preexisting hepatic damage, previous infection with *Pneumocystis carinii* or *Cryptosporidium parvum*, transplantation before 5 years of age, conventional or low-intensity conditioning regimens, use of unrelated donors or T-cell–depleted marrow, or the occurrence of GvHD.

Discussion

Supportive treatment of CD40L deficiency varies slightly between European centers but all patients receive immunoglobulin replacement, prophylactic antibiotics for *Pneumocystis carinii* pneumonia, granulocyte colony-stimulating factor for intractable neutropenia, as well as antibacterial treatment and nutritional support. Long-term prognosis remains poor despite supportive treatment, and hepatic disease is the major cause of death.[8]

For patients with established hepatic disease, planning the most appropriate treatment remains difficult, as occult cryptosporidial infection is very likely to reactivate during the posttransplantation period despite the use of prophylactic antimicrobials and can lead to further compromise of hepatic function. Hepatic biopsy yields useful information regarding hepatic damage, but should be considered only if there is biochemical or radiologic evidence of disease. Surprisingly, despite preexisting hepatic disease being a risk factor for VOD in HSCT, only 4 patients experienced this complication even though most patients received standard European conditioning protocols containing busulphan, known to be associated with an increased risk of VOD.[24] Fludarabine/melphalan conditioning regimens generally cause less acute toxicity than conventional regimens and may be preferable in patients with preexisting hepatic disease.[19] For patients who present with end-stage hepatic disease related to CD40L deficiency, a combination of orthotopic hepatic transplantation followed by a nonmyeloablative reduced-intensity, chemotherapy-conditioned bone marrow transplantation has been successful in one case (patient 37).[16] Interestingly, conventional and molecular diagnostic methods failed to show any evidence of cryptosporidial infection in this patient at any stage. However, HSCT should be done as soon as possible after orthotopic hepatic transplantation because of the high risk of severe cryptosporidial infection in the new liver and consequent rapid deterioration of hepatic function. Better detection of cryptosporidial carriage and infection using polymerase chain reaction has been developed and may allow better identification of patients at higher risk.[18] However, at the moment good anticryptosporidial drugs are not available, although a combination of drugs such as paromomycin, nitazoxanide, and azithromycin may be of some use in suppressing infection.[25]

Previous *Pneumocystis carinii* pneumonia did not increase the risk of death following HSCT, but preexisting lung damage was strongly associated with mortality. It may be that preexisting lung damage is a predictive marker for latent viral or fungal infection. Alternatively, patients with preexisting lung damage may be in generally poorer condition and tolerate transplantation less well. It is of note that although severe GvHD was not significantly different between the 2 groups, all 4 patients with GvHD greater than grade II died, and this association may be more apparent in a larger series. Transplantation using whole marrow to achieve early T-cell recovery would be a logical approach to limit cryptosporidial or other infective disease, but, in this study, 7 of 12 cases engrafted after receiving T-cell–depleted marrow and T-cell depletion was not associated with an increased mortality. The results using T-cell–depleted and whole marrow from unrelated donors are very encouraging, with 68% of patients surviving, similar to recent European results reported for matched unrelated donor transplants for other T-cell immunodeficienies.[26] However, the use of antigen-mismatched donors was associated with death or autologous reconstitution.

The most difficult question remains the timing of HCST. In patients without preexisting hepatic disease, HSCT was successful in 13 (72%) of 18 patients, with 4 deaths and 1 autologous reconstitution. These results are similar to those achieved when young, relatively well children with other T-cell immunodeficiencies such as Wiskott-Aldrich syndrome[27] undergo transplantation, where early HSCT is more successful than that done at a later age. Many patients remain very well, leading near normal lives on supportive treatment, which includes the use of boiled water to reduce the risk of cryptosporidial disease. Also, there may be an understandable reluctance to risk a 20% or greater chance of death following HSCT when it is not certain which patients will ultimately develop fatal hepatic disease. One approach in CD40L deficiency may be to administer supportive therapy and monitor closely for evidence of hepatic disease and other complications, including lung damage, with HSCT performed at the earliest sign of complications, possibly using a low-intensity conditioning regimen. An alternative would be to recommend early HSCT using a full conditioning regimen. These questions will be answered only by continuing careful collection of detailed longitudinal follow-up data on the incidence of complications and the survival of patients treated by HSCT early with full conditioning, later with low-intensity conditioning or without HSCT and full supportive care only. It will be particularly important to identify adverse risk factors for each treatment strategy so that we can determine who should undergo transplantation and when HSCT should be performed. These results from across Europe show that, overall, HSCT is curative in nearly 60% of CD40L patients, with preexisting lung disease appearing to be the most important adverse risk factor.

Appendix

The following colleagues participated in this study by the European Group for Blood and Bone Marrow Transplantation and the European Society for Immunodeficiencies: M. Abinun, A. Aiuti, D. Bensoussan, H. Gaspar, A. R. Gennery, A. J. Cant, E. G. Davies, A. Fasth, T. J. Flood, W. Friedrich, S. Blanche, P. Landais, R. Seger, N. Wulffraat, C. Steward, H. Ozsahin, P. Veys, A. Fischer, R. G. M. Bredius, L. D. Notarangelo, S. Matthes-Martin, P. Bordigoni, M. Cavazzana-Calvo, S. Muller, J. Vossen, T. Gungor, J. Ortega, A. O'Meara, A. Will, F. Porta, M. Slatter, A. C. Lankester, I. Andre-Schmutz, S. Corbacioglu, Y. Camcioglu, T. Espanol, B. Gerritsen, F. Le Deist, C. I. E. Smith, A. Van Royen-Kerhhof, D. Moshous, A. Thrasher, P. de Coppi, A. Bhattacharya, M. Hoenig, K. Kalwak, N. Perez, S. Caillat-Zucman, S. Hacein-Bey, O. Danos, P. Aubourg, N. Cartier, and J. Stary.

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