Hematopoietic stem cell transplantation for CD40 ligand deficiency: Results from an EBMT/ESID-IEWP-SCETIDE-PIDTC study

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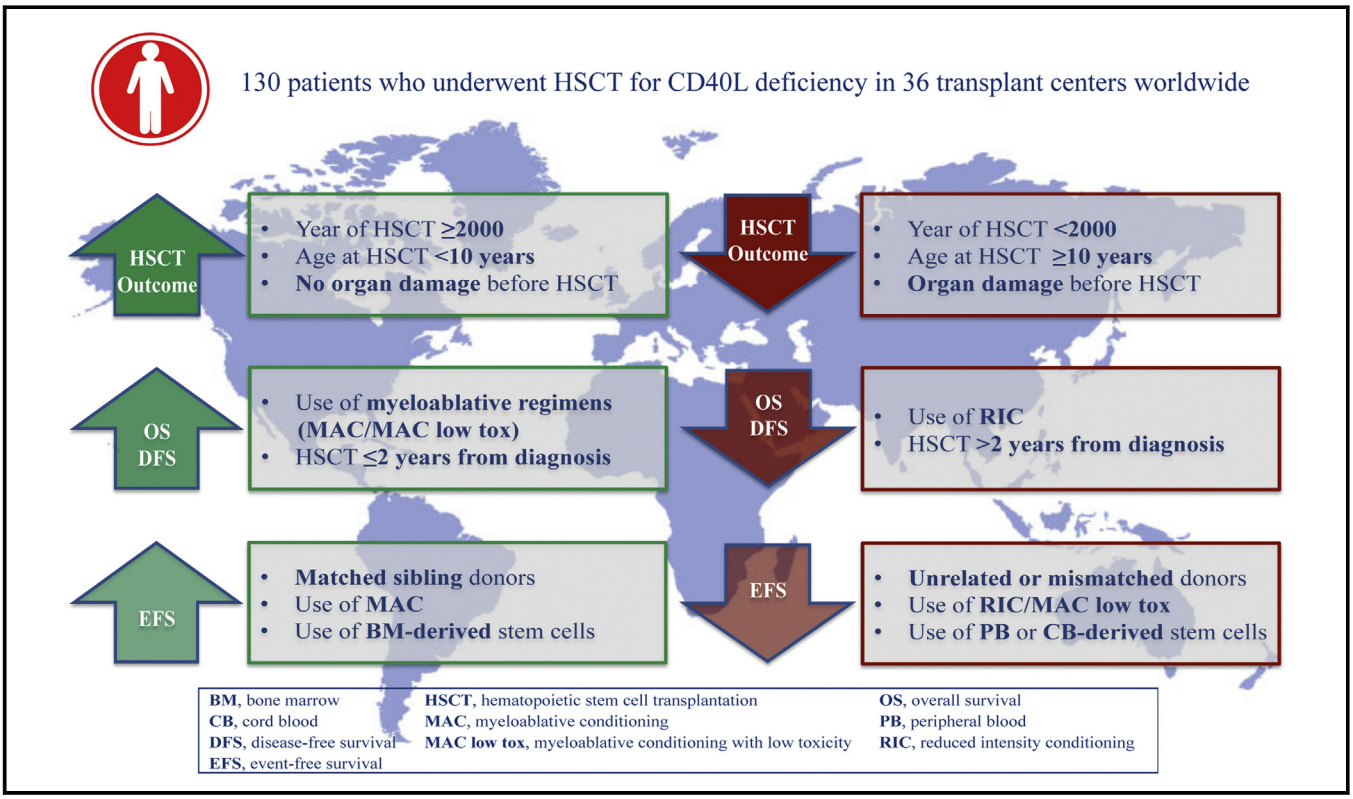
GRAPHICAL ABSTRACT



Background: CD40 ligand (CD40L) deficiency, an X-linked primary immunodeficiency, causes recurrent sinopulmonary, *Pneumocystis* and *Cryptosporidium* species infections. Long-term survival with supportive therapy is poor. Currently, the only curative treatment is hematopoietic stem cell transplantation (HSCT).

Objective: We performed an international collaborative study to improve patients' management, aiming to individualize risk factors and determine optimal HSCT characteristics.

Methods: We retrospectively collected data on 130 patients who underwent HSCT for CD40L deficiency between 1993-2015. We analyzed outcome and variables' relevance with respect to survival and cure.

Results: Overall survival (OS), event-free survival (EFS), and disease-free survival (DFS) were 78.2%, 58.1%, and 72.3% 5 years after HSCT. Results were better in transplantations performed in 2000 or later and in children less than 10 years old at the time of HSCT. Pre-existing organ damage negatively influenced outcome. Sclerosing cholangitis was the most important risk factor. After 2000, superior OS was achieved with matched donors. Use of myeloablative regimens and HSCT at 2 years or less from diagnosis associated with higher OS and DFS. EFS was best with matched sibling donors, myeloablative conditioning (MAC), and bone marrow–derived stem cells. Most rejections occurred after reduced-intensity or nonmyeloablative conditioning, which associated with poor donor cell engraftment. Mortality occurred mainly early after HSCT, predominantly from infections. Among survivors who ceased immunoglobulin replacement, T-lymphocyte chimerism was 50% or greater donor in 85.2%.

Conclusion: HSCT is curative in patients with CD40L deficiency, with improved outcome if performed before organ damage development. MAC is associated with better OS, EFS, and DFS. Prospective studies are required to compare the risks of HSCT with those of lifelong supportive therapy. (J Allergy Clin Immunol 2019;143:2238-53.)

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CD40 ligand (CD40L) deficiency (X-linked hyper-IgM syndrome type 1 [OMIM#308230])[1,2] is a rare X-linked primary immunodeficiency (PID) caused by mutations in *CD40LG* on chromosome Xq26.3-Xq27.1, which encodes the transmembrane CD40L glycoprotein (CD154, OMIM#300386).[3-8] Mutations in *CD40LG* result in altered costimulatory T-lymphocyte function,[9] which impairs B-lymphocyte isotype switching, antibody production, and dendritic cell signaling. Myeloid cell function and development are also impaired.[10,11] This leads to increased susceptibility to bacterial and intracellular pathogens.

Patients usually present in early childhood with recurrent upper and lower respiratory tract infections and *Pneumocystis jirovecii* pneumonia.[12,13] Acute or chronic diarrhea is frequently associated with *Cryptosporidium* species infection, which can lead to severe biliary tract disease, especially sclerosing cholangitis and cirrhosis and rarely cholangiocarcinoma, hepatocellular carcinoma, and adenocarcinoma.[14]

An increased frequency of central nervous system infections (enteroviral meningoencephalitis[15] and JC virus progressive multifocal leukoencephalopathy),[16] often resulting in neurodegeneration,[12,17] has been reported.

Historically, long-term survival with conservative therapy has been poor, with 20% to 50% of patients surviving to the third decade.[12,18,19] Hepatic disease and severe infections represent the major causes of death,[12] and many patients have chronic comorbidities.[18] More recent data show a median survival time from diagnosis of 25 years in 109 patients with X-linked hyper-IgM syndrome.[20]

Currently, the only curative treatment is hematopoietic stem cell transplantation (HSCT). Numerous published case reports[21-36] and single-center experiences[37-42] report encouraging results, especially with an HLA-matched sibling donor (MSD). However, there is a risk of complications, and overall survival (OS) is not optimal.[18] In the European retrospective analysis of 38 patients with CD40L deficiency receiving HSCT,[43] OS was 68%, with 32% of patients dying from infection-related complications, particularly severe cryptosporidiosis. Transplantation was curative in 58% of patients, 72% of those without hepatic disease. Pre-existing lung disease was the most important adverse risk factor.

The choice of performing early HSCT using myeloablative conditioning (MAC) or a later transplantation with reduced-intensity conditioning (RIC) or treating patients with full supportive treatment only is still debated. Guidelines for the management of these patients were proposed by the European Society for Blood and Marrow Transplantation (EBMT)/European Society for Immunodeficiencies (ESID) Inborn Errors Working Party (IEWP) in 2011.[44] Recommendations about HSCT based on donor type and disease-related complication status favored HSCT at diagnosis when an MSD was available and medical support until development of early complications for matched unrelated donors (MUDs) or mismatched unrelated donors (MMUDs) and progressive organ damage for mismatched family donors (MMFDs). A recently published study[45] reported improved survival in 29 Japanese patients undergoing HSCT (OS, 86.2%), with better event-free survival (EFS) and disease-free survival (DFS) in children younger than 5 years of age at the time of transplantation. A multicenter study comparing outcomes with or without HSCT showed an 85% OS in 67 patients in the transplantation group.[20]

We report the results of a retrospective international collaborative study on patients who underwent HSCT for CD40L deficiency between 1993 and 2015, reported in the Stem Cell Transplant for Primary Immune Deficiencies in Europe (SCETIDE) and EBMT registries and from North American Primary Immune Deficiency Treatment Consortium (PIDTC) centers. We analyzed the outcome and relevance of different variables with respect to survival and cure rate after HSCT, aiming to individualize specific risk factors for patients and determine the optimal timing and type of HSCT.

Abbreviations used

BM:	Bone marrow
CD40L:	CD40 ligand
DFS:	Disease-free survival
DLI:	Donor lymphocyte infusion
EBMT:	European Society for Blood and Marrow Transplantation
EFS:	Event-free survival
ESID:	European Society for Immunodeficiencies
FU:	Follow-up
GVHD:	Graft-versus-host disease
HSCT:	Hematopoietic stem cell transplantation
IEWP:	Inborn Errors Working Party
MAC:	Myeloablative conditioning
MAC low tox:	Myeloablative conditioning with low toxicity
MMFD:	Mismatched family donor
MMUD:	Mismatched unrelated donor
MSD:	Matched sibling donor
MUD:	Matched unrelated donor
NMA:	Nonmyeloablative
OS:	Overall survival
PBSC:	Peripheral blood stem cell
PID:	Primary immunodeficiency
PIDTC:	Primary Immune Deficiency Treatment Consortium
RIC:	Reduced-intensity conditioning
SCETIDE:	Stem Cell Transplant for Primary Immune Deficiencies in Europe
UCB:	Umbilical cord blood

METHODS

Data collection

Transplantation centers known to have performed HSCT in CD40L-deficient patients were identified from SCETIDE and EBMT registries (for European, Saudi Arabian, and Australian centers) and through the network of PIDTC centers in the United States.

Retrospective data collection on the outcome of HSCT was performed with a comprehensive questionnaire for 130 patients with CD40L deficiency undergoing transplantation in 36 centers in 18 countries over 4 continents (see Table E1 in this article's Online Repository at www.jacionline.org) between 1993 and 2015, with a follow-up (FU) between 0.2 and 17.6 years (median, 4.1 years). Data from 35 patients have been previously published.*

Patients in whom the diagnosis of CD40L deficiency was based on molecular genetic analysis, evidence of absent protein, or both were included

*References [1, 20, 21, 33, 34, 36, 39, 42, 43], and [46-49].

TABLE I. Clinical features of CD40L-deficient patients before the first HSCT

Patients' features before HSCT	Total*	All patients (n = 130), median (range)	HSCT up to 1999 (n = 24), median (range)	HSCT since 2000 (n = 106), median (range)	*P* value
Age at diagnosis (mo)	126	11.0 (0-131)	13.0 (3-129)	10.7 (0-131)	.2466
Age at HSCT (y)	130	4.0 (0.5-38.3)	8.5 (1.0-18.1)	3.4 (0.5-38.3)	**.0012**
Interval between diagnosis and HSCT (y)	126	2.0 (0-27.4)	3.9 (0.9-16.2)	1.5 (0-27.4)	**.0012**

	Total*	No.	Percent	No.	Percent	No.	Percent	*P* value
CD40L expression	87							.4525
Absent		71	82	11	92	60	80	
Low		16	19	1	8	15	20	
Age at HSCT (y)	130							**.0320**
0-5		79	61	10	42	69	65	
5-10		26	20	5	21	21	20	
>10		25	19	9	37	16	15	
Organ damage before HSCT	119	45	38	15	71	30	31	**.0005**
Infections before HSCT								
All	129	117	91	22	96	95	89	.6919
URTI	124	60	48	14	67	46	45	.0659
LRTI	125	86	69	15	71	71	68	.7756
PJP	108	47	44	7	39	40	44	.6643
Cryptosporidium species	118	29	25	9	47	20	20	**.0189**
Need of ventilation	106	38	36	6	38	32	36	.8812
Chronic lung disease	114	17	15	5	29	12	12	.1305
Neutropenia	123	57	46	11	52	46	45	.5422
Oral ulcers	122	26	21	6	29	20	20	.3869
Failure to thrive	125	37	30	7	33	30	29	.6812
Protracted diarrhea	126	31	25	10	48	21	20	**.0073**
Liver disease†	126	33	26	11	50	22	21	**.0052**
Sclerosing cholangitis	125	28	22	9	43	19	18	**.0211**
Autoimmunity	111	6	5	1	7	5	5	.5636
Malignancies	119	3	3	2	10	1	1	.0800
IG supplementation	125	123	98	19	90	104	100	**.0271**
Cryptosporidium species prophylaxis	100	31	31	7	54	24	28	.1035
PJP prophylaxis	113	109	97	15	88	94	98	.1068

Organ damage was defined as the presence of chronic lung disease, liver alterations (sclerosing cholangitis or liver fibrosis or hepatitis), or both. Significant *P* values ($P < .05$) are shown in boldface.

IG, Immunoglobulins; *LRTI*, lower respiratory tract infection; *PJP*, *Pneumocystis jirovecii* pneumonia; *URTI*, upper respiratory tract infection.

*Number of patients with available data.

†All liver alterations, including also ascending cholangitis, mild hepatic portal inflammation, and minimal alterations.

in the study. Five (3.8%) patients had no available molecular diagnosis or protein expression data but were included based on their clinical history and presentation. Of these, 3 underwent transplantation before 2000 and died. At that time, molecular diagnosis was not always performed, and it was not possible to pursue diagnosis after death.

Centers were responsible for acquiring informed consent from patients and families for data collection and for quality of data entry.

Patients' characteristics

Patients' clinical features before HSCT are summarized in Table I by year of HSCT, showing significant differences between the 2 historical cohorts. In particular, patients who underwent transplantation before 2000 underwent transplantation at an older age and at a greater interval after diagnosis, and they were clinically more compromised (greater organ damage, especially liver disease, before transplantation).

Median age at diagnosis was 11 months (range, 0-131 months) and was not significantly influenced by historical period. Forty-seven patients received a diagnosis in the first 6 months of life, 11 at birth because of a positive family history. CD40L protein expression on activated $CD4^+$ T lymphocytes was available for 87 (66.9%) patients, absent in the majority (81.6%), and most frequently quantified by using flow cytometry. Diagnosis was confirmed by CD40L gene analysis in 108 (83.1%) patients, which showed mainly deletions and missense mutations (see Table E2 in this article's Online Repository at www.jacionline.org). CD40L expression before HSCT did not significantly differ in patients with these types of mutations.

Additional details on the cohort's clinical characteristics are reported in the Methods section in this article's Online Repository at www.jacionline.org.

Transplantation

Patients' performance status at the time of transplantation was determined based on the Lansky or Karnofsky score according to age. Most patients (70.2%) who underwent transplantation after 2000 had a score of 90 or greater at first HSCT. These data were unavailable for most transplantations performed before 2000.

Characteristics of first HSCTs, second HSCTs, boosts, and donor lymphocyte infusions (DLIs) are summarized in Tables II and E3 in this article's Online Repository at www.jacionline.org. Conditioning regimens were grouped according to their intensity and toxicity features into the following 4 types: MAC, myeloablative conditioning with low toxicity (MAC low tox), RIC,[50,51] and nonmyeloablative (NMA) conditioning (see Fig E1 and Table E4 in this article's Online Repository at www.jacionline.org). MAC was the most commonly used conditioning regimen for first transplantations in the historical group (92%), whereas after 2000, the use of RIC and MAC low tox regimens has increased (24% and 20%, respectively; $P = .0034$).

TABLE II. Characteristics of the first HSCT performed on 130 CD40L-deficient patients

First HSCT characteristics	Total*	All patients (n = 130)		HSCT up to 1999 (n = 24)		HSCT since 2000 (n = 106)		*P* value
		No.	Percent	No.	Percent	No.	Percent	
Conditioning regimen	129							**.0034**
MAC		79	61	22	92	57	54	
MAC low tox		21	16	0	0	21	20	
RIC		27	21	2	8	25	24	
NMA		2	2	0	0	2	2	
GVHD prophylaxis	129							1.0000
Yes		123	95	23	96	100	95	
No		6	5	1	4	5	5	
Donor type	123							.3092
MSD		37	30	10	45	27	27	
MUD		46	37	7	32	39	39	
ad. vol.		46	100	7	100	39	100	
UCB		0	0	0	0	0	0	
MMUD		36	29	5	23	31	31	
ad. vol.		29	81	5	100	24	77	
UCB		7	19	0	100	7	23	
MMFD		4	3	0	0	4	4	
Stem cell source	129							**.0006**
BM		86	67	24	100	62	59	
PBSC		33	25	0	0	33	31	
UCB		10	8	0	0	10	10	

Significant *P* values ($P < .05$) are shown in boldface.
ad. vol., Adult volunteer; *NMA*, nonmyeloablative conditioning.
*Number of patients with available data.

NMA was used in 2 first and 2 second transplantations. Because of the low numbers in this group, this was not included in statistical analyses. Because no data about busulfan pharmacokinetics (area under the curve) were available, busulfan-containing regimens were divided between MAC and RIC groups based on the total dose of busulfan administered in case of combination with fludarabine (14.3-25.0 mg/kg in MAC and 4.0-13.6 mg/kg in RIC, see Fig E1). In the other cases classification as MAC was based on other features (eg, combination with cyclophosphamide) and not solely on busulfan dose.

Donor type was defined as follows: MSD, MUD (10/10, 12/12, or 8/8 HLA match), and MMUD (with ≥1 mismatch) and MMFD (with ≥1 mismatch), usually a haploidentical parent. Data about methods used for HLA match testing were available for only 51.3% of the procedures, with molecular techniques used in the majority of cases (75.3%). Data from donors with unavailable or inaccurate information about degree of matching (number of loci studied < 8 for nonsibling donors) were excluded from statistical analysis.

MSDs were the preferred donor types before 2000. The proportion of unrelated donors has since increased for both matched and mismatched donors (39% and 31%, respectively), mainly represented by adult volunteers (Table II).

The stem cell source was bone marrow (BM), peripheral blood stem cells (PBSCs), and umbilical cord blood (UCB). Until 1999, BM was the only stem cell source used for first HSCT. Use of PBSCs and UCB became subsequently more common (31% and 10% HSCT, respectively; $P = .0006$; Table II).

T-lymphocyte depletion of the graft was performed in 28 procedures, mainly through positive selection of $CD34^+$ cells (n = 19). This technique was used in all cases of PBSC transplantations from MMFD (n = 4) and in 8 MMUD and 7 MUD transplants. In 6 recent unrelated donor PBSC transplantations performed in a single center since 2012, T-cell receptor αβ depletion was used. *Ex vivo* graft manipulation details are reported (see Table E5 in this article's Online Repository at www.jacionline.org). *In vivo* T-lymphocyte depletion was performed mainly by using antithymocyte globulin (51.3%) and alemtuzumab (20%), especially in the unrelated donor setting (see Table E4 and data not shown).

Graft-versus-host disease (GVHD) prophylaxis was used in most procedures (92%). No additional GVHD prophylaxis was administered in 8 of 19 transplantations with $CD34^+$ cell selection and in 1 boost. GVHD prophylaxis regimen was based on cyclosporine administration in 88.4% of cases, either alone (25.4%) or in combination with other drugs, mainly methotrexate (29.7%), mycophenolate mofetil (19.6%), or corticosteroids (9.5%). Acute GVHD was graded according to EBMT guidelines and defined as severe when grade 3 or greater. Chronic GVHD was classified as extensive or limited based on the clinical severity and extent of target organ involvement.

Donor chimerism was defined as complete if 95% or more cells were of donor origin, partial if between 5% and 95% cells were of donor origin, and absent if donor cells represented 5% or less of total cells. Partial chimerism analysis on purified cell subpopulations (granulocytes, $CD3^+$ T lymphocytes, and $CD19^+$ B lymphocytes) was analyzed in a subgroup of patients subdivided into predominantly donor (50% to 94%) and predominantly recipient (6% to 49%) cells. Fluorescence *in situ* hybridization or molecular testing based on short-tandem repeats analysis was used to monitor donor cell chimerism.

Additional details are reported in the Methods section in this article's Online Repository.

Statistical analysis

The description of continuous variables was done by using medians and ranges or interquartile ranges, whereas the comparison between groups was based on the Wilcoxon rank sum test. Categorical variables were analyzed through frequency distributions and compared by using the χ^2 or Fisher exact test, as appropriate.

OS, EFS, and DFS calculations were performed both in the whole cohort of patients and in the subgroups of patients undergoing transplantation before (historical cohort) or since 2000. Comparisons of these 2 groups are shown in Figs 1 and 2 and Fig E2 in this article's Online Repository at www.jacionline.org. Results from the analyses focused on most patients undergoing recent transplantation, which are more representative of current clinical practice, are reported in Table III. EFS was calculated as the time from HSCT to the first of the following events: graft failure/absent engraftment; need for second HSCT, boost, or DLI; grade 4 acute GVHD or extensive chronic GVHD;

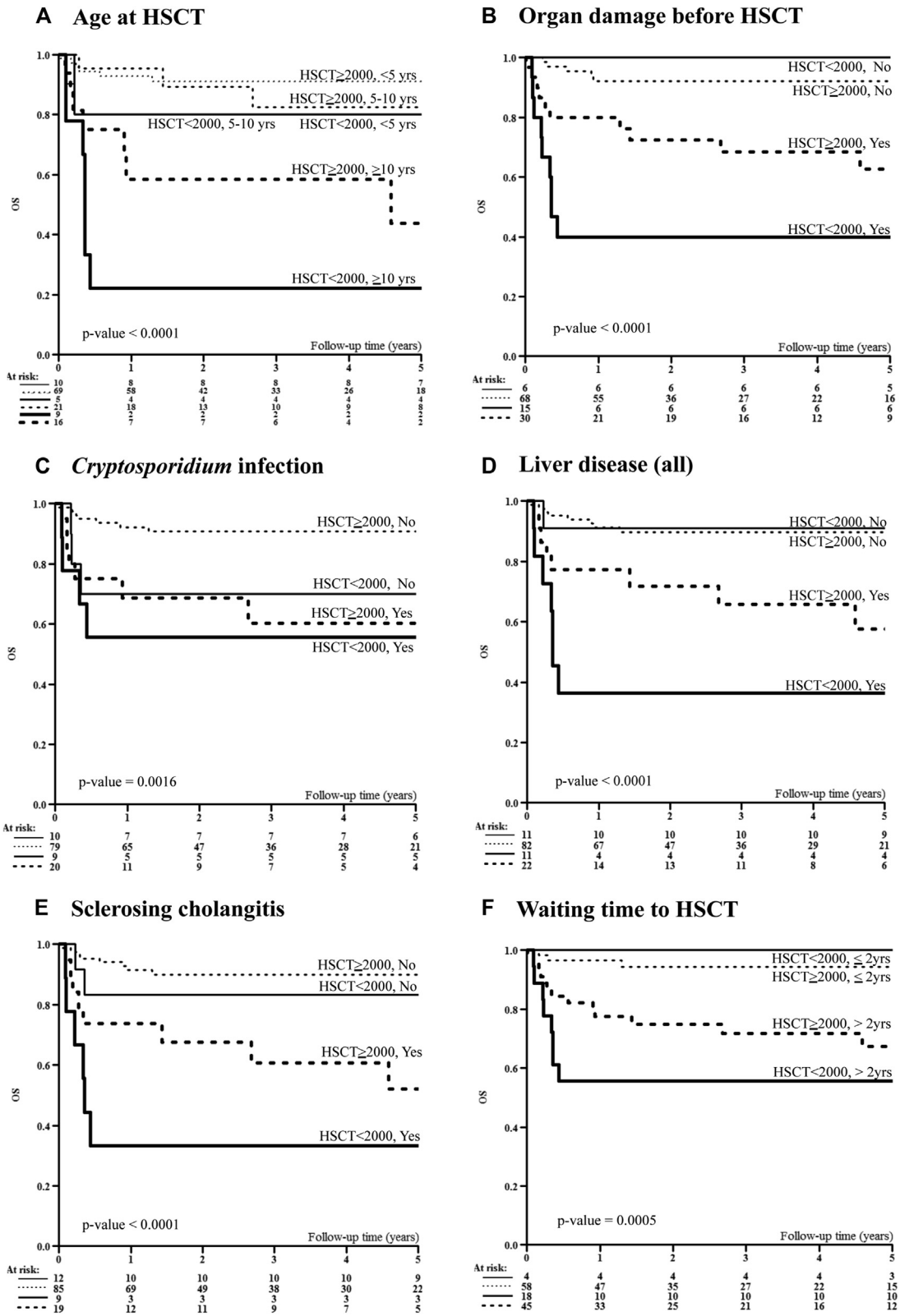


FIG 1. Characteristics influencing OS in patients receiving first HSCT before/after 2000. **A,** Age at HSCT. Survival curves of patients less than 5 and 5 to 10 years old at HSCT undergoing transplantation before 2000 are superimposed. **B,** Organ damage before HSCT. **C,** *Cryptosporidium* species infection before HSCT. **D,** All liver alterations. **E,** Sclerosing cholangitis. **F,** Waiting time to HSCT from diagnosis. Under each graph, the number of patients at risk at each FU time point after HSCT is reported for all patient groups. OS curves of different patient groups are represented by *solid* or *dashed lines*. For each of them, a specific label is reported near the corresponding curve.

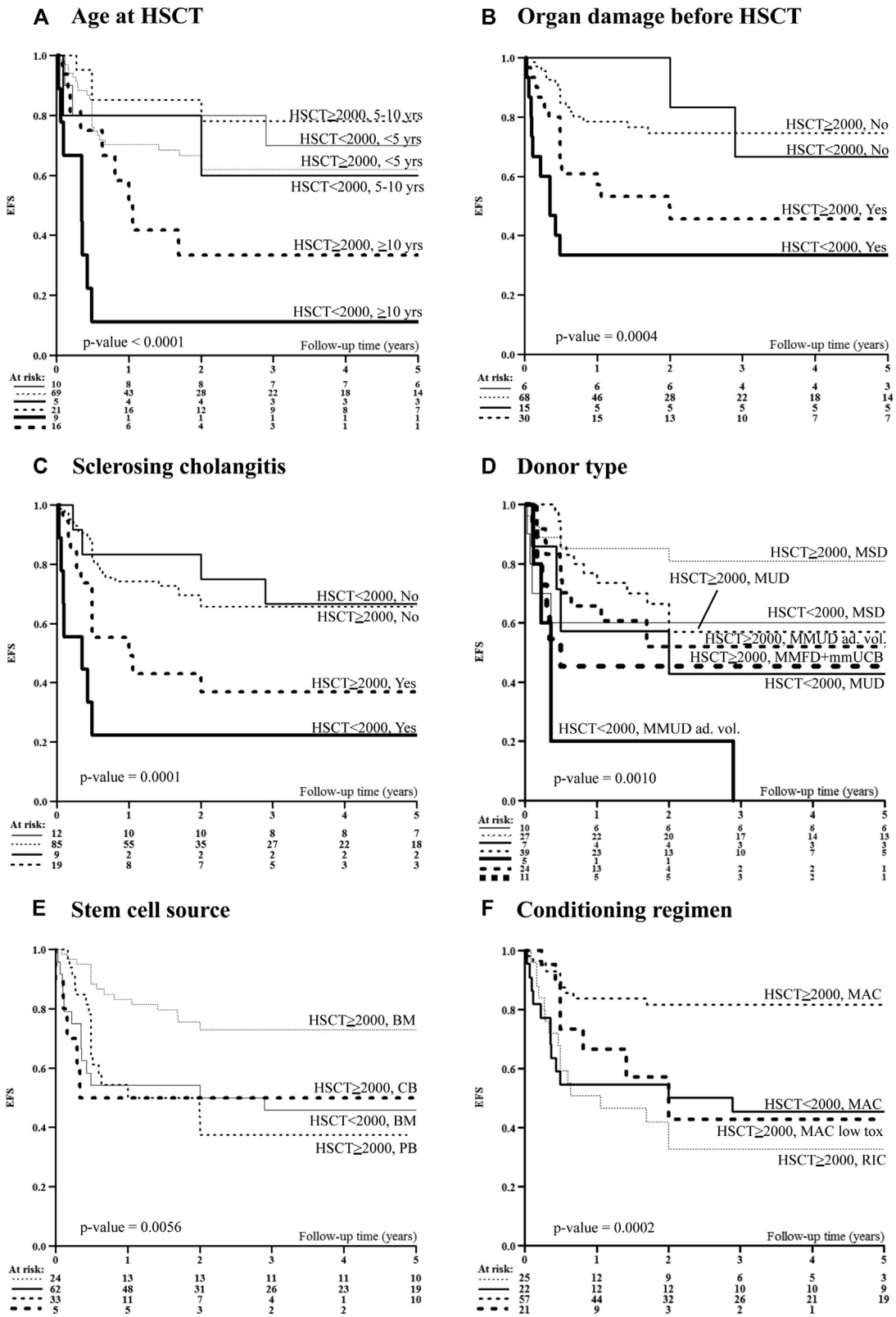


FIG 2. Characteristics influencing EFS in patients receiving first HSCT before/after 2000. **A,** Age at HSCT. **B,** Organ damage before HSCT. **C,** Sclerosing cholangitis before HSCT. **D,** Donor type. **E,** Source of stem cells. **F,** Conditioning regimen. Under each graph, the number of patients at risk at each FU time point after HSCT is reported for all patient groups. EFS curves of the different groups are represented by *solid* or *dashed lines*. For each of them, a specific label is reported near the corresponding curve. *CB*, Cord blood; *PB*, peripheral blood.

TABLE III. OS, EFS, and DFS in CD40L-deficient patients undergoing transplantation since the year 2000

	OS						EFS						DFS					
Characteristics	**No. of events/no. of patients***	**2-y FU (%)**	**SE (%)**	**5-y FU (%)**	**SE (%)**	***P* value**	**No. of events/no. of patients***	**2-y FU (%)**	**SE (%)**	**5-y FU (%)**	**SE (%)**	***P* value**	**No. of events/no. of patients***	**2-y FU (%)**	**SE (%)**	**5-y FU (%)**	**SE (%)**	***P* value**
Overall	16/106	86.1	3.5	82.2	4.3	—	37/106	64.2	3.6	61.3	5.1	—	20/106	78.7	4.5	77.1	4.7	—
Age at HSCT (y)						**.0005**						**.0238**						**.0001**
<5	6/69	91.0	3.5	91.0	3.5		24/69	64.3	6.1	62.1	6.3		8/65	85.4	4.9	85.4	4.9	
5-10	3/21	89.3	7.2	82.4	9.4		4/21	85.2	7.9	78.1	9.3		4/26	85.5	7.9	79.8	9.2	
≥10	7/16	58.3	13.8	43.8	16.1		9/16	33.3	13.3	33.3	13.3		8/15	38.1	14.3	38.1	14.3	
Age at diagnosis (mo)						.2777						**.0148**						.06
<12	7/59	89.6	4.0	86.8	4.8		15/59	72.8	6.1	72.8	6.1		8/60	87.2	4.6	84.4	5.3	
>12	9/45	80.6	6.2	75.8	7.5		22/45	51.0	8.0	44.6	8.2		12/43	64.8	8.5	64.7	8.5	
Time between diagnosis and HSCT (y)						**.0014**						.1226						**.0025**
≤2	3/59	94.3	3.2	94.3	3.2		17/59	69.7	6.5	66.8	6.9		4/53	90.5	4.6	90.5	4.6	
>2	13/45	74.8	6.6	67.2	7.9		20/45	55.8	7.7	52.8	7.8		16/50	65.5	7.4	62.5	7.7	
Organ damage before HSCT						**.0014**						**.0071**						**<.0001**
No	5/68	92.2	3.4	92.2	3.4		16/68	74.5	5.6	74.5	5.6		4/60	92.9	3.4	92.9	3.4	
Yes	10/30	72.4	8.4	62.7	9.8		15/30	49.5	9.6	45.7	9.6		12/28	58.3	9.7	53.9	10.0	
Chronic lung disease						.2545						.1433						.1026
No	10/85	89.0	3.5	86.9	4.0		24/85	71.0	5.2	69.0	5.4		11/79	85.1	4.5	82.7	5.0	
Yes	3/12	73.3	13.2	73.3	13.2		6/12	45.8	15.0	45.8	15.0		4/12	64.8	14.3	64.8	14.3	
Cryptosporidium species infection (gastrointestinal)						**.001**						.0603						**<.0001**
No	7/79	90.7	3.4	90.7	3.4		23/79	69.9	5.5	67.9	5.7		7/74	89.7	4.0	89.7	4.0	
Yes	7/20	68.8	10.7	60.2	12.3		9/20	50.0	12.1	50.0	12.1		8/18	55.7	13.2	44.6	14.5	
Protracted diarrhea						**.0023**						.5314						**.0371**
No	8/84	90.2	3.3	90.2	3.3		28/84	65.8	5.6	61.9	5.9		10/76	84.4	4.7	84.4	4.7	
Yes	8/21	70.2	10.2	56.3	12.2		9/21	56.1	11.0	56.1	11.0		8/22	65.5	10.7	60.1	11.1	
Sclerosing cholangitis						**.0003**						**.0126**						**<.0001**
No	8/85	90.0	3.4	90.0	3.4		26/85	67.7	5.5	65.7	5.6		8/79	88.3	4.0	88.3	4.0	
Yes	8/19	67.5	11.0	52.1	12.9		11/19	43.0	12.0	36.8	11.8		10/18	46.0	12.4	38.3	12.5	
Liver disease†						**.002**						.0666						**.0009**
No	8/82	89.7	3.5	89.7	3.5		26/82	66.7	5.6	64.6	5.8		10/80	85.3	4.4	85.3	4.4	
Yes	8/22	71.8	9.9	57.6	12.1		11/22	49.7	11.4	44.2	11.4		10/22	53.8	11.6	47.1	12.0	
Pneumonias						.6865						.7624						.6436
No	6/33	84.2	6.5	76.5	9.4		13/33	65.4	8.5	56.7	9.3		7/32	71.4	9.5	71.4	9.5	
Yes	10/71	86.7	4.2	84.4	4.6		23/71	64.6	6.7	64.6	6.7		11/65	82.9	5.0	80.2	5.5	
PJP						.6862						.9663						.9081
No	6/50	87.2	4.9	87.2	4.9		16/50	68.0	6.9	64.9	7.2		8/51	82.0	6.0	82.0	6.0	
Yes	6/40	87.2	5.4	83.1	6.5		13/40	63.6	8.3	63.6	8.3		6/35	83.6	6.9	78.3	8.2	
URTI						.4377						.1809						.1457
No	7/57	88.3	4.5	84.6	5.7		16/57	66.6	7.1	66.6	7.1		7/55	86.1	5.5	82.0	6.6	
Yes	9/46	82.4	5.7	78.5	6.6		20/46	60.0	7.3	54.8	7.6		11/40	70.0	7.7	70.0	7.7	

(Continued)

TABLE III. *(Continued)*

Characteristics	OS						EFS						DFS					
	No. of events/no. of patients*	2-y FU (%)	SE (%)	5-y FU (%)	SE (%)	*P* value	No. of events/no. of patients*	2-y FU (%)	SE (%)	5-y FU (%)	SE (%)	*P* value	No. of events/no. of patients*	2-y FU (%)	SE (%)	5-y FU (%)	SE (%)	*P* value
Need of ventilation before HSCT						.5732						.8708						.6827
No	7/58	89.2	4.2	86.2	5.0		19/58	65.9	6.7	63.3	6.9		10/55	80.8	5.9	77.4	6.6	
Yes	5/32	82.7	7.2	82.7	7.2		10/32	67.3	8.6	67.3	8.6		4/29	84.1	7.4	84.1	7.4	
Neutropenia						.3152						.3861						.8773
No	10/56	82.6	5.3	79.3	6.0		17/56	67.3	6.7	67.3	6.7		10/55	80.8	6.0	77.1	6.7	
Yes	5/46	88.8	4.7	88.4	4.7		18/46	62.1	7.6	55.9	8.0		7/39	79.2	7.2	79.2	7.2	
Oral ulcers						.3384						.8886						.8351
No	9/81	89.7	3.5	87.6	4.0		26/81	68.1	5.5	64.2	5.8		13/81	82.4	4.8	80.2	5.1	
Yes	4/20	83.8	8.6	73.3	12.4		7/20	61.5	11.5	61.5	11.5		2/14	80.2	12.8	80.2	12.8	
FTT						.868						.74						.4987
No	11/74	87.4	3.9	81.7	5.5		25/74	63.3	5.9	63.3	5.9		11/69	84.1	4.7	81.6	5.2	
Yes	5/30	81.8	7.4	81.8	7.4		12/30	63.4	9.5	51.9	10.7		6/27	70.6	10.6	70.6	10.6	
No *Cryptosporidium* species prophylaxis before HSCT						.8896						.9309						.9141
No	6/63	84.8	4.7	84.8	4.7		21/63	65.7	6.4	63.1	6.6		10/62	80.9	5.6	80.9	5.6	
Yes	3/24	87.5	6.8	87.5	6.8		8/24	61.9	10.9	61.9	10.9		3/21	85.7	7.6	85.7	7.6	
Conditioning regimen						**.0073**						**<.0001**						**.0031**
MAC	5/57	92.7	3.5	90.0	4.3		10/57	81.6	5.3	81.6	5.3		6/58	91.0	3.9	88.3	4.6	
RIC	8/25	71.8	9.1	62.8	11.5		16/25	41.9	10.2	32.6	9.8		9/23	55.0	11.6	55.0	11.6	
MAC low tox	1/21	93.3	6.4	93.3	6.4		8/21	42.8	15.8	42.8	15.8		1/17	83.3	15.2	83.3	15.2	
NMA‡	1/2	50.0	35.4	‖	‖		2/2	0	§	‖	‖		2/3	33.3	27.2	33.3	27.2	
Donor type						**.0373**						.0605						.2619
MSD	3/27	88.8	6.1	88.8	6.1		5/27	85.0	6.9	80.8	7.8		4/27	88.8	6.1	84.6	7.1	
MUD	2/39	94.0	4.1	94.0	4.1		13/39	61.6	9.0	56.9	9.5		5/38	94.2	4.0	77.6	9.3	
MMUD ad. vol.	7/24	72.7	9.8	58.1	15.2		10/24	52.1	11.9	52.1	11.9		7/24	72.6	9.8	63.6	12.0	
MMFD + mmUCB	3/11	81.8	11.6	70.1	14.7		6/11	45.5	15.0	45.5	15.0		2/11	90.9	8.7	77.9	14.1	
Stem cell source						.0936						**.0035**						.1123
BM	6/62	91.7	3.6	88.3	4.8		15/62	75.5	5.8	73.0	6.1		8/60	84.1	5.3	84.1	5.3	
PBSC	7/33	78.4	8.0	72.8	9.2		17/33	43.6	10.1	37.4	10.4		10/36	65.2	10.0	58.7	10.9	
UCB	3/10	70.0	14.5	70.0	14.5		5/10	50.0	15.8	50.0	15.8		2/8	75.0	15.3	75.0	15.3	

Organ damage was defined as the presence of chronic lung disease, liver alterations (sclerosing cholangitis or liver fibrosis or hepatitis), or both. EFS and OS were calculated from the first HSCT, whereas DFS was calculated from the last procedure (ie, second HSCT, boost, or DLI), and thus the analyses were performed considering the covariates at the proper procedure. Significant *P* values ($P < .05$) are shown in boldface.

ad. vol., Adult volunteer; *FTT*, failure to thrive; *mm*, mismatched; *PJP*, *Pneumocystis jirovecii* pneumonia; *URTI*, upper respiratory tract infection.

*Number of patients with available data.

†All liver alterations, including ascending cholangitis, mild hepatic portal inflammation, and minimal alterations.

‡The NMA group is reported for descriptive purposes only but has not been included in the statistical analyses (log-rank test) because of its low numbers.

§SEs were not estimable at this time point.

‖No subjects at risk at this time point.

requirement for immunoglobulin supplementation for more than 2 years after HSCT; or death. Events for calculation of DFS were the ongoing requirement of immunoglobulin supplementation 2 years after the last procedure and death, whereas the only event considered for OS was death from any cause. Patients observations were censored at the date of last contact when no events were observed. The Kaplan-Meier method was used to estimate the probabilities of OS, EFS, and DFS, with SEs calculated according to the methods of Greenwood. Curves were compared by using the log-rank test, and pairwise comparisons were adjusted for multiplicity according to the method of Sidek, whereas the Cox proportional hazard model was used for multivariable analyses. All tests were performed 2-sided, with a .05 level of significance.

Analyses were performed in SAS 9.3 (SAS Institute, Cary, NC) and R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) software.

RESULTS

Overall survival

Data from 154 procedures were collected: 130 first, 13 second, and 1 third HSCT; 6 cell boosts (infusions of cells from the same donor without conditioning); and 4 DLIs. Most were performed since 2000. Median age at first transplantation was 4.0 years (range, 0.5-38.3 years). Patients from the historical cohort underwent transplantation at an older age (median, 8.5 years) compared with those treated after 2000 (median, 3.4 years; $P = .0012$). Median time interval between diagnosis and HSCT was 2.0 years, although it was slightly higher for HSCT before 2000 (3.9 years, $P = .0012$, Table I).

OS after first HSCT improved,[43] reaching 81% and 78.2% at 2 and 5 years, respectively. In particular, as observed in patients with other PIDs, outcome improved after 2000, likely because of improvement in transplant-related procedures and patient management (5-year OS before 2000, 58.3%; OS since 2000, 82.2%; $P = .0030$).

Patients undergoing transplantation at less than 5 years of age reached nearly 90% OS at 2 and 5 years after HSCT. Those older than 10 years at treatment had a 37.8% OS at 5 years ($P < .0001$). This "age effect" was also observed in patients undergoing transplantation since 2000, although a slight improvement in OS was noted in older patients (OS of 43.8% at 5 years, Fig 1, *A*, and Table III). Age at diagnosis (<12 vs >12 months) did not influence OS. Waiting time between diagnosis and HSCT had an effect on outcome, with significantly better survival for those undergoing transplantation within 2 years from diagnosis (Fig 1, *F*).

Pre-existing organ damage (mainly chronic lung disease, liver dysfunction, or both) before HSCT negatively influenced outcome (OS of 61.5% at 2 years and 55.6% at 5 years; without organ damage: OS of 92.9% at 2 and 5 years; $P < .0001$). Liver disease, especially sclerosing cholangitis, was the most important adverse risk factor (OS of 51.2% and 46.9% at 5 years, respectively; $P < .0001$), followed by protracted diarrhea (OS of 55.5% at 5 years, $P = .0002$) and gastrointestinal infection by *Cryptosporidium* species (OS of 59.6% at 5 years, $P = .0004$). These clinical features were confirmed to negatively influence outcome also in patients undergoing most recent transplantations, even if less profoundly (Fig 1, *B-E*, and Table III). The presence of chronic lung disease, previously a significant risk factor,[43] did not significantly influence survival in recent transplantations. Type of CD40L gene mutation, previous clinical history of respiratory tract infections, including *Pneumocystis jirovecii* pneumonia, requirement of ventilation before transplantation, neutropenia, oral ulcers, failure to thrive, and absent *Cryptosporidium* species prophylaxis before HSCT had no significant influence on OS.

Use of myeloablative conditioning regimens resulted in better survival as compared with RIC after the year 2000 ($P = .0073$), with significant differences emerging at pairwise comparison between MAC low tox or MAC and RIC ($P = .0197$ and $P = .0258$, respectively; see Table E6 in this article's Online Repository at www.jacionline.org). Of note, OS in patients receiving MAC improved in recent years (Table III and see Fig E3, *A*, in this article's Online Repository at www.jacionline.org).

Finally, a significant difference in OS emerged between different donor types (whole cohort, $P = .0198$; >2000, $P = .0373$), with better survival achieved with matched donors (both sibling and unrelated donors). However, at pairwise comparison, the difference in OS between MUDs and MMUDs was attenuated in most recent years ($P = .0545$), reflecting an improved outcome also in the MMUD setting. Moreover, among adult volunteer donors, there seemed to be a negative trend in OS, with increasing number of mismatches (Table III and see Fig E3, *B*, and Table E7 in this article's Online Repository at www.jacionline.org).

EFS

EFS after first HSCT was 62.6% and 58.1% at 2 and 5 years, respectively, with only a slight improvement after the year 2000 (Table III). It was very low (25.2%) in patients undergoing transplantation at 10 years of age or older, but an improvement was observed in recent years in this subgroup (Fig 2, *A*). Age at diagnosis significantly influenced EFS, which appeared better in those receiving early diagnosis (<1 year of age), whereas the time interval from diagnosis to HSCT was not relevant (Table III and data not shown).

Pre-existing organ damage significantly affected EFS, in particular the presence of sclerosing cholangitis, both in historical and recent transplantations, in spite of an improvement in the latter (Fig 2, *B* and *C*, and Table III). Other clinical features before HSCT and genotype did not strongly influence EFS.

MAC was associated with greater EFS (81.6% at 5 years in patients undergoing transplantation since 2000, $P < .0001$; Fig 2, *F*, and Table III) as compared with MAC low tox and RIC (see Table E6), possibly explained by better engraftment of donor cells with this regimen or use in less compromised patients. Stem cell source resulted in significant differences, with best EFS associated with BM (73% at 5 years' FU in patients undergoing transplantation since 2000; Fig 2, *E*, and Table III).

In recent years, no significant differences in EFS emerged between donor types in univariate analysis (Fig 2, *D*, and Table III). However, multivariable EFS analysis, which was performed on patients undergoing transplantation after 2000 with complete data (n = 96), showed donor type and conditioning regimen to be the most significant influences. In particular, patients receiving HSCT from mismatched or MUD donors showed a 4.2- and 3.3-fold increase, respectively, in the hazard of event compared with those from MSDs ($P = .0189$ and $P = .0607$). RIC use was associated with a 3.2-fold increased hazard ratio, as compared with MAC ($P = .0323$). The presence of pre-existing organ damage before HSCT was associated with a 2.7-fold increased hazard ($P = .1036$). Pretransplantation sclerosing cholangitis and age at HSCT had no relevant role on EFS (see Table E8 in this article's Online Repository at www.jacionline.org).

Results of DFS analysis are described in the Results section and Fig E2 in this article's Online Repository at www.jacionline.org.

Causes of death

Twenty-six deaths were reported, most of them transplant-related (n = 22 [84.6%]). Most occurred within 6 months of HSCT (n = 20 [76.9%]), mainly caused by infections (see Fig E4 in this article's Online Repository at www.jacionline.org). Liver failure was the cause of death of 2 patients with pre-existing sclerosing cholangitis who experienced severe liver GVHD, *Cryptosporidium* species infection, and veno-occlusive disease after transplantation. Graft rejection was reported as the primary cause of death in 3 patients.

Four non–transplantation-related deaths were caused by progression of original disease. In 2 cases neurologic complications occurred, with progressive neurodegeneration in 1 patient and worsening progressive multifocal leukoencephalopathy in another patient with a history of JC virus encephalitis before transplantation. In the other 2 cases infection (n = 1) and deteriorating liver function (n = 1) were complicated by previous graft rejection (Table IV).

Rejection

Eighteen patients (14.8% of 122 patients with available data) experienced graft rejection after first transplantation (Table IV). Most occurred within 6 months of HSCT (72.2%), mainly after unrelated donor transplantation (83.3%, 10 MUDs and 5 MMUDs, of which 3 were adult volunteers and 2 were UCB). The stem cell source was BM, PBSCs, or UBC in 8, 8, and 2 patients, respectively. Positive selection of $CD34^+$ cells was performed in 3 procedures. RIC was the most common conditioning regimen (n = 8), followed by MAC (n = 5), MAC low tox (n = 3), and NMA (n = 2). Most patients experienced infections in the first 6 months of FU after first transplantation, mainly of viral origin. No signs of acute GVHD were observed in 72.2% of patients in this subgroup.

Most patients who rejected their first HSCT received further therapeutic interventions (10 second HSCT, 1 third HSCT, and 1 cell boost) after a median of 11.7 months from the first transplantation. Most were alive at the last FU (81.8%), and in 66.7% immunoglobulin supplementation could be discontinued. Seven patients did not receive additional cell therapy procedures. Three of these patients continued supportive care with immunoglobulin supplementation and are alive, whereas the remaining 4 died. Deaths occurred at a median of 25 months after HSCT, mainly because of disease progression (infections and deteriorating liver function). Donor type, stem cell source, and occurrence of viral infections early after HSCT or acute GVHD did not significantly influence the risk of rejection.

Information on additional procedures can be found in the Results section and Table E3 in this article's Online Repository at www.jacionline.org.

Engraftment and cure rate

Transplantation resulted in complete or partial donor chimerism in most patients that was stable over time to the last FU (Fig 3, *A*). Data about lineage-specific donor chimerism were available only for a subgroup of patients. Median lineage-specific donor chimerism remained stable at 88% or greater up to the last FU (>1 year after last procedure) in both granulocytes and T lymphocytes, whereas in B lymphocytes a slight reduction in donor chimerism was observed over time (median donor chimerism, 75%; Fig 3, *B*). At the last available FU (>1 year) after the last procedure (see Fig E5 in this article's Online Repository at www.jacionline.org), donor cell engraftment in granulocytes ($CD15^+$ cells) and T lymphocytes ($CD3^+$ cells) was complete or predominantly donor in 78.1% and 82.9% patients with available data, respectively, whereas in B lymphocytes a greater percentage of predominantly recipient chimerism was observed (35.7% patients).

Decreasing lineage-specific chimerism was observed over time in 27.8% of transplantations (with FU ≥1 year among those with available data). However, in another 25% of transplantations, increasing donor cell chimerism in T- and B-lymphocyte subpopulations was observed (Fig 4, *A*). In this subgroup 3 patients received DLI infusion with a favorable effect on donor cell chimerism.

Among survivors who ceased immunoglobulin replacement at 2 or more years after the last procedure and for whom data were available, T-lymphocyte chimerism was complete or predominantly donor in 85.2%. B-cell chimerism was full donor in 7 and predominantly recipient (range, 18% to 43% donor chimerism) in 5 of them (Fig 4, *B*).

A greater percentage of complete donor chimerism (63.2%) was observed in transplantations in which patients did not experience viral infections after HSCT (Fig 4, *C*). Moreover, viral infections after HSCT might have influenced T-lymphocyte chimerism kinetics: in the majority of transplantations in which decreasing T-lymphocyte chimerism was observed (91.7%), viral infections occurred in early FU, likely favoring expansion of autologous lymphocytes to replenish the niche (Fig 4, *D*, and data not shown).

Immune reconstitution and data regarding complications (see Table E9 in this article's Online Repository at www.jacionline.org) can be found in the Results section in this article's Online Repository.

DISCUSSION

This is the largest HSCT series for CD40L deficiency collected worldwide to date. It includes data from 130 patients undergoing transplantation over more than 20 years. Interestingly, comparison of the 2 historical cohorts of patients treated before and after 2000 clearly shows how patients' features have changed over time, mainly thanks to improvement in diagnostic tools and clinical management. Most recent patients have undergone transplantation at a younger age, with a shorter time interval after diagnosis and lower organ damage burden. All these factors have contributed to the general HSCT outcome improvement observed in the past years.

These differences, although interesting, represented a difficulty in data analysis that was hampered by the presence of potential confounding between variables. For this reason, for main outcome measures, we analyzed historical periods separately. In particular, we decided to perform multivariate analysis only on the most recent transplantation cohort because it could not be performed with inclusion of the "period effect" because of statistical model limitations. Moreover, although the heterogeneity induced by the period is relevant, we think that evaluation of the more recent patient cohort is more interesting because it reflects more closely the current clinical practice.

Other limitations of the study are represented by the sample heterogeneity typical of retrospective observational studies,

TABLE IV. Transplant features, therapeutic intervention, and outcome in 18 patients who experienced graft rejection after the first HSCT for CD40L deficiency

Patient no.	Year of first HSCT	First HSCT stem cell source	First HSCT donor type	First HSCT conditioning regimen	Timing of rejection/ decreasing chimerism	Therapeutic intervention (mo after first HSCT)	Infections in early FU*	Acute GVHD (grade)	Outcome (at last FU)
8	2012	BM	MUD	RIC (Flu/Mel/ATG)	6 mo FU	Second HSCT (28.4)	ADV, EBV Bacterial sepsis	Yes (grade I)	Alive (on IVIG)
9	2012	PBSC (TCRαβ depleted)	MUD	MAC low tox (Treo/Flu/ATG)	6 mo FU	Second HSCT (8)	ARVI	Yes (grade II)	Alive (off Ig)
15	2007	BM	MSD	RIC (Flu/Mel/ alemtuzumab)	>12 mo FU (6 y)‡	None	ADV, *Cryptosporidium* species	No	Alive (on IVIG)
33	2009	PBSC	MUD	NMA (Flu/ATG)	12 mo FU‡	Second HSCT (15.4)§	HHV6, *Cryptosporidium* species	No	Alive (on IVIG)
37	1996	BM (positive selection of $CD34^+$ cells)	MUD	MAC (Bu/Cy/ aLFA1-2)	6 mo FU	None	No	No	Alive (on IVIG)
41	2001	PBSC (positive selection of $CD34^+$ cells)	MMFD (haplo)	MAC (Bu/Cy/ATG)	6 mo FU	None	Whipworm	No	Deceased
49a	2001	BM (positive selection of $CD34^+$ cells)	MUD	MAC (Bu/Cy/ATG)	6 mo FU	Second HSCT (12.5)	HHV6, ADV CVL infection	No	Alive (off Ig)
74	2014	BM	MUD	MAC low tox (Treo/Flu/ Alemtuzumab)	19 mo FU‡	Second HSCT (21.4)	CMV, parainfluenza URTI	No	Alive (on IVIG)
77	2004	PBSC	MMUD	MAC low tox (Treo/Flu/ATG)	6 mo FU	Second HSCT (10.9) Third HSCT (31.1)	CMV reactivation Clostridium difficile	No	Alive (off Ig)
83	2001	BM	MMUD	RIC (Flu/Mel/ATG)	12 mo FU	None	EBV, *Cryptosporidium* species BK virus	Yes (grade I)	Deceased
85	2003	BM	MSD	RIC (Flu/Mel/ alemtuzumab)	6 mo FU	Second HSCT (21.1)	No	No	Alive (off Ig)
86	2006	PBSC	MUD†	NMA (Flu/Cy/ alemtuzumab + anti-CD45)	6 mo FU	None	Mycobacteria (gut)	No	Deceased
89	2011	PBSC	MUD	RIC (Flu/Mel/ alemtuzumab)	>12 mo FU (3 y)	None	ADV	No	Alive (on SCIG)
98	2007	UCB	MMUD	MAC (Bu/Cy/ATG)	<1 mo FU	Second HSCT (1.3)	CMV	No	Alive (off Ig)
102	1997	BM (T-cell depleted)	MUD	MAC (Bu-Cy-ATG + in vivo LFA1 CD2)	<1 mo FU	Cell boost (1.1)	Aspergillus species, Gram - sepsis	No	Deceased
107	2011	PBSC	MUD†	RIC (Flu/Mel/ alemtuzumab)	<3 mo FU	Second HSCT (3.3)	NA	NA	Alive (off Ig)
124	2014	PBSC (CD45RA depleted)	MMUD	RIC (Bu/Flu/TT/ATG)	<3 mo FU	None	ADV, rhinovirus *Cryptosporidium* species	No	Deceased
125	2003	UCB	MMUD	RIC (Bu/Flu/ATG)	<2 mo FU	Second HSCT (2)	NA	NA	Deceased

ADV, Adenovirus; *aLFA*, anti-lymphocyte function-associated antigen; *ATG*, antithymocyte globulin; *ARVI*, acute respiratory viral infection; *Bu*, busulfan; *CMV*, cytomegalovirus; *CVL*, central venous line; *Cy*, cyclophosphamide; *Flu*, fludarabine; *Gram -*, Gram-negative; *HHV6*, human herpes virus 6; *Ig*, immunoglobulins; *IVIG*, intravenous immunoglobulins; *Mel*, Melphalan; *NA*, not available; *RSV*, respiratory syncytial virus; *SCIG*, subcutaneous immunoglobulins; *TCR*, T-cell receptor; *Treo*, treosulfan; *URTI*, upper respiratory tract infection.

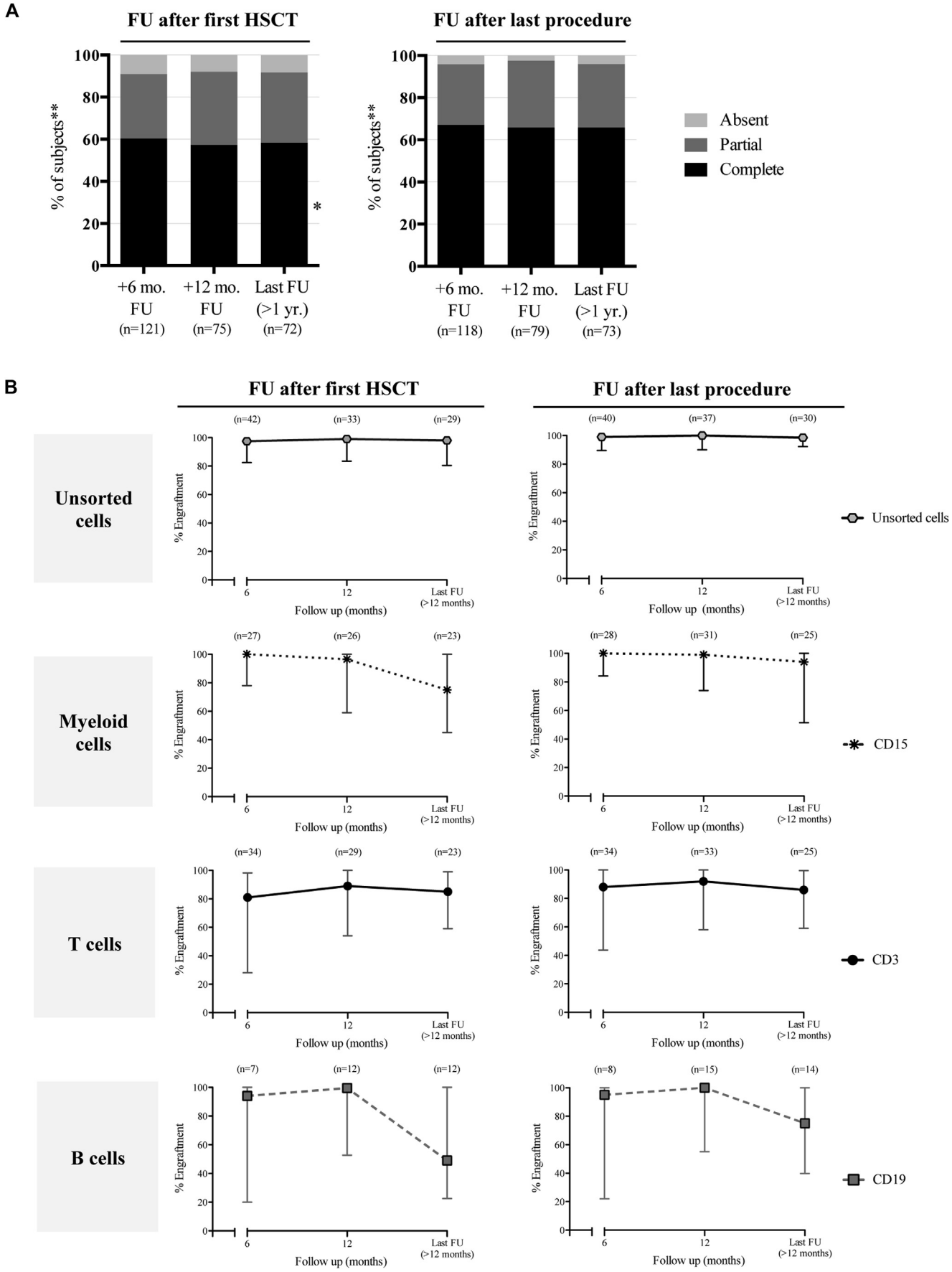
*First 6 months after first HSCT.

†Numbers of HLA loci studied were not specified.

‡Chimerism decreasing since 6 months of FU.

§This patient also received 2 liver transplantations, 1 before the first HSCT and 1 after the second HSCT. He also experienced chronic GVHD after the second HSCT.

including many different centers and spanning over long time frames, and by unavoidable intrinsic correlations between variables, such as the choice of conditioning regimen and the patient's clinical status. Furthermore, despite the fact that the total number of patients included in the study is the highest ever collected for this disease, analyses on patient subgroups were limited by small sample size, especially when evaluating different conditioning regimens, donor types, and lineage-specific donor cell chimerism. This makes it difficult to draw strong conclusions, especially at the longest FU, but our study


A
FU after first HSCT
FU after last procedure
% of subjects**
100
80
60
40
20
0
*
+6 mo. FU (n=121)
+12 mo. FU (n=75)
Last FU (>1 yr.) (n=72)
+6 mo. FU (n=118)
+12 mo. FU (n=79)
Last FU (>1 yr.) (n=73)
Absent
Partial
Complete
B
FU after first HSCT
FU after last procedure
Unsorted cells
Myeloid cells
T cells
B cells
% Engraftment
Follow up (months)
6
12
Last FU (>12 months)
(n=42) (n=33) (n=29)
(n=40) (n=37) (n=30)
(n=27) (n=26) (n=23)
(n=28) (n=31) (n=25)
(n=34) (n=29) (n=23)
(n=34) (n=33) (n=25)
(n=7) (n=12) (n=12)
(n=8) (n=15) (n=14)
Unsorted cells
CD15
CD3
CD19

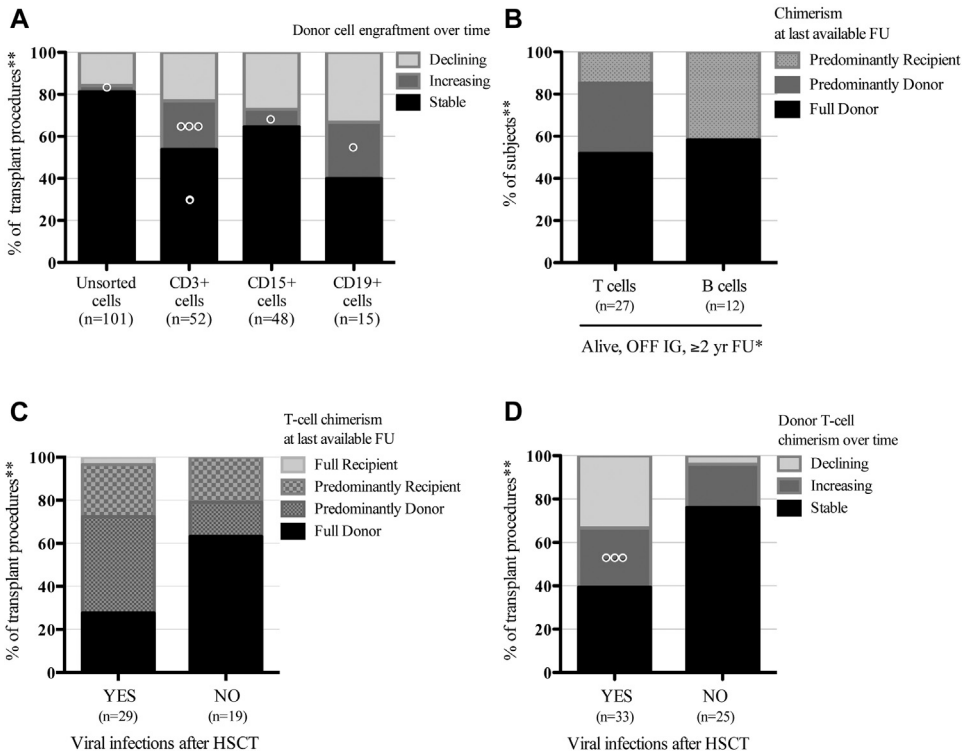


FIG 4. Engraftment kinetics and T-cell chimerism. **A,** Donor cell engraftment kinetics represented by the percentage of transplantation procedures in which increasing, decreasing, or stable donor cell engraftment was observed over time 1 or more years after the last procedure. °One or °°°3 patients received DLIs. Data on unsorted cells, sorted myeloid cells ($CD15^+$), B lymphocytes ($CD19^+$), and T lymphocytes ($CD3^+$) are reported. **B,** T- and B-cell chimerism at last FU in survivors off immunoglobulin replacement *(IG)* at 2 or more years after the last procedure (*). **C,** T-cell chimerism at last FU, according to the occurrence of viral infections after HSCT (yes/no). **D,** Donor T-cell chimerism kinetics over time (increasing/declining/stable), according to the occurrence of viral infections after HSCT (yes/no). °°°Three patients received DLIs. **Percentage of transplantations (or subjects) with available data.

provides a number of novel and interesting findings that should be further explored in the future.

In spite of these difficulties, a number of important new observations emerge from this report. First, OS after transplantation is now 80%, although there remain significant differences between those undergoing transplantation at less than 10 years of age and those undergoing transplantation when older, even in more recent years. Linked with this was a superior survival in those undergoing transplantation within 2 years of the diagnosis of CD40L deficiency and in those without organ damage, specifically liver disease. Importantly, in recent years, transplants from MSDs and MUDs reached similarly good results in terms of OS but not EFS, which remained lower with unrelated or mismatched donors. Most patients who received MAC showed complete engraftment at last FU, whereas RIC was associated with absent engraftment. New conditioning regimens, specifically MAC low tox, had superior OS and DFS, but not EFS, as compared with RIC. This could likely be explained by the tendency to reach a lower level of myeloid chimerism over time in patients who received these conditioning regimens, which might reflect decreased stem cell engraftment.

DFS was more likely with the use of myeloablation. Patients who ceased immunoglobulins were stable over time, even if additional procedures (repeat HSCT, boost infusions) were required to attain this in some cases. Among those with FU of 2 years or greater, median CD40L expression on activated $CD4^+$ T cells was 49% in those who stopped immunoglobulin supplementation and 14.5% in those who still needed it. T-lymphocyte chimerism was complete or predominantly donor in most cured patients, but unfortunately, a minimum T-cell donor percentage reliably associated with immunoglobulin independence could not be retrieved based on available data.

FIG 3. Donor cell engraftment after first HSCT and after the last procedure. **A,** Overall donor cell engraftment over time represented by percentages of subjects with complete, partial, or absent engraftment on unsorted cells at different time points after the first HSCT *(left panel)* and after the last procedure *(right panel)*. *Three patients with full chimerism received DLIs. **Percentage of those with available data. **B,** Median lineage-specific donor cell engraftment over time at different time points after the first HSCT *(left panels)* and after the last procedure *(right panels)*. Data on unsorted cells, sorted myeloid cells (CD15), T lymphocytes (CD3), and B lymphocytes (CD19) are reported. For each median value, interquartile range is plotted, and the number of subjects for whom data were available at each FU is reported in parentheses.

Deaths were mainly related to transplantation-associated complications, including graft rejection, although a few were due to progression of pre-existing neurologic disease. The rejection rate was 15%, usually occurring early after transplantation, although retransplantation was usually successful. Among those who rejected their first transplant, only 11.1% received HSCT from MSDs, which was in line with the finding of lower EFS in transplants from other donor types.

A higher percentage of complete donor chimerism (63.2%) was observed in transplantations in which patients did not experience viral infection after HSCT. Moreover, viral infection after HSCT might have influenced T-lymphocyte chimerism kinetics: in the majority of transplants in which decreasing T-lymphocyte chimerism was observed (91.7%), viral infections occurred in early FU, likely favoring the expansion of autologous T lymphocytes to replenish the niche.

Although we did not compare our results with those in patients not undergoing transplantation, previous reports have demonstrated similar survival as ours, although with improved quality of life in those undergoing HSCT.[20] However, from our data, clear trends emerge. HSCT is curative, but best results continue to be seen in younger patients, who have the least organ damage and are infection free. Furthermore, MAC is associated with a better immunological outcome than RIC regimens, again favoring earlier HSCT.

There is a need for prospective studies directly comparing risks of HSCT with those of lifelong immunoglobulins and prophylaxis. Additionally, advances in gene therapy, and particularly gene editing, might be attractive as a potential therapeutic alternative for those for whom HSCT is too risky because of associated clinical features and poor donor options, particularly given that infusion of gene-corrected T lymphocytes might be curative.[52]

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Key messages

- **HSCT can be curative in patients with CD40L deficiency, with the best outcome if performed before 10 years of age and without organ damage, especially sclerosing cholangitis.**
- **Superior OS was achieved with matched donors. HSCT early after diagnosis and use of myeloablative regimens resulted in greater OS and DFS. EFS resulted improved with MSDs, MAC, and BM as stem cell source.**
- **Reduced intensity and nonmyeloablative conditioning were associated with poor donor cell engraftment.**

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