

Clinical features and hematopoietic stem cell transplantations for CD40 ligand deficiency in Japan

Kanako Mitsui-Sekinaka, MD,^a Kohsuke Imai, MD, PhD,^{a,b} Hiroki Sato, MS,^c Daisuke Tomizawa, MD, PhD,^b Michiko Kajiwarra, MD, PhD,^d Masayuki Nagasawa, MD, PhD,^b Tomohiro Morio, MD, PhD,^b and Shigeaki Nonoyama, MD, PhD^a *Saitama and Tokyo, Japan*

Background: The long-term outcome of X-linked hyper-IgM syndrome (XHIM) caused by mutations in *CD40LG* is poor, and the only curative treatment is hematopoietic stem cell transplantation (HSCT).

Objective: We sought to determine the clinical features and factors affecting outcomes in patients with XHIM.

Methods: We enrolled and retrospectively analyzed data from 56 Japanese patients with XHIM, including 29 patients who received HSCT.

Results: The long-term survival rate was poor in those not undergoing HSCT (overall survival rate at 40 years of age, 28.2%). The overall survival rate of patients undergoing HSCT ($n = 29$) was significantly higher than that of those not undergoing HSCT ($n = 27$, $P = .0231$). Moreover, event-free and disease-free survival rates were significantly greater in patients 5 years old or younger at the time of transplantation ($n = 14$) than in older patients ($n = 15$).

Conclusion: On the basis of these results, we concluded that HSCT improved the outcomes of patients with XHIM and that an age of 5 years or younger was optimal for the timing of HSCT because persistent infections and severe organ damage were frequently observed in patients older than 6 years. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: CD40 ligand, hematopoietic stem cell transplantation, *Pneumocystis jirovecii*, *Cryptosporidium parvum*, *Cryptococcus neoformans*, primary immunodeficiency, hyper-IgM syndrome, combined immunodeficiency, class-switch recombination

X-linked hyper-IgM syndrome (XHIM) is a rare primary immunodeficiency disease caused by mutations in *CD40LG*, which encodes the CD40 ligand (CD40L) and is located at Xq26.3-27. *CD40LG* mutations cause defective functioning of

Abbreviations used

CD40L: CD40 ligand
G-CSF: Granulocyte colony-stimulating factor
GVHD: Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
IVIG: Intravenous immunoglobulin substitution
OS: Overall survival
PCP: *Pneumocystis jirovecii* pneumonia
RIC: Reduced-intensity conditioning
XHIM: X-linked hyper-IgM syndrome

CD40L, a membrane-bound protein expressed on activated CD4⁺ T lymphocytes.¹⁻³ CD40L binds to CD40, a receptor on B cells, and induces immunoglobulin class-switching. Therefore patients with XHIM exhibit impaired immunoglobulin class-switching from IgM to other isotypes, resulting in the manifestation of hyper-IgM syndrome.^{4,5} Moreover, defective functioning of CD40L causes T-cell dysfunction because of the disordered activation of antigen-presenting cells, such as dendritic cells, and the reduced expression of costimulatory signals, such as CD80, to antigen-presenting cells.^{6,7}

As a result of this impaired antibody class-switching and T-cell dysfunction, increased susceptibility to infections is the most prominent clinical problem affecting patients with XHIM. Clinically, these patients experience bacterial and opportunistic infections. In particular, patients with XHIM frequently contract *Pneumocystis jirovecii* pneumonia (PCP) during infancy, which is fatal without adequate treatment. Diarrhea is another common complication that is often associated with *Cryptosporidium* species infection, which can also contribute to ascending or sclerosing cholangitis or liver cirrhosis.⁸ Patients with XHIM also have infections caused by other pathogenic organisms, such as herpes simplex virus, varicella-zoster virus, cytomegalovirus, *Candida* species, *Histoplasma capsulatum*, *Aspergillus* species, and *Cryptococcus* species.^{9,10}

The rapid and appropriate administration of antibiotics is required for bacterial infections, and granulocyte colony-stimulating factor (G-CSF) should be administered, if needed. In addition, intravenous immunoglobulin substitution (IVIG) and subcutaneous immunoglobulin substitution are partially efficacious treatments for recurrent bacterial infections of the respiratory tract. However, retrospective studies in Europe revealed poor long-term survival despite IVIG substitution.⁹ Chemoprophylaxis with trimethoprim-sulfamethoxazole is highly effective for preventing PCP. Despite such treatments and prophylaxis, long-term survival remains far from satisfactory because of T-cell dysfunction. In addition, many other complications are of concern. Neutropenia is a complication in 50% to 70% of patients with XHIM; autoimmune diseases and malignancy are

From the Departments of ^aPediatrics and ^cPublic Health, National Defense Medical College, Saitama; ^bthe Department of Pediatrics, Tokyo Medical and Dental University; and ^dthe Department of Transfusion Medicine, Medical Hospital, Tokyo Medical and Dental University.

Supported by grants from the Japanese Ministry of Defense; the Japanese Ministry of Health, Labour, and Welfare; and the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Disclosure of potential conflict of interest: T. Morio has received payment for lectures from CSL Bering, Chugai Pharmaceutical, and Teijin. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 5, 2014; revised February 5, 2015; accepted for publication February 13, 2015.

Corresponding author: Kohsuke Imai, MD, PhD, Department of Pediatrics, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo, Japan. E-mail: kimai.ped@tmd.ac.jp.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaci.2015.02.020>

TABLE I. Clinical features of patients undergoing or not undergoing HSCT

	All patients	Patients not undergoing HSCT	Patients undergoing HSCT	P value*
No. of patients	56	27	29	
Age at diagnosis (y), median (range)	1.5 (0.25-37)	2 (0.4-37)	1 (0.25-16)	.0208*
<i>CD40LG</i> mutation				
Splicing defects	10	8	2	.0375*
Missense mutation	15	8	7	.7655
Deletion	20	6	14	.0541
Nonsense mutation	10	5	5	1.000
Undetermined	1	0	1	1.000
Laboratory data at diagnosis				
Mean IgG (mg/dL)	147.6 (range, 0-744)	122.6	175	.3679
Mean IgA (mg/dL)	18.9 (range, 0-104)	17.8	20.1	.8005
Mean IgM (mg/dL)	450.2 (range, 28-2100)	420.5	481.2	.6716
Neutropenia	26	11 (40.7%)	15 (51.7%)	.4537
Outcome				
Alive	38	13	25	
Dead	18	14	4	.0038*

* $P < .05$.

also frequently observed.^{9,10} Complications other than recurrent infections should not be ignored because they are sometimes fatal.

Hematopoietic stem cell transplantation (HSCT) has been recommended as a curative treatment for patients with XHIM. In Europe, according to published data concerning HSCT for XHIM, HSCT was curative therapy for nearly 60% of patients with XHIM; however, the timing of HSCT presented the greatest challenge.¹¹ According to the European Group for Blood and Marrow Transplantation/European Society for Immunodeficiencies guidelines for HSCT for primary immunodeficiencies, which were updated in 2011, it can be concluded that patients with new diagnoses of XHIM require optimal management, including PCP prophylaxis, IVIG replacement, *Cryptosporidium* species avoidance, and organ disease monitoring. The guidelines further recommend performing HSCT, the timing of which depends on the available donor type. HSCT should be performed at diagnosis for patients without organ damage and with a matched sibling donor.

We have adopted a very similar XHIM treatment strategy in Japan as that used in Europe. In general, after diagnosis of XHIM, we recommend HSCT to all the patients and their parents. After obtaining agreement for HSCT, having enough organ capacity for HSCT, and finding available donors, we perform HSCT.

We previously reported a successful outcome after HSCT for patients with XHIM (8 cases) in Japan.^{12,13} On the other hand, according to a study conducted in the United States, only 5 (6.3%) of 79 registered patients received HSCT because the XHIM prognosis was supported by early diagnosis and supportive therapy. The mortality rate in that study did not exceed 10.1%.¹⁰ In contrast, the mortality rate in both European studies was approximately 32%.¹¹ It is unclear which factors contributed to this discrepancy.

In the present study we retrospectively analyzed the clinical features, prognosis, and results of HSCT to evaluate the efficacy of HSCT as a treatment for XHIM. To date, our study is the largest analysis of patients with XHIM in Japan.

METHODS

This retrospective study involved 56 Japanese patients who were given genetic diagnoses of XHIM through direct *CD40LG* sequencing at the

National Defense Medical College, Tokyo Medical and Dental University, or Kazusa DNA Research Institute between 1998 and 2012. Written informed consent was obtained from the patients' parents before sequence analysis. Twenty-nine of 56 patients received HSCT and were followed up at between 1 and 23 years. Some of the cases were reported elsewhere.¹²⁻¹⁴ The study was approved by the Institutional Review Board of the National Defense Medical College, Japan.

Clinical characteristics

We analyzed the patients' clinical characteristics at diagnosis, including age, mutation patterns, serum immunoglobulin levels, white blood cell counts and differentiation, infectious episodes, and other complications. We further assessed treatment after diagnosis, including IVIG, G-CSF, and HSCT. Twenty-nine patients who underwent HSCT were also assessed with regard to the transplantation procedure, and the posttransplantation data, including descriptions of infective episodes, engraftment details, complications, and outcomes, were analyzed retrospectively.

Statistical analysis

The Student *t* test and Fisher exact test were used for statistical analyses, and the Kaplan–Meier product-limit method was used for survival analyses. Comparisons of survival distributions were performed with the log-rank test, and a *P* value of less than .05 was considered significant. The survival analysis start time was the date of birth or transplantation. HSCT was censored in the overall survival (OS) analysis.

All analyses were performed with GraphPad Prism, version 5.0a, for Macintosh (GraphPad Software, San Diego, Calif) and JMP, version 10 (SAS Institute, Cary, NC).

RESULTS

Clinical characteristics of patients at diagnosis

Patients' characteristics are listed in Table I. All 56 patients were male, and the median age at diagnosis was 1.5 years (range, 0.25-37 years). In our study deletion was the most frequent type of mutation (20 deletions, 10 nonsense mutations, 15 missense mutations, 10 splice mutation, and 1 unknown mutation; see Table E1 in this article's Online Repository at www.jacionline.org). None of the patients in this study expressed CD40L on activated T cells, as determined by using fluorescence-activated cell sorting analysis.

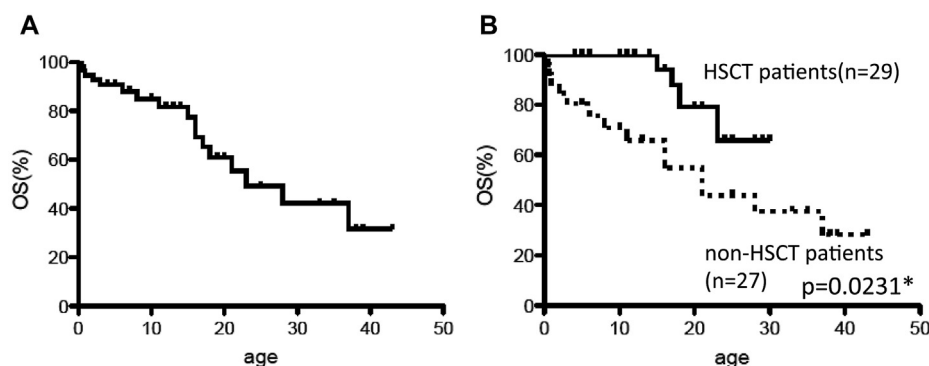


FIG 1. A, OS of all registered patients ($n = 56$). Median survival time was 23 years. Patients undergoing HSCT were censored from OS analysis at HSCT. **B**, The *solid line* indicates the OS of patients undergoing HSCT ($n = 29$); the *dashed line* indicates the OS of patients not undergoing HSCT ($n = 27$).

At the time of diagnosis, patients presented with hyper-IgM and low IgG and IgA levels; 46% of patients exhibited neutropenia. G-CSF was administered to neutropenic patients when needed, and some patients required regular administration. All patients began receiving IVIG after their receiving a diagnosis of immunodeficiency. HSCT was performed for 29 (51.8%) patients. Table I shows the clinical features of both patients receiving HSCT and those not receiving HSCT. Although there was no significant difference between the 2 groups, except for the age at diagnosis and mutation pattern, there was a strikingly large difference in outcome.

OS of patients undergoing and those not undergoing HSCT

Fig 1, A, presents the OS of all registered patients ($n = 56$). The median survival duration was 23 years, and OS at 30 and 40 years of age was 42.1% and 31.6%, respectively. The OS of patients undergoing HSCT ($n = 29$, 100% at 10 years and 65.9% at 30 years) was significantly better than that of patients not undergoing HSCT ($n = 27$, 62.5% at 10 years and 35% at 30 years; $P = .0231$; Fig 1, B).

Cause of death

Eighteen (32.1%) of 56 patients died during the observation period, which was from 1 to 23 years (mean, 6.4 years). Patients not undergoing HSCT died of infection (PCP in 5 patients, *Cryptococcus neoformans* meningitis in 1 patient, JC virus-associated progressive multifocal leukoencephalitis in 1 patient, and encephalitis of unknown origin in 1 patient), malignancies (bladder tumor relapse in 1 patient and undifferentiated sarcoma of the liver relapse in 1 patient), liver failure (2 patients), traffic accident (1 patient), and unknown cause (1 patient, Table II). Among patients undergoing HSCT, 2 died of infections, 1 died of acute graft-versus-host disease (GVHD), and 1 died of progressive liver failure (see Table E2 in this article's Online Repository at www.jacionline.org).

HSCT procedures and outcomes

Table III lists the details of HSCT. The median age at transplantation was 7 years (range, 2–23 years). Of these patients, 14 were aged 5 years or younger, and 15 were aged at least 6 years. There were no significant differences between the 2 groups other

TABLE II. Causes of death in patients not undergoing HSCT

Causes of death of patients not undergoing HSCT (age at death)	No.
Infection	8
PCP (6 mo, 8 mo, 11 mo, 3 y, and 16 y)	5
<i>Cryptococcus neoformans</i> meningitis (6 y)	1
JCV-PML (37 y)	1
Encephalitis, origin unknown (16 y)	1
Malignancy	2
Relapse of bladder tumor (21 y)	1
Relapse of undifferentiated sarcoma of the liver (11 y)	1
Liver failure (8 and 28 y)	2
Miscellaneous	2
Traffic accident (21 y)	1
Unknown (2 y)	1

JCV-PML, Progressive multifocal leukoencephalitis caused by JC virus.

than the existence of pretransplantation organ damage. Stem cell sources were either bone marrow ($n = 12$) or peripheral blood stem cells ($n = 1$) from genotypically identical siblings, HLA 6/6 phenotypically matched unrelated bone marrow ($n = 13$), or 6/6–5/6 matched unrelated cord blood ($n = 3$). Sixteen patients received myeloablative conditioning comprising busulfan (16 mg/kg) and cyclophosphamide (200 mg/kg) according to the 2004 European Society for Immunodeficiencies/European Group for Blood and Marrow Transplantation guidelines, 2 received antithymocyte globulin or antilymphocyte globulin in addition to busulfan/cyclophosphamide, 1 received total body irradiation at 12 Gy and cyclophosphamide, and 10 patients received reduced-intensity conditioning (RIC) regimens. There were 5 patients with pretransplantation organ damage. Three of them received myeloablative conditioning regimens (2 received busulfan/cyclophosphamide and 1 received total body irradiation/cyclophosphamide), and 2 received RIC regimens. Eight of 10 patients without pretransplantation organ damage received RIC regimens to avoid long-term complications. We analyzed the frequency of full donor chimerism among patients without pretransplantation organ damage, comparing those receiving busulfan/cyclophosphamide ($n = 16$) and RIC ($n = 8$) regimens. Fourteen (87.5%) of 16 patients receiving busulfan/cyclophosphamide HSCT and 4 (50%) of 8 patients receiving RIC HSCT achieved full donor chimerism ($P = .1288$). Of the patients receiving busulfan/cyclophosphamide-HSCT, 1 experienced rejection, and 1 experienced mixed chimerism, whereas of the patients receiving

TABLE III. Details of HSCT procedures

	All	Transplantation at 0~5 y old	Transplantation at ≥6 y old	P value*
No. of patients	29	14	15	
Age at diagnosis (y), median (range)	1 (0.25-16)	1 (0.25-3)	1 (0.25-16)	.9772
Age at transplantation (y), median (range)	7 (2-23)	3 (2-5)	15 (7-23)	<.0001*
Pretransplantation organ damage	5	0	5	.0421*
Donor source				
Matched sibling BM	12	4	8	.2635
Matched sibling PBSC	1	0	1	1.0000
Matched unrelated BM	13	8	5	.2723
Cord blood	3	2	1	.5977
Conditioning				
BU/CY	18	10	8	.4497
TBI/CY	1	0	1	1.0000
RIC regimens	10	4	6	.6999
Infused CD34 ⁺ cell dose (×10 ⁶ cells/kg), mean (range)	3.4 (0.087-9.1)	3.21 (0.2-9.1)	3.55 (0.087-9.0)	.5867

Patients undergoing HSCT were divided into 2 groups undergoing transplantation at 0 to 5 years (n = 14) and greater than 6 years (n = 15) old. There were no significant differences between the 2 groups other than pretransplantation organ damage. RIC regimens included the following: (1) fludarabine (125 mg/m²) plus melphalan (140 mg/m²) with or without ATG and with or without TBI (2-4 Gy; n = 6); (2) fludarabine (150 mg/m²) plus busulfan (6.4 mg/kg) plus cyclophosphamide (60 mg/kg; n = 2); (3) fludarabine (125 mg/m²) plus melphalan (140 mg/m²) plus cyclophosphamide (3 g/m²) plus ATG plus TBI (3 Gy; n = 1); and (4) fludarabine (125 mg/m²) plus cyclophosphamide (3 g/m²) with or without TBI (3 Gy; n = 1).

ATG, Antithymocyte globulin; BM, bone marrow; BU, busulfan; CY, cyclophosphamide; PBSC, peripheral blood-derived stem cell; TBI, total body irradiation.

*P < .05.

RIC-HSCT, 2 died of transplant-related mortality, 1 experienced rejection, and 1 experienced mixed chimerism.

Four patients (aged 15, 17, 18, and 23 years at the time of HSCT) died within 100 days after HSCT because of acute respiratory distress syndrome, followed by pulmonary aspergillosis, multiple-organ failure caused by sepsis (*Burkholderia cepacia*) and cryptosporidiosis, acute GVHD (gut), and liver failure, respectively (see Table E2). Twenty-five patients remain alive (the follow-up period ranged from 1-23 years).

Table IV lists the details and outcomes of HSCT. Twenty (80%) of 25 living patients were fully engrafted, and 22 (88%) remain free of IVIG substitution. Graft failure was observed in 3 patients despite myeloablative conditioning, and 1 patient was engrafted after a second HSCT. Mixed chimerism was observed in 3 patients; 1 received a busulfan/

cyclophosphamide regimen, and the others received an RIC regimen. All 3 patients required IVIG substitution for more than 1 year after HSCT.

Pretransplantation status of patients undergoing HSCT

Infectious episodes and other complications. These patients experienced recurrent bacterial infections, such as otitis media, sinusitis, pneumonia, and perianal abscesses, and opportunistic infections, including PCP (9 patients), *Cryptosporidium parvum* infection (3 patients), tuberculosis, aspergillosis, cytomegalovirus pneumonitis, cryptococcosis, and Kaposi sarcoma. All PCP infections were observed when the patients were 0 to 4 years old, whereas all *C parvum* infections were observed in older patients.

In particular, patients older than 6 years experienced not only infections but also other complications, such as bronchiectasis (2 patients), Crohn disease–related perforation of the gut, proteinuria, failure to thrive, osteoporosis, sclerosing cholangitis, and hepatic encephalopathy (see Table E3 in this article's Online Repository at www.jacionline.org).

Organ damage at transplantation. Before HSCT, 5 of 29 patients undergoing HSCT had organ damage (eg, pulmonary failure, liver failure, or gut complications); all were older than 6 years at the time of transplantation (Fig 2).

Posttransplantation complications

Thirteen patients had various types of infections after HSCT, including pulmonary aspergillosis (4 patients), PCP (2 patients), *C parvum* infection (2 patients), and viral encephalitis (2 patients). Two of these patients had severe fatal infections (see Table E2), and 1 patient with EBV encephalitis presented with residual neurologic sequelae, despite successful treatment for EBV infection.

Two patients had hemophagocytosis, which resolved after administration of steroids, immunosuppressive drugs, and/or etoposide. In spite of successful treatment for hemophagocytosis, 1 patient had secondary graft failure, and another died 50 days after

TABLE IV. Posttransplantation status of 29 patients undergoing HSCT

	All	Transplantation at 0-5 y old	Transplantation at ≥6 y old	P value
No. of patients	29	14	15	
Outcome, alive/dead	25/4	14/0	11/4	.0996
Fully engrafted	20	12	8	.1086
Mixed chimeras	3	1	2	1.0000
Rejected	2	1	1	1.0000
GVHD				
aGVHD, grade 0~1	15	7	8	1.0000
Grade 2~3	8	5	3	.4270
Grade 4	4	1	3	.5977
cGVHD	5	4	1	.1686
Infection	13	6	7	1.0000
Other complications*	12	3	9	.0604
IVIG substitution ≥1 y	3	1	2	1.0000

Data included outcome, GVHD, infection, and other complications after first HSCT only.

aGVHD, Acute graft-versus host disease; cGVHD, chronic graft-versus-host disease.

*Other complications included graft failure, mixed chimeras, thrombocytopenia, hemophagocytic lymphohistiocytosis, renal failure, hepatic veno-occlusive disease, liver failure, chronic subdural hematoma, and brain herniation.

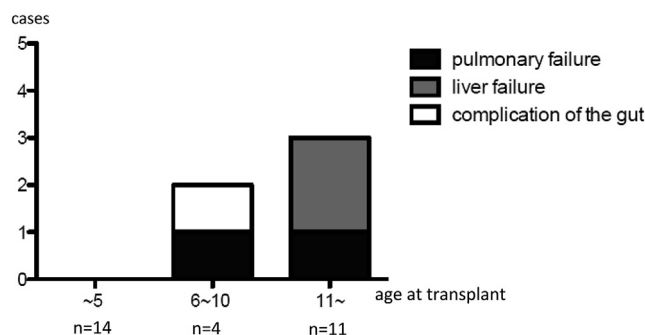


FIG 2. Before transplantation, 5 patients had organ damage, such as pulmonary failure, liver failure, and/or intractable diarrhea. There were no cases of organ damage before transplantation among patients aged 0 to 5 years.

HSCT of acute GVHD (gut) that occurred subsequent to methicillin-resistant *Staphylococcus aureus* sepsis and hemophagocytosis. Grade 4 acute GVHD was observed in 4 patients. Five patients had chronic GVHD that resolved after immunosuppressive treatment, including steroids and tacrolimus.

Survival analysis of patients undergoing HSCT

Fig 3 shows OS, event-free survival, and disease-free survival rates of patients undergoing HSCT. *Event* was defined as transplant-related mortality, graft failure, grade 4 acute GVHD, severe organ damage, and/or a status requiring IVIG for longer than 1 year after HSCT, and *disease free* was defined as a patient who was fully engrafted and free from IVIG for longer than 1 year without permanent organ damage (eg, not requiring dialysis or respiratory ventilation or exhibiting severe neurologic sequelae).

In all analyses patients aged 5 years or younger at the time of transplantation exhibited significantly better prognoses than did older patients.

DISCUSSION

This analysis highlights the excellent efficacy of HSCT for patients with XHIM, despite their poor natural prognosis. The incidence of organ damage or noninfectious complications, such as autoimmune diseases and malignancy, was increased in patients older than 6 years despite the use of IVIG, trimethoprim-sulfamethoxazole, and G-CSF therapies. These results provide evidence that HSCT performed for patients younger than 5 years comprises a curative and feasible therapy for XHIM.

Of the patients' characteristics, the clinical and mortality data were compatible with those in a European study.⁹ *CD40LG* genotypes differed; the most common mutations in Japan are deletions (35.7%), whereas missense mutations were more common in Europe (39.5%)¹⁵ and the United States (22%).¹⁰ However, *CD40LG* mutations are distributed unequally, and the genotype-phenotype correlation is unclear, except in cases with splicing mutations that permit a low level of CD40L expression, thus exhibiting a mild phenotype.¹⁶ Although all patients in this study lacked CD40L expression on activated T cells, as determined by using fluorescence-activated cell sorting analysis, and manifested the clinically typical XHIM phenotype, the indications for HSCT in patients with XHIM with some amount of CD40L expression need to be analyzed in further study.

Patients with XHIM have recurrent and subclinical infections to varying degrees because of T-cell dysfunction. Therefore special attention should be paid to symptoms of infection even if no infection is apparent because infections frequently become clinically evident after HSCT. In this study the most common cause of death was infection, particularly PCP. In our cohort the first infectious episode was PCP in 14 patients, and this was fatal in 5 patients. Thus early diagnosis and prompt medical intervention are required, as seen in patients with severe combined immunodeficiency disease.¹⁷ Even for patients with good infection control during childhood, regular lifetime care is warranted because rare opportunistic infections, including JC virus progressive multifocal leukoencephalopathy, could occur in patients not undergoing HSCT. In addition, liver failure is frequently associated with *Cryptosporidium* species infection,⁸ as observed in the patients in this study. Patients with XHIM cannot easily clear *Cryptosporidium* species infections. Therefore they are recommended to use boiled or filtered water to prevent *Cryptosporidium* species infection, and it is necessary to monitor these patients for signs of *Cryptosporidium* species infection. Recently, CD40 agonist antibody¹⁸ or recombinant CD40L¹⁹ was tried to eliminate *Cryptosporidium* species infection in patients with XHIM.

Ultimately, HSCT is required to overcome T-cell dysfunction-related infections, but of course, it is not always a safe procedure. Four HSCT-related deaths occurred, and all affected patients were older than 15 years at transplantation. Three presented with organ damage at transplantation. One patient without organ damage underwent HSCT, followed by an RIC regimen and died of severe acute GVHD.

The OS of patients undergoing HSCT was significantly better than that of patients not undergoing HSCT. The characteristic differences between patients undergoing HSCT and patients not undergoing HSCT were age at diagnosis and mutation type. Evidently, the timing of HSCT is a major issue. The present analysis, which focused on pretransplantation organ damage, revealed that the incidence of organ damage increased in patients older than 6 years. Therefore we performed a survival comparison of patients aged 5 years or younger with those aged 6 years or older at transplantation. There were no background differences between the 2 groups other than the incidence of pretransplantation organ damage. However, OS, event-free survival, and disease-free survival were all significantly greater in the younger group. These findings suggest that pretransplantation organ damage is the most critical risk factor for a poor outcome. For the older patients without pretransplantation organ damage, HSCT might be successful, as in younger patients, but further studies will be needed to answer the question.

This study had some limitations. For example, some points of the HSCT procedures varied on a per-case basis, and no optimal regimen has yet been established. Regarding the conditioning regimens, busulfan/cyclophosphamide myeloablative regimens were used for 18 of 29 patients undergoing HSCT with remarkable outcomes. On the other hand, RIC regimens have been recently considered preferable from the perspective of preventing long-term complications. In the present study we could not demonstrate whether busulfan/cyclophosphamide or RIC regimens were advantageous in terms of outcome because the sample size was too small and the drug dose and combination were variable. Further research will be required to address these issues.

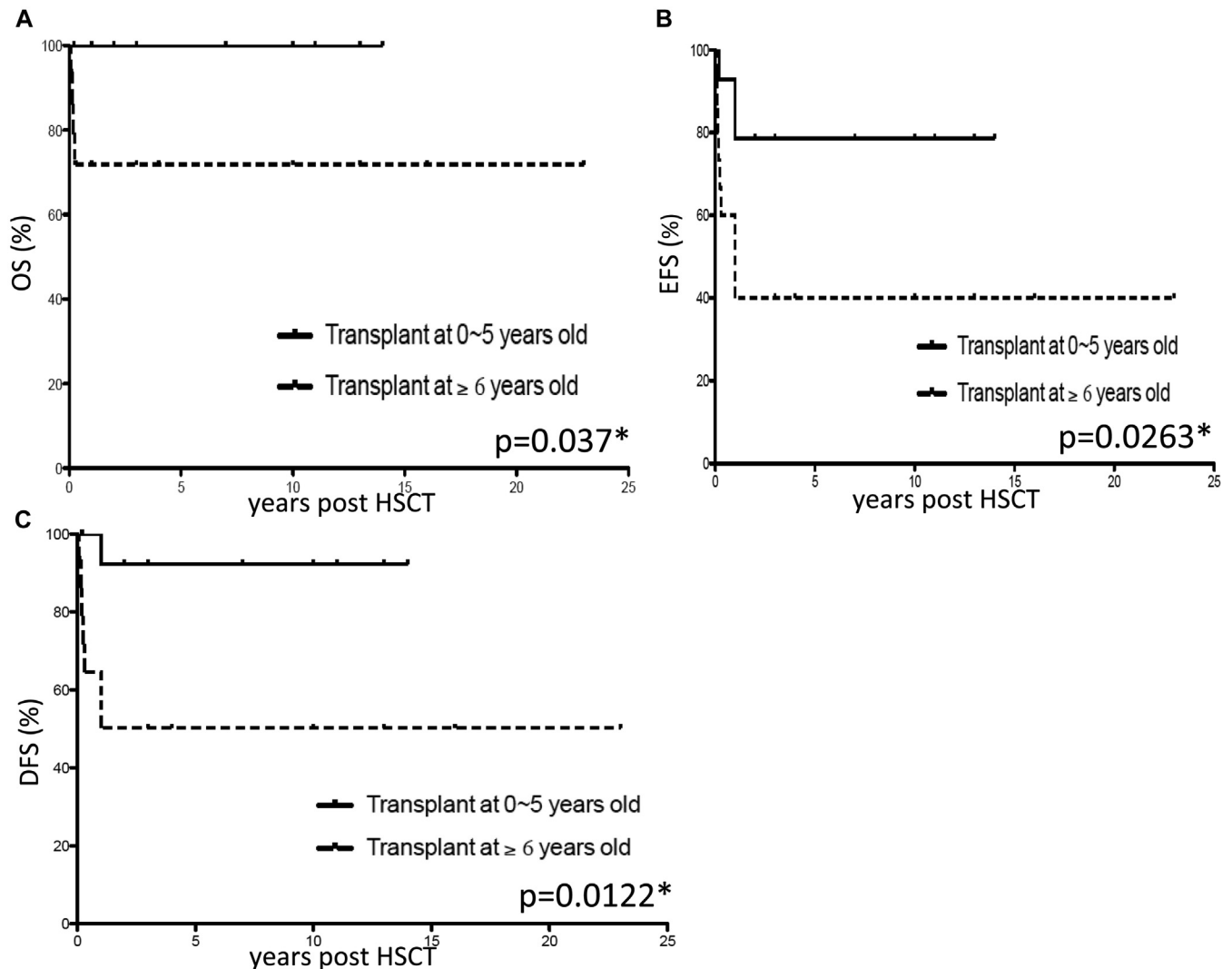


FIG 3. OS, event-free survival (EFS), and disease-free survival (DFS) rates of 29 patients undergoing HSCT. The solid line indicates survival rates of patients aged 0 to 5 years at transplantation ($n = 14$). The dashed line indicates survival rates of patients older than 6 years at transplantation ($n = 15$). **A**, OS. **B**, EFS, with event defined as HSCT-related death, graft failure, grade 4 GVHD, severe organ damage, and a requirement for IVIG for longer than 1 year after HSCT. **C**, DFS, with disease-free status defined as full engraftment and freedom from IVIG for longer than 1 year with no permanent organ damage (eg, not requiring dialysis or respiratory ventilation or exhibiting severe neurologic sequelae).

In conclusion, HSCT from HLA-matched related or unrelated donors (including cord blood) is both curative and feasible for patients with XHIM. However, strict infection control is required. HSCT should be performed for patients 5 years of age or younger because the risks of various complications and organ damage increase in patients older than 6 years. Future issues to address include good management of HSCT-related toxicities and long-term complications.

We thank Drs Ryoji Kobayashi, Miho Ohshima, Yoji Sasahara, Keisuke Kato, Nobuyuki Miura, Yukie Arahata, Toshinao Kawai, Takao Kohsaka, Kazunaga Agematsu, Kihei Terada, Shunichi Kato, Masafumi Hasui, Syoji Shiomi, Naohisa Kawamura, Mitsuhiko Nambu, Ryuta Nishikomori, Takahiro Yasumi, Mizuka Miki, Hiroko Inada, Yasuhiro Okamoto, and Nobuyuki Hyakuna for data collection. We also thank Dr Osamu Ohara for sequencing analysis of the *CD40LG* gene.

Key messages

- Long-term survival in patients with XHIM was poor, mainly because of susceptibility to infections caused by T-cell dysfunction.
- HSCT improved the outcomes of patients with XHIM.
- Patients 5 years or younger at the time of transplantation achieved significantly higher event-free and disease-free survival rates than seen in older patients.

REFERENCES

1. Aruffo A, Farrington M, Hollenbaugh D, Li X, Milatovich A, Nonoyama S, et al. The CD40 ligand, gp39, is defective in activated T cells from patients with X-linked hyper-IgM syndrome. *Cell* 1993;72:291-300.
2. Korthäuer U, Graf D, Mages HW, Brière F, Padayachee M, Malcolm S, et al. Defective expression of T-cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. *Nature* 1993;361:539-41.

3. DiSanto JP, Bonnefoy JY, Gauchat JF, Fischer A, de Saint Basile G. CD40 ligand mutations in x-linked immunodeficiency with hyper-IgM. *Nature* 1993;361:541-3.
4. Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. *Immunol Rev* 2009;229:152-72.
5. Bhushan A, Covey LR. CD40:CD40L interactions in X-linked and non-X-linked hyper-IgM syndromes. *Immunol Res* 2001;24:311-24.
6. Caux C, Massacrier C, Vanbervliet B, Dubois B, Van Kooten C, Durand I, et al. Activation of human dendritic cells through CD40 cross-linking. *J Exp Med* 1994;180:1263-72.
7. Van Kooten C, Banchereau J. Functions of CD40 on B cells, dendritic cells and other cells. *Curr Opin Immunol* 1997;9:330-7.
8. Hayward AR, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, et al. Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. *J Immunol* 1997;158:977-83.
9. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, et al. Clinical spectrum of X-linked hyper-IgM syndrome. *J Pediatr* 1997;131:47-54.
10. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. *Medicine (Baltimore)* 2003;82:373-84.
11. Gennery AR, Khawaja K, Veys P, Bredius RG, Notarangelo LD, Mazzolari E, et al. Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993-2002. *Blood* 2004;103:1152-7.
12. Tomizawa D, Imai K, Ito S, Kajiwara M, Minegishi Y, Nagasawa M, et al. Allogeneic hematopoietic stem cell transplantation for seven children with X-linked hyper-IgM syndrome: a single center experience. *Am J Hematol* 2004;76:33-9.
13. Tsuji Y, Imai K, Morinishi Y, Kogawa K, Morino M, Nonoyama S. Successful unrelated cord blood transplantation for a patient with CD40 ligand deficiency. *Haematologica* 2007;92:1727-8.
14. Nonoyama S, Shimadzu M, Toru H, Seyama K, Nunoi H, Neubauer M, et al. Mutations of the CD40 ligand gene in 13 Japanese patients with X-linked hyper-IgM syndrome. *Hum Genet* 1997;99:624-7.
15. Notarangelo LD, Peitsch MC, Abrahamsen TG, Bachelot C, Bordigoni P, Cant AJ, et al. CD40lbase: a database of CD40L gene mutations causing X-linked hyper-IgM syndrome. *Immunol Today* 1996;17:511-6.
16. Seyama K, Nonoyama S, Gangsaas I, Hollenbaugh D, Pabst HF, Aruffo A, et al. Mutations of the CD40 ligand gene and its effect on CD40 ligand expression in patients with X-linked hyper IgM syndrome. *Blood* 1998;92:2421-34.
17. Hoshino A, Imai K, Ohshima Y, Yasutomi M, Kasai M, Terai M, et al. Pneumothorax in patients with severe combined immunodeficiency. *Pediatr Int* 2014;56:510-4.
18. Fan X, Upadhyaya B, Wu L, Koh C, Santín-Durán M, Pittaluga S, et al. CD40 agonist antibody mediated improvement of chronic *Cryptosporidium* infection in patients with X-linked hyper IgM syndrome. *Clin Immunol* 2012;143:152-61.
19. Jain A, Kovacs JA, Nelson DL, Migueles SA, Pittaluga S, Fanslow W, et al. Partial immune reconstitution of X-linked hyper IgM syndrome with recombinant CD40 ligand. *Blood* 2011;118:3811-7.