Outcome of hematopoietic cell transplantation for DNA double-strand break repair disorders

Slack, James

2018-01

Slack , J , Albert , M H , Balashov , D , Belohradsky , B H , Bertaina , A , Bleesing , J , Booth , C , Buechner , J , Buckley , R H , Ouachee-Chardin , M , Deripapa , E , Drabko , K , Eapen , M , Feuchtinger , T , Finocchi , A , Gaspar , H B , Ghosh , S , Gillio , A , Gonzalez-Granado , L I , Grunebaum , E , Gungor , T , Heilmann , C , Helminen , M , Higuchi , K , Imai , K , Kalwak , K , Kanazawa , N , Karasu , G , Kucuk , Z Y , Laberko , A , Lange , A , Mahlaoui , N , Meisel , R , Moshous , D , Muramatsu , H , Parikh , S , Pasic , S , Schmid , I , Schuetz , C , Schulz , A , Schultz , K R , Shaw , P J , Slatter , M A , Sykora , K-W , Tamura , S , Taskinen , M , Wawer , A , Wolska-Kusnierz , B , Cowan , M J , Fischer , A , European Soc Blood Marrow , European Soc Immunodeficiencies , Stem Cell Transplant , Ctr Int Blood Marrow & Primary Immunodeficiency Treatment 2018 , ' Outcome of hematopoietic cell transplantation for DNA double-strand break repair disorders ' , Journal of Allergy and Clinical Immunology , vol. 141 , no. 1 , pp. 322-+ . https://doi.org/10.1016/j.jaci.2017.02.036

http://hdl.handle.net/10138/298620
https://doi.org/10.1016/j.jaci.2017.02.036

publishedVersion

Outcome of hematopoietic cell transplantation for DNA double-strand break repair disorders

James Slack, MD,[a] Michael H. Albert, MD,[b] Dmitry Balashov, PhD,[c] Bernd H. Belohradsky, MD,[b] Alice Bertaina, PhD,[d] Jack Bleesing, PhD,[e] Claire Booth, PhD,[f] Jochen Buechner, PhD,[g] Rebecca H. Buckley, MD,[h] Marie Ouachée-Chardin, MD,[i] Elena Deripapa, MD,[c] Katarzyna Drabko, MD,[j] Mary Eapen, MD,[k] Tobias Feuchtinger, MD,[l] Andrea Finocchi, PhD,[nn] H. Bobby Gaspar, PhD,[f] Sujal Ghosh, MD,[f,m] Alfred Gillio, MD,[n] Luis I. Gonzalez-Granado, MD,[o] Eyal Grunebaum, MD,[p] Tayfun Güngör, MD,[q] Carsten Heilmann, MD,[r] Merja Helminen, PhD,[s] Kohei Higuchi, MD,[t] Kohsuke Imai, PhD,[u] Krzysztof Kalwak, MD,[v] Nubuo Kanazawa, PhD,[w] Gülsün Karasu, MD,[x] Zeynep Y. Kucuk, MD,[e] Alexandra Laberko, MD,[c] Andrzej Lange, MD,[y] Nizar Mahlaoui, MD,[z,aa] Roland Meisel, MD,[m] D. Moshous, PhD,[aa] Hideki Muramatsu, PhD,[bb] Suhag Parikh, MD,[oo] Srdjan Pasic, PhD,[cc] Irene Schmid, MD,[b] Catharina Schuetz, PhD,[dd] Ansgar Schulz, MD,[dd] Kirk R. Schultz, MD,[ee] Peter J. Shaw, MD,[ff] Mary A. Slatter, MD,[a,gg] Karl-Walter Sykora, PhD,[hh] Shinobu Tamura, PhD,[ii] Mervi Taskinen, MD,[jj] Angela Wawer, MD,[kk] Beata Wolska-Kusnierz, PhD,[ll] Morton J. Cowan, MD,[mm] Alain Fischer, PhD,[aa] and Andrew R. Gennery, MD,[a,gg] on behalf of the Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation and the European Society for Immunodeficiencies, Stem Cell Transplant for Immunodeficiencies in Europe (SCETIDE), the Center for International Blood and Marrow Transplant Research, and the Primary Immunodeficiency Treatment Consortium

Newcastle upon Tyne and London, United Kingdom; Munich, Tübingen, Düsseldorf, Ulm, and Hannover, Germany; Moscow, Russia; Rome, Italy, Cincinnati, Ohio; Oslo, Norway; Durham, NC; Paris, France; Lublin, Wroclaw, and Warsaw, Poland; Milwaukee, Wis; Hackensack, NJ; Madrid, Spain; Toronto, Ontario, and Vancouver, British Columbia, Canada; Zurich, Switzerland; Copenhagen, Denmark; Tampere and Helsinki, Finland; Osaka, Tokyo, Wakayama, and Nagoya, Japan; Istanbul, Turkey; Belgrade, Serbia; Westmead, Australia; and San Francisco, Calif

Background: Rare DNA breakage repair disorders predispose to infection and lymphoreticular malignancies. Hematopoietic cell transplantation (HCT) is curative, but coadministered chemotherapy or radiotherapy is damaging because of systemic radiosensitivity. We collected HCT outcome data for Nijmegen breakage syndrome, DNA ligase IV deficiency, Cernunnos–XRCC4-like factor (Cernunnos-XLF) deficiency, and ataxia-telangiectasia (AT).

Methods: Data from 38 centers worldwide, including indication, donor, conditioning regimen, graft-versus-host disease, and outcome, were analyzed. Conditioning was classified as myeloablative conditioning (MAC) if it contained radiotherapy or alkylators and reduced-intensity conditioning (RIC) if no alkylators and/or 150 mg/m^2 fludarabine or less and 40 mg/kg cyclophosphamide or less were used.

Results: Fifty-five new, 14 updated, and 18 previously published patients were analyzed. Median age at HCT was 48 months (range, 1.5-552 months). Twenty-nine patients underwent transplantation for infection, 21 had malignancy, 13 had bone marrow failure, 13 received pre-emptive transplantation, 5 had

From [a]the Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne; [b]Dr. von Hauner University Children's Hospital, Ludwig-Maximilians-Universität, Munich; [c]the Immunology and Hematopoietic Stem Cell Transplantation Department, Federal Research Center for Pediatric Hematology, Oncology and Immunology, Moscow; [d]the Stem Cell Transplant Unit, Department of Hematology and Oncology, Ospedale Pediatrico Bambino Gesù, Rome; [e]the Division of Bone Marrow Transplantation and Immune Deficiency, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati; [f]Infection, Immunity, Inflammation, Molecular and Cellular Immunology Section, UCL Great Ormond Street Institute of Child Health, London; [g]the Department of Pediatric Hematology and Oncology, Oslo University Hospital, Oslo; [h]Duke University School of Medicine, Departments of Pediatrics and Immunology, Duke University Medical Center, Durham; [i]the Paediatric BMT Unit, Robert Debre Hospital, Paris; [j]the Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation, Medical University of Lublin; [k]the Center for International Blood and Marrow Transplant Research, Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee; [l]the Department of Haematology and Oncology, University Children's Hospital Tübingen; [m]the Division of Pediatric Stem Cell Therapy, Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Center of Child and Adolescent Health, Heinrich-Heine-University, Düsseldorf; [n]Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack; [o]the Immunodeficiencies, Hematology & Oncology Unit, Pediatrics, Hospital 12 Octubre, and Universidad Complutense, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid; [p]the Division of Immunology and Allergy, Hospital for Sick Children, University of Toronto; [q]the Division of Stem Cell Transplantation, University Children's Hospital Zürich; [r]BørneUngeKlinikken, Copenhagen; [s]the Paediatric Research Center, University Hospital of Tampere; [t]Osaka Medical Center and Research Institute for Maternal and Child Health; [u]the Department of Community Pediatrics, Perinatal and Maternal Medicine, Tokyo Medical and Dental University; [v]the Department of Pediatric Hematology, Oncology and BMT, Wroclaw Medical University; the Departments of [w]Dermatology and [ii]Hematology and Oncology, Wakayama Medical University; [x]Bahcesehir University Faculty of Medicine, Göztepe Medicalpark Hospital Pediatric Stem Cell Transplantation Unit, Istanbul; [y]Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences / Lower Silesian Center for Cellular Transplantation, Wrocław; [z]the French National Reference Center for Primary Immune Deficiencies (CEREDIH), Necker Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris; [aa]the Immuno-Hematology Unit, Necker Children's Hospital, Assistance Publique Hôpitaux de Paris; [bb]the Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya; [cc]the Mother and Child Health Institute, Medical Faculty, University of Belgrade; [dd]the Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm; [ee]the Michael Cuccione Childhood Cancer Research Program, BC Children's Hospital and Child and Family Research Institute, Vancouver; [ff]the Department of Oncology, Children's Hospital at Westmead; [gg]the Primary Immunodeficiency Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne; [hh]the Department of Pediatric Hematology Oncology, Hannover Medical; [jj]the Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, Helsinki University Hospital; [kk]Paediatric Haematology & Oncology, Kinderklinik der Technische Universität München, Krankenhaus München-Schwabing, Munich; [ll]the Department of Immunology, Children's Memorial Health Institute, Warsaw; [mm]the Allergy Immunology and Blood and Marrow Transplant Division, University of California San Francisco Benioff Children's Hospital; [nn]the Department of Systems Medicine, University of Rome "Tor Vergata", Unit of Immune and Infectious Diseases, Children's Hospital Bambino Gesù, Rome; and [oo]Duke University School of Medicine, Pediatric Blood and Marrow Transplant Program, Duke University Medical Center, Durham.

multiple indications, and 6 had no information. Twenty-two received MAC, 59 received RIC, and 4 were infused; information was unavailable for 2 patients. Seventy-three of 77 patients with DNA ligase IV deficiency, Cernunnos-XLF deficiency, or Nijmegen breakage syndrome received conditioning. Survival was 53 (69%) of 77 and was worse for those receiving MAC than for those receiving RIC ($P = .006$). Most deaths occurred early after transplantation, suggesting poor tolerance of conditioning. Survival in patients with AT was 25%. Forty-one (49%) of 83 patients experienced acute GvHD, which was less frequent in those receiving RIC compared with those receiving MAC (26/56 [46%] vs 12/21 [57%], $P = .45$). Median follow-up was 35 months (range, 2-168 months). No secondary malignancies were reported during 15 years of follow-up. Growth and developmental delay remained after HCT; immune-mediated complications resolved.
Conclusion: RIC HCT resolves DNA repair disorder–associated immunodeficiency. Long-term follow-up is required for secondary malignancy surveillance. Routine HCT for AT is not recommended. (J Allergy Clin Immunol 2018;141:322-8.)

Key words: *Ataxia-telangiectasia, Cernunnos-XLF deficiency, DNA repair disorders, DNA ligase IV deficiency, hematopoietic stem cell transplantation, Nijmegen breakage syndrome*

Abbreviations used

aGvHD:	Acute graft-versus-host disease
AT:	Ataxia-telangiectasia
ATG:	Anti-thymocyte globulin
ATM:	Ataxia-telangiectasia mutated
cGvHD:	Chronic graft-versus-host disease
Cernunnos-XLF:	Cernunnos–XRCC4-like factor
DNA-dsb:	DNA double-strand break
GvHD:	Graft-versus-host disease
HCT:	Hematopoietic cell transplantation
LIG4:	DNA ligase IV deficiency
MAC:	Myeloablative conditioning
NBS:	Nijmegen breakage syndrome
NHEJ:	Nonhomologous end-joining
NHEJ1:	Nonhomologous end-joining factor 1
NK:	Natural killer
PTLD:	Posttransplantation lymphoproliferative disorder
RAG:	Recombination-activating gene
RIC:	Reduced-intensity conditioning
SCID:	Severe combined immunodeficiency

Maintenance of genomic stability requires repair of DNA that was damaged through endogenous processes, such as meiotic and mitotic replication errors, and exogenous processes, including exposure to oxidizing radicals, DNA-damaging chemicals, and UV and ionizing radiation. Several repair pathways regulate the cell cycle and recognize and repair DNA damage. One of the most serious events to threaten genomic stability, DNA double-strand breaks (DNA-dsbs), if left unchecked will lead to loss of genomic material, mutagenesis, and oncogenesis or cell death.[1] Two pathways are used to repair such damage: homologous recombination, which functions primarily in dividing cells and the S phase and requires a homologous template to maintain replication accuracy, and non–template-dependent nonhomologous end-joining (NHEJ), which is used particularly during phases of the cell cycle when a homologous template is not present. The latter is an especially error-prone process, with some loss of DNA information at the site of the DNA-dsb.[2]

Development of normal adaptive immunity requires generation of a wide range of T- and B-lymphocyte receptors to recognize unique antigen/MHC combinations and provides effective defense against a broad repertoire of pathogens. Many genetically diverse receptors are generated in the thymus and bone marrow by breaking, stochastically rearranging, and rejoining DNA sequences coding for antigen receptors, a process known as VDJ recombination. Additional diversity is created in B lymphocytes during immunoglobulin class-switch recombination and somatic hypermutation. The DNA repair mechanisms required to maintain somatic genomic stability are also used during lymphocyte VDJ recombination to repair intermediate DNA hairpins and physiologic DNA-dsbs created after activation of recombination-activating gene (RAG) 1

M.J.C. was supported by the Division of Allergy, Immunology, and Transplantation; the National Institute of Allergy and Infectious Diseases; the Intramural Research Program of the National Institute of Allergy and Infectious Diseases; and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health (U54-AI082973). M.E. was funded in part by Public Health Service grant U24-CA76518 from the National Cancer Institute; the National Heart, Lung, and Blood Institute; and the National Institute of Allergy and Infectious Diseases. L.I.G.-G. was supported by a grant from Fondo de Investigación Sanitaria (FIS-PI16/2053). H.B.G. is supported by the Great Ormond Street Hospital Children's Charity and by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital and University College London.

Disclosure of potential conflict of interest: M. H. Albert has personally received money for expert testimony from Biotest; grants from GlaxoSmithKline for other works; payment for lectures from Jazz; stock options from Amgen, BMS, and Biotest; and travel expenses from Neovii. R. H. Buckley's institution has received grant money from the Primary Immune Deficiency Treatment Consortium (PIDTC) for other works, is personally a board member of the Immune Deficiency Foundation, is employed by Duke University, has received royalties from UpToDate, and received travel expenses from the National Institutes of Health (NIH) and IDF. H. B. Gaspar has personally received board membership consultancy fees and stock options from Orchard Therapeutics. L. I. Gonzalez-Granado's institution has received grant FIS-PI16/2053 from Fonde de Investiagción Sanitaiia. T. Güngör has personally received board membership from the CGD Society UK and consultancy fees from Novartis. K. Imai's institution has received a grant from the Japanese Ministry of Health, Labor and Welfare for work outside this manuscript; has personally received consultancy fees from CSL Behring KK and Novartis pharma KK; and has received payment for lectures from CSL Behring KK and Novartis pharma KK. R. Meisel has received consultancy fees from Amgen and has received travel expenses from Neovii Biotech and Jazz Pharmaceuticals. A. Schulz's institution has received travel expenses from the European Society for Blood and Marrow Transplantation. M. J. Cowan's institution has received grant U54 AI 082973 from the NIH for this work and grants U54-AI082973, CLIN1-08363, and CLIN2-09504 from the California Institute of Regenerative Medicine for other works and has personally received board membership from Bluebird Bio, royalties from UpToDate, and stock options from Homology Medicines and Exogen Bio. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 2, 2016; revised January 25, 2017; accepted for publication February 6, 2017.

Available online April 7, 2017.

Corresponding author: Andrew R. Gennery, MD, Clinical Resource Building, Floor 4, Block 2 Great North Children's Hospital, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom. E-mail: a.r.gennery@ncl.ac.uk.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2017.02.036

and 2.[3] Seven ubiquitously expressed proteins are associated with NHEJ-Ku70/80 and DNA protein kinase catalytic subunit, which stabilize the DNA break; the DNA endo/exonuclease Artemis, which is important for processing RAG-induced hairpin intermediate joins; and the DNA ligase IV and Cernunnos–XRCC4-like factor (Cernunnos-XLF), which together are responsible for the ligation step. Additionally, ataxia-telangiectasia mutated (ATM) and nibrin proteins are involved in the initial cell-cycle arrest and recruitment of NHEJ proteins to the breakage site (see Fig E1 in this article's Online Repository at www.jacionline.org).[4]

Defects in the lymphoid-specific RAG1/2 proteins lead to T lymphocyte–negative, B lymphocyte–negative, natural killer (NK) lymphocyte–positive ($T^-B^-NK^+$) severe combined immunodeficiency (SCID).[5] Defects in Artemis, DNA protein kinase catalytic subunit, DNA ligase IV, and Cernunnos-XLF proteins also lead to $T^-B^-NK^+$ SCID and combined immunodeficiencies, often associated with other developmental anomalies, particularly microcephaly in patients with DNA ligase IV and Cernunnos-XLF deficiency, as a result of the ubiquitous expression of these proteins.[6-14] Hematopoietic cell transplantation (HCT) is curative for $T^-B^-NK^+$ SCID, but best results with donor myeloid chimerism and long-term immune reconstitution are obtained if preparative chemotherapy is administered before transplantation.[15] However, in Artemis-deficient radiosensitive patients with SCID, although overall survival is equivalent to that of patients with RAG-deficient SCID, significant long-term sequelae result from administration of alkylating agents, which are required to gain donor stem cell engraftment with sustained long-term thymopoiesis. The use of alkylating chemotherapy does not result in increased short-term toxicities or increased transplant-related mortality, but long-term effects on growth and development are observed because of the effect of chemotherapy on other somatic cells that harbor the genetic defect.[15] Similar significant effects of chemotherapy are seen in patients with Fanconi anemia (OMIM 227650) and dyskeratosis congenita (OMIM 127550), both of which are DNA fragility syndromes.[16,17] Given the systemic nature of the DNA-dsb defect in other DNA-dsb repair disorders and the finding that the radiosensitivity is generally more severe than in patients with Artemis deficiency, it is possible that preadministration of DNA-damaging chemotherapy before transplantation will lead to significant systemic morbidity and possible increased mortality.

Because of the primary immunodeficiency phenotype and the frequent occurrence of malignancy, a number of patients with DNA-dsb repair disorders have undergone HCT.[10-13,18-28] To assess outcomes of HCT for DNA-dsb repair disorders, we surveyed patients undergoing transplantation for DNA ligase IV deficiency (LIG4), Cernunnos-XLF deficiency (XLF; or nonhomologous end-joining factor 1 [NHEJ1]), Nijmegen breakage syndrome (NBS), and ataxia-telangiectasia (AT) using baseline data from Stem Cell Transplant for Primary Immune Deficiencies in Europe, the Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation registry, the Center for International Blood and Marrow Transplant Research, and the North American Primary Immune Deficiency Treatment Consortium and supplemented with additional information from individual centers, where available. Patients with mutations in *RAG1/2* and *DCLRE1C* (encoding Artemis) were excluded from the study because HCT outcomes for these conditions have been reported recently.[15]

METHODS

Data collection

Data on patients with defined mutations in *LIG4* (OMIM 606593), *NBN* (OMIM 602667), *NHEJ1* (OMIM 611290), and *ATM* (OMIM 607585) who underwent HCT were gathered from the Inborn Errors Working Party of European Society for Blood and Marrow Transplantation, Stem Cell Transplant for primary Immune Deficiencies in Europe, the Center for International Blood and Marrow Transplant Research, and the North American Primary Immunodeficiency Treatment Consortium. Further patients were identified from previously published data and case reports. Centers with identified patients completed a questionnaire to gather data on genetic diagnosis, patients' demographics, reason for HCT, type and source of HCT, conditioning regimen used, rates and severity of graft-versus-host disease (GvHD), and survival after HCT. Inclusion criteria were any patient having a confirmed genetic diagnosis and having undergone HCT.

The reason to offer HCT was defined as any category or combination of the following:

- infection (defined as any listed severe infection or recurrent infections);
- malignancy;
- bone marrow failure (defined as leukopenia, anemia, or thrombocytopenia without the presence of infection or malignancy);
- autoimmunity; and
- pre-emptive.

Conditioning was categorized as either MAC or RIC. MAC was defined as any regimen using high-dose alkylating agents, typically melphalan or busulphan, thiotepa, or total-body irradiation at any dose. Although a low-dose 200- to 400-cGy regimen can normally be considered nonmyeloablative, we reasoned that radiation-sensitive cells were best not exposed to ionizing radiation. If the regimen did not use alkylating agents and/or had doses of fludarabine of 150 mg/m^2 or less and cyclophosphamide of 40 mg/kg or less, it was defined as RIC.[29] A modified Fanconi regimen was based on 120 to 150 mg/m^2 fludarabine (30 mg/m^2/d in 4-5 divided doses), 20 to 40 mg/kg cyclophosphamide (in 4 divided doses) with or without anti-thymocyte globulin (ATG) or alemtuzumab serotherapy,[30,31] or 180/m^2 fludarabine (in 6 divided doses), 1.6 mg/kg busulphan (in 2 divided doses), and 40 mg/kg cyclophosphamide (in 2 divided doses).[32] The use of targeted agents, such as antibodies (eg, alemtuzumab) did not affect classification of the conditioning.

The primary outcome measured was survival. Secondary outcome measures sought were presence, severity, and outcome of GvHD, or other transplant-related complications.

Analysis

Significance of results was determined by using the Fisher exact test with 2×2 contingency tables. A 2-tailed P value of .05 or less was considered significant. Kaplan-Meier curves were created based on last known status at the time at which the questionnaire was received; cases in which survival was not listed have been excluded from the survival analysis. All statistics were calculated with GraphPad Prism 6 software (GraphPad Software, La Jolla, Calif).

RESULTS

Data were collected from 38 centers worldwide, culminating in 55 newly identified patients and 14 previously published patients with updated new information, producing new information on 69 patients. Available data from 18 previously published cases[10-14,18-28] were included, where possible, totaling 87 cases. The median age of patients at HCT was 48 months (range, 1.5-552 months), and 47 were male (54%).

Mutations in *LIG4* were most commonly represented in 36 patients (32 unpublished or with new information, see Table E1 in this article's Online Repository at www.jacionline.org), 26 with *NBN* mutations (17 unpublished or with new information, see Table E2 in this article's Online Repository at www.jacionline.org), 17 with *NHEJ1* mutations (12 unpublished

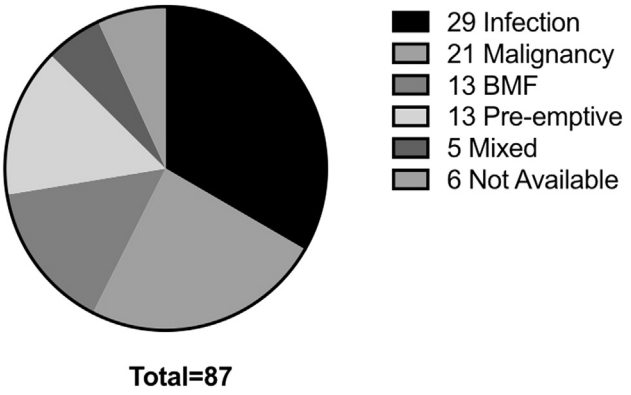

FIG 1. Indication for HCT. *BMF,* Bone marrow failure.

or with new information, see Table E3 in this article's Online Repository at www.jacionline.org), and 8 with *ATM* mutations (all with new information, 2 previously published, updated in this report; see Table E4 in this article's Online Repository at www.jacionline.org). All patients received allogeneic hematopoietic stem cells, except 2 published patients who died immediately before HCT while receiving MAC but whose data were included in the study.

Information was provided on the primary reason for HCT in 83 patients (Fig 1). Significant or repeated infections were the most commonly cited reason (29 [35%] patients, 12 with *LIG4* mutations and 11 with *NHEJ1* mutations), 13 (15%) patients underwent transplantation for bone marrow failure, and 21 (24%) patients underwent transplantation for malignancy (17 with *NBN* mutations). Thirteen (15%) patients underwent transplantation pre-emptively on the basis of an SCID-like diagnosis, 10 with *LIG4* mutations. Five patients had a mixture of the above indications, and in 6 patients the reason for HCT was not available.

Twenty-two patients received MAC, and 59 received RIC, of which 30 were based on a modified Fanconi anemia conditioning regimen. Four patients received a stem cell infusion without prior conditioning; data were unavailable for 2 patients. Two received radiotherapy (5 and 2 Gy, respectively) as part of the conditioning regimen.

Survival

Of patients with LIG4, Cernunnos-XLF deficiency, and NBS, there were survival data for 77, of whom 73 received conditioning. Overall survival was 53 (69%) of 77 (Fig 2, *A*), 2 of whom died from relapse of malignancy, resulting in a transplant-related survival of 71%. One patient with NBS rejected the graft and is alive with disease. One rejected and succumbed to malignancy. Survival among those receiving MAC was significantly worse at 41% (7/17) compared with 79% (44/56) for those receiving RIC ($P = .006$; Fig 2, *B*), describing 2 patients who died of malignancy relapse as survivors. There was no significant difference in transplant-related mortality between those who received a modified Fanconi or other RIC regimen ($P = .13$). The Kaplan-Meier curve demonstrates that the majority of deaths occur early in the course of transplantation, particularly in those receiving MAC, suggesting poor tolerance of the conditioning regimen.

In patients with AT, overall survival was 25%. Of the 2 patients who survived, both received a modified Fanconi conditioning

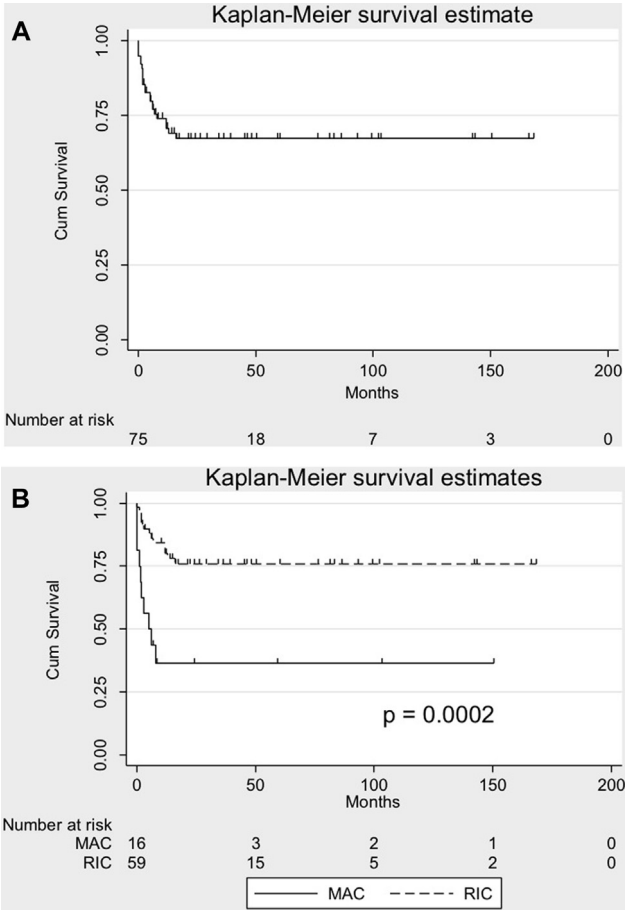

FIG 2. Probabilities of overall survival. **A,** Kaplan-Meier curve showing overall survival of 74 patients with LIG4, Cernunnos-XLF deficiency, and NBS. **B,** Kaplan-Meier curve demonstrating differences in survival of 74 patients with LIG4, Cernunnos-XLF deficiency, and NBS undergoing transplantation with RIC or MAC regimens.

regimen, and neither experienced GvHD, unlike all patients who received MAC. The 6 patients who died experienced GvHD grade 2 or 3 (67%), despite well-matched donors. Death was due to multiorgan failure, viral activation, or posttransplantation lymphoproliferative disorder (PTLD).

Transplant-related survival in the entire cohort for whom data were available was 66% (56/85), with a survival of 75% (45/60) after RIC and 32% (7/22) after MAC ($P = .0006$). There was no significant difference in outcome between those who underwent HCT for malignancy (12/22 survivors) or for other indications (37/57 survivors, $P = .44$). There was no significant difference in survivors for those receiving RIC (11/17) or MAC (1/5) conditioning when malignancy was the reason for HSCT ($P = .14$). There was also no significant difference in survivors for those receiving RIC (5/25) or MAC (4/9) when infection was the reason for HSCT ($P = .09$). There were too few patients who underwent transplantation for bone marrow failure to make a similar comparison.

There were no differences in survival between donor sources, irrespective of whether matched sibling, matched unrelated, or mismatched unrelated donors were used (18/25, 20/27, and 5/8, respectively).

GvHD

Data on the presence or absence of acute graft-versus-host disease (aGvHD) was available for 83 patients; aGvHD was present in 41 (49%) of these. Of the reported patients with aGvHD, 24 (59%) had mild (grade 1-2) and 15 (37%) had severe (grade 3-4) aGvHD (a grade was unavailable for 2 patients). Rates of aGvHD were lower in the RIC group, 26 (46%) of 56 cases for whom data were available, compared with the MAC group, in whom 12 (57%) of 21 cases experienced aGvHD, although this was not statistically significant ($P = .45$). Three of 4 patients who received infused stem cells with no preconditioning experienced grade 1, 3, and 4 aGvHD respectively. There was no significant difference in survival between those experiencing grade 0 or 1 compared with those receiving grade 2 to 4 aGvHD ($P = .22$).

Mortality

Overall mortality was 29 (34%) of 84; information was unavailable for 2 previously published patients.[24] Two patients died of multiorgan failure during the conditioning process; both received full MAC. Eleven others died of multiorgan failure after transplantation, making multiorgan failure the most common cause of death (45%). Eleven deaths were predominantly infectious (38%).

Other complications

The most common non-aGvHD complication was viremia caused by adenovirus, cytomegalovirus, EBV, or a combination, which was reported in 24 (30%) of 79 patients, 6 of whom died. There were 6 (8%) cases of EBV-related PTLD. Six (8%) patients experienced severe mucositis, and 14 (18%) had chronic graft-versus-host disease (cGvHD). Seven patients rejected the graft: 2 after stem cell infusion (1 with serotherapy), 2 after T lymphocyte–depleted transplantations (1 MAC and 1 RIC), and 3 after MAC or RIC transplantations. Patients receiving RIC were less likely to experience severe mucositis, veno-occlusive disease, or PTLD than those who received MAC (7/59 vs 8/22, $P = .0215$).

Follow-up

Given the retrospective and multi-institutional nature of the study, detailed information regarding long-term (>5 years) follow-up was scarce. Median length of follow-up was 35 months (range, 2-168 months). No secondary malignancies were reported during the follow-up period, which, although short overall, includes patients with almost 15 years of follow-up. Pre-existing growth restriction and developmental issues appear to remain after HCT: a more detailed examination would be required to determine whether HCT ameliorates these features. A predisposition to infection or hematologic cytopenia existing before HCT appears to have been abolished.

DISCUSSION

Many patients with DNA-dsb repair defects exhibit immunodeficiency, ranging from mild to severe combined immunodeficiency, and are at increased risk of lymphoid malignancy. Allogeneic HCT is curative for many immunodeficiencies.[33] Establishment of effective DNA repair mechanisms in lymphoid progenitors leading to restoration of functional adaptive immunity might prevent the future development of lymphoid malignancy in this cohort of patients. Lymphoid malignancy is difficult to treat effectively when established because of the aggressive nature of the tumors and poor tolerance of patients to cytotoxic radiotherapy and chemotherapy.[34] Therefore it is a reasonable strategy to consider HCT in these patients. However, because most patients have some residual immunity and NK cells are present even in the SCID phenotype, rejection and poor stem cell engraftment are likely without some preparative cytoreductive preconditioning. However, the systemic nature of the genetic defect increases the risk of substantial morbidity or mortality from chemotherapy or ionizing radiation administered before transplantation. Only a few small case series of patients with DNA-dsb repair defects undergoing HCT have been published. To date, there has been no formal large case series from which to gauge experience.

We now report a multi-institutional retrospective survey on outcomes of HCT for 55 previously unpublished patients and update information for 18 previously reported patients with DNA-dsb repair defects. We have demonstrated that HCT can correct the hematopoietic defect and underlying immunodeficiency. Furthermore, we have demonstrated that survival is significantly superior when RIC is used. It is likely that chemotherapy agents, especially alkylating agents, induce systemic double-strand breaks, which are not readily repaired because of the underlying genetic defect. These systemic double-strand breaks can contribute to the early mortality seen after myeloablative therapy. This intolerance, which manifests clinically as severe toxicity sometimes followed by higher-grade GvHD, suggests that when considering HCT, an RIC regimen should be used in patients with known ionizing radiation sensitivity and/or proved diagnosis of a DNA-dsb repair defect and that radiotherapy should be omitted. Given the equivalence of outcome results when comparing modified Fanconi anemia–based regimens with other reduced-intensity regimens, the former might be preferred. Longer-term follow-up is required to determine the effect of HCT on future prevention of lymphoid malignancy.

The rate of aGvHD overall was 49%, of which 37% was grade 3 or 4. The rate of cGvHD was 18%. The incidence of severe (grade 3-4) aGvHD and cGvHD is higher than that reported for transplantation of patients with other primary immunodeficiencies.[35-38] It is not clear whether this is due to the greater use of matched unrelated donors rather than matched sibling donors (although in the modern era outcome of HCT with matched siblings or unrelated donors approaches equivalence), particularly in those receiving RIC. Significant comorbidities might also have contributed to the increased incidence of GvHD. However, it could be that the underlying molecular defect causing impaired DNA repair and reduced cellular repair capability predisposes to GvHD after cellular damage, as found in patients with Fanconi anemia or dyskeratosis congenita.[17,39]

Patients showed a range of other early post-HCT complications in addition to GvHD. Most common were viral reactivations, which in the case of EBV led to PTLD in 6 patients. Severe mucositis and veno-occlusive disease were commonly encountered.

Three patients experienced veno-occlusive disease, and 2 who underwent transplantation for malignancy experienced relapse of the primary malignancy. Three patients had autoimmune thyroid disease, and autoimmune cytopenias were also manifest.

Within this patient cohort, there are few data on long-term follow-up. Transplantation, unsurprisingly given the systemic nature of the defect, appears not to improve the effects of the primary disease on growth or neurologic development. It might be, as in patients with Artemis-SCID, that use of any alkylating agent leads to long-term sequalae.[15] It will be difficult to predict whether growth or development has been improved or deteriorated as a result of chemotherapy given the scarce data available on the natural history of these diseases and the variability of the phenotype already reported. However, determining the long-term and late beneficial and adverse effects of HCT in DNA-dsb defects will be important to provide details about the utility of this treatment approach. A recent report on a cohort of patients with mutations in *NBN* documented poor survival in those with malignancy.[24] Given the good survival outcome in this cohort among those who received RIC regimens, a pre-emptive approach to transplantation can be considered. Therefore long-term follow-up to determine the frequency of secondary malignancies will be of particular importance; although it has not been reported thus far in other primary immunodeficiency transplant series, it is a well-recognized complication in patients undergoing transplantation for Fanconi anemia.[39]

Although the outcome of HCT in patients with mutations in *LIG4*, *NBN*, and *NHEJ1* is favorable, particularly when RIC regimens are used, the data for patients with AT undergoing HCT are disappointing. Whether this is specifically due to the use of MAC regimens or the presence of malignancy, precipitating transplantation as a therapeutic option is not clear. With current results, it is difficult to recommend HCT as a treatment option for patients with AT, except in clinical trials. In contrast, patients with the other conditions described have transplantation outcomes similar to those with other primary immunodeficiencies when choosing RIC. Therefore transplantation could be considered more favorably as a pre-emptive therapeutic approach, particularly if radiotherapy is omitted from the conditioning regimen and low-intensity conditioning regimens are used. However, the high rate of posttransplantation complications, including GvHD, remains a concern and should drive the development of alternative low or nontoxic conditioning approaches that relieve these patients of the deleterious effects of alkylating therapy but enable full T- and B-lymphocyte reconstitution. In the meantime, careful follow-up is required to observe further systemic benefits from transplantation, if any, and importantly to monitor for long-term adverse events. In the future, gene therapy might be an acceptable alternative treatment strategy for this group of patients.

Clinical implications: HCT cures DNA breakage repair disorders. Patients with Cernunnos-XLF deficiency, LIG4, and NBS receiving alkylator or radiotherapy preconditioning have worse survival than those receiving RIC.

REFERENCES

1. Wang C, Lees-Miller SP. Detection and repair of ionizing radiation-induced DNA double strand breaks: new developments in nonhomologous end joining. Int J Radiat Oncol Biol Phys 2013;86:440-9.
2. Waters CA, Strande NT, Wyatt DW, Pryor JM, Ramsden DA. Nonhomologous end joining: a good solution for bad ends. DNA Repair (Amst) 2014;17:39-51.
3. Goodarzi AA, Jeggo PA. The repair and signaling responses to DNA double-strand breaks. Adv Genet 2013;82:1-45.
4. Woodbine L, Gennery AR, Jeggo PA. The clinical impact of deficiency in DNA non-homologous end-joining. DNA Repair (Amst) 2014;17:9-20.
5. Schwarz K, Gauss GH, Ludwig L, Pannicke U, Li Z, Lindner D, et al. RAG mutations in human B cell-negative SCID. Science 1996;274:97-9.
6. Moshous D, Callebaut I, de Chasseval R, Corneo B, Cavazzana-Calvo M, Le Deist F, et al. Artemis, a novel DNA double-strand break repair/V(D)J recombination protein, is mutated in human severe combined immune deficiency. Cell 2001;105:177-86.
7. Moshous D, Pannetier C, de Chasseval R, le Deist F, Cavazzana-Calvo M, Romana S, et al. Partial T and B lymphocyte immunodeficiency and predisposition to lymphoma in patients with hypomorphic mutations in Artemis. J Clin Invest 2003;111:381-7.
8. van der Burg M, Ijspeert H, Verkaik NS, Turul T, Wiegant WW, Morotomi-Yano K, et al. A DNA-PKcs mutation in a radiosensitive T-B- SCID patient inhibits Artemis activation and nonhomologous end-joining. J Clin Invest 2009;119:91-8.
9. Woodbine L, Neal JA, Sasi NK, Shimada M, Deem K, Coleman H, et al. PRKDC mutations in a SCID patient with profound neurological abnormalities. J Clin Invest 2013;123:2969-80.
10. O'Driscoll M, Cerosaletti KM, Girard PM, Dai Y, Stumm M, Kysela B, et al. DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. Mol Cell 2001;8:1175-85.
11. Buck D, Moshous D, de Chasseval R, Ma Y, le Deist F, Cavazzana-Calvo M, et al. Severe combined immunodeficiency and microcephaly in siblings with hypomorphic mutations in DNA ligase IV. Eur J Immunol 2006;36:224-35.
12. Enders A, Fisch P, Schwarz K, Duffner U, Pannicke U, Nikolopoulos E, et al. A severe form of human combined immunodeficiency due to mutations in DNA ligase IV. J Immunol 2006;176:5060-8.
13. van der Burg M, van Veelen LR, Verkaik NS, Wiegant WW, Hartwig NG, Barendregt BH, et al. A new type of radiosensitive T-B-NK+ severe combined immunodeficiency caused by a LIG4 mutation. J Clin Invest 2006;116:137-45.
14. Buck D, Malivert L, de Chasseval R, Barraud A, Fondanèche MC, Sanal O, et al. Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. Cell 2006;124:287-99.
15. Schuetz C, Neven B, Dvorak CC, Leroy S, Ege MJ, Pannicke U, et al. SCID patients with ARTEMIS vs RAG deficiencies following HCT: increased risk of late toxicity in ARTEMIS-deficient SCID. Blood 2014;123:281-9.
16. Deeg HJ, Socié G, Schoch G, Henry-Amar M, Witherspoon RP, Devergie A, et al. Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. Blood 1996;87:386-92.
17. Gadalla SM, Sales-Bonfim C, Carreras J, Alter BP, Antin JH, Ayas M, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with dyskeratosis congenita. Biol Blood Marrow Transplant 2013;19:1238-43.
18. Gruhn B, Seidel J, Zintl F, Varon R, Tönnies H, Neitzel H, et al. Successful bone marrow transplantation in a patient with DNA ligase IV deficiency and bone marrow failure. Orphanet J Rare Dis 2007;2:5.
19. Grunebaum E, Bates A, Roifman CM. Omenn syndrome is associated with mutations in DNA ligase IV. J Allergy Clin Immunol 2008;122:1219-20.
20. Straathof KC, Rao K, Eyrich M, Hale G, Bird P, Berrie E, et al. Haemopoietic stem cell transplantation with antibody-based minimal intensity conditioning. Lancet 2009;374:912-20.
21. Albert MH, Gennery AR, Greil J, Cale CM, Kalwak K, Kondratenko I, et al. Successful Stem cell transplantation for Nijmegen breakage syndrome. Bone Marrow Transplant 2010;45:622-6.
22. Woźniak M, Krzywoń M, Hołda MK, Goździk J. Reduced-intensity conditioning umbilical cord blood transplantation in Nijmegen breakage syndrome. Pediatr Transplant 2015;19:E51-5.
23. Stajner T, Vasiljević Z, Vujić D, Marković M, Ristić G, Mićić D, et al. Atypical strain of *Toxoplasma gondii* causing fatal reactivation after hematopoietic stem cell transplantation in a patient with an underlying immunological deficiency. J Clin Microbiol 2013;51:2686-90.
24. Dai Y, Kysela B, Hanakahi LA, Manolis K, Riballo E, Stumm M, et al. Nonhomologous end joining and V(D)J recombination require an additional factor. Proc Natl Acad Sci U S A 2003;100:2462-7.
25. Faraci M, Lanino E, Micalizzi C, Morreale G, Di Martino D, Banov L, et al. Unrelated hematopoietic stem cell transplantation for Cernunnos-XLF deficiency. Pediatr Transplant 2009;13:785-9.
26. Çağdaş D, Özgür TT, Asal GT, Revy P, De Villartay JP, van der Burg M, et al. Two SCID cases with Cernunnos-XLF deficiency successfully treated by hematopoietic stem cell transplantation. Pediatr Transplant 2012;16:E167-71.
27. Ghosh S, Schuster FR, Binder V, Niehues T, Baldus SE, Seiffert P, et al. Fatal outcome despite full lympho-hematopoietic reconstitution after allogeneic stem cell transplantation in atypical ataxia telangiectasia. J Clin Immunol 2012;32:438-40.

28. Ussowicz M, Musiał J, Duszeńko E, Haus O, Kałwak K. Long-term survival after allogeneic-matched sibling PBSC transplantation with conditioning consisting of low-dose busilvex and fludarabine in a 3-year-old boy with ataxia-telangiectasia syndrome and ALL. Bone Marrow Transplant 2013;48:740-1.
29. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009;15:1628-33.
30. de la Fuente J, Reiss S, McCloy M, Vulliamy T, Roberts IA, Rahemtulla A, et al. Non-TBI stem cell transplantation protocol for Fanconi anaemia using HLA-compatible sibling and unrelated donors. Bone Marrow Transplant 2003; 32:653-6.
31. Available at: https://www.ebmt.org/Contents/About-EBMT/Who-We-Are/Scientific Council/Documents/EBMT_ESIDGUIDELINESFORINBORNERRORSFINAL 2011.pdf. Accessed October 16, 2016.
32. Chao MM, Ebell W, Bader P, Beier R, Burkhardt B, Feuchtinger T, et al. Consensus of German transplant centers on hematopoietic stem cell transplantation in Fanconi anemia. Klin Padiatr 2015;227:157-65.
33. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of haematopoietic stem cells and long term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? J Allergy Clin Immunol 2010;26:602-10, e1-11.
34. Wolska-Kusnierz B, Gregorek H, Chrzanowska K, Piątosa B, Pietrucha B, Heropolitańska-Pliszka E, et al. Nijmegen breakage syndrome: clinical and immunological features, long-term outcome and treatment options. J Clin Immunol 2015;35:538-49.
35. Güngör T, Albert MH, Teira P, Slatter M, Stüssi G, Stepensky P, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet 2014;838:436-48.
36. Booth C, Gilmour KC, Veys P, Gennery AR, Slatter MA, Chapel H, et al. X-linked Lymphoproliferative Disease due to SAP/SH2D1A deficiency: a multicentre study on the manifestations, management and outcome of the disease. Blood 2011;117: 53-62.
37. Mahlaoui N, Pellier I, Mignot C, Jais JP, Bilhou-Nabéra C, Moshous D, et al. Characteristics and outcome of early-onset, severe forms of Wiskott-Aldrich syndrome. Blood 2013;121:1510-6.
38. Ouachee-Chardin M, Elie C, de Saint Basile G, Le Deist F, Mahlaoui N, Picard C, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics 2006;117:e743-50.
39. Peffault de Latour R, Porcher R, Dalle JH, Aljurf M, Korthof ET, Svahn J, et al. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. Blood 2013; 122:4279-86.

REFERENCES

E1. O'Driscoll M, Cerosaletti KM, Girard PM, Dai Y, Stumm M, Kysela B, et al. DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. Mol Cell 2001;8:1175-85.

E2. Buck D, Moshous D, de Chasseval R, Ma Y, le Deist F, Cavazzana-Calvo M, et al. Severe combined immunodeficiency and microcephaly in siblings with hypomorphic mutations in DNA ligase IV. Eur J Immunol 2006;36:224-35.

E3. Enders A, Fisch P, Schwarz K, Duffner U, Pannicke U, Nikolopoulos E, et al. A severe form of human combined immunodeficiency due to mutations in DNA ligase IV. J Immunol 2006;176:5060-8.

E4. van der Burg M, van Veelen LR, Verkaik NS, Wiegant WW, Hartwig NG, Barendregt BH, et al. A new type of radiosensitive T-B-NK+ severe combined immunodeficiency caused by a LIG4 mutation. J Clin Invest 2006;116:137-45.

E5. Deeg HJ, Socié G, Schoch G, Henry-Amar M, Witherspoon RP, Devergie A, et al. Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. Blood 1996;87:386-92.

E6. Grunebaum E, Bates A, Roifman CM. Omenn syndrome is associated with mutations in DNA ligase IV. J Allergy Clin Immunol 2008;122:1219-20.

E7. Straathof KC, Rao K, Eyrich M, Hale G, Bird P, Berrie E, et al. Haemopoietic stem cell transplantation with antibody-based minimal intensity conditioning. Lancet 2009;374:912-20.

E8. Tamura S, Higuchi K, Tamaki M, Inoue C, Awazawa R, Mitsuki N, et al. Novel compound heterozygous DNA ligase IV mutations in an adolescent with a slowly-progressing radiosensitive-severe combined immunodeficiency. Clin Immunol 2015;160:255-60.

E9. Albert MH, Gennery AR, Greil J, Cale CM, Kalwak K, Kondratenko I, et al. Successful Stem cell transplantation for Nijmegen breakage syndrome. Bone Marrow Transplant 2010;45:622-6.

E10. Woźniak M, Krzywoń M, Hołda MK, Goździk J. Reduced-intensity conditioning umbilical cord blood transplantation in Nijmegen breakage syndrome. Pediatr Transplant 2015;19:E51-5.

E11. Wolska-Kusnierz B, Gregorek H, Chrzanowska K, Piątosa B, Pietrucha B, Heropolitańska-Pliszka E, et al. Nijmegen breakage syndrome: clinical and immunological features, long-term outcome and treatment options. J Clin Immunol 2015;35:538-49.

E12. Stajner T, Vasiljević Z, Vujić D, Marković M, Ristić G, Mićić D, et al. Atypical strain of Toxoplasma gondii causing fatal reactivation after hematopoietic stem cell transplantation in a patient with an underlying immunological deficiency. J Clin Microbiol 2013;51:2686-90.

E13. Dai Y, Kysela B, Hanakahi LA, Manolis K, Riballo E, Stumm M, et al. Nonhomologous end joining and V(D)J recombination require an additional factor. Proc Natl Acad Sci U S A 2003;100:2462-7.

E14. Faraci M, Lanino E, Micalizzi C, Morreale G, Di Martino D, Banov L, et al. Unrelated hematopoietic stem cell transplantation for Cernunnos-XLF deficiency. Pediatr Transplant 2009;13:785-9.

E15. Çağdaş D, Özgür TT, Asal GT, Revy P, De Villartay JP, van der Burg M, et al. Two SCID cases with Cernunnos-XLF deficiency successfully treated by hematopoietic stem cell transplantation. Pediatr Transplant 2012;16:E167-71.

E16. Ghosh S, Schuster FR, Binder V, Niehues T, Baldus SE, Seiffert P, et al. Fatal outcome despite full lympho-hematopoietic reconstitution after allogeneic stem cell transplantation in atypical ataxia telangiectasia. J Clin Immunol 2012;32:438-40.

E17. Ussowicz M, Musiał J, Duszeńko E, Haus O, Kałwak K. Long-term survival after allogeneic-matched sibling PBSC transplantation with conditioning consisting of low-dose busilvex and fludarabine in a 3-year-old boy with ataxia-telangiectasia syndrome and ALL. Bone Marrow Transplant 2013;48:740-1.

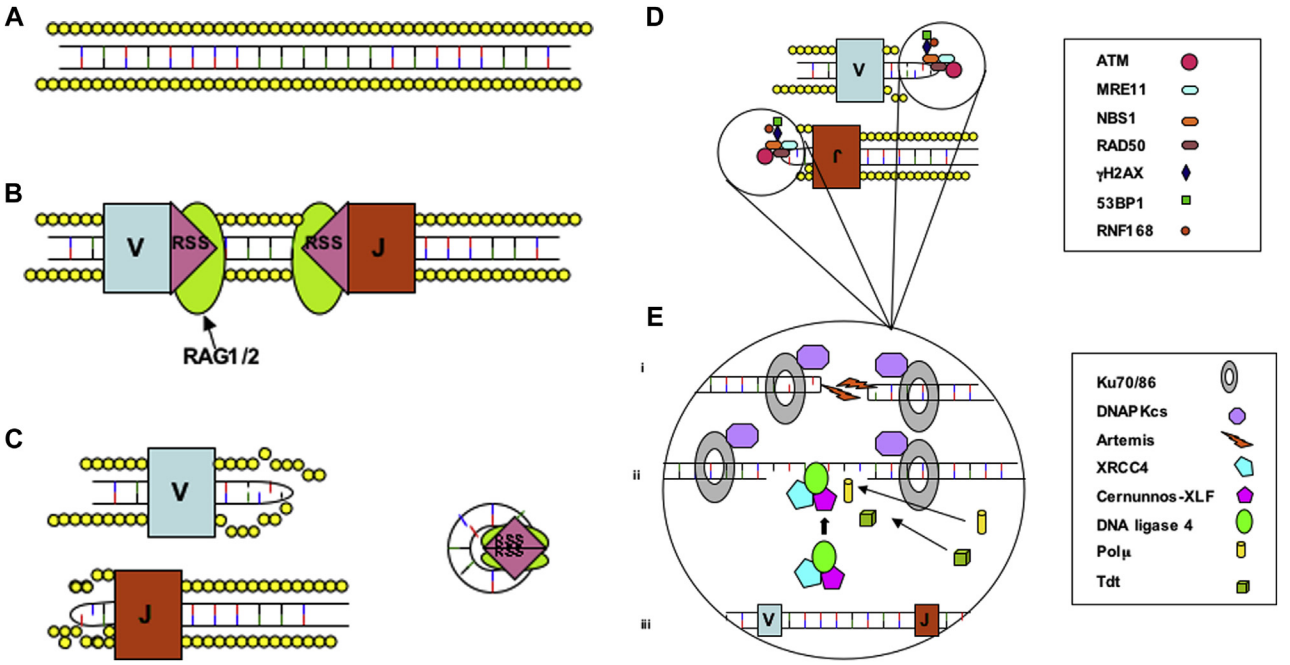

FIG E1. V(D)J Recombination. **A,** DNA is uncoiled at transcription "factories" within the cell, where the associated recombination and repair proteins colocalize. **B,** Lymphoid-specific RAG1/2 proteins recognize and bind the recombination signal sequences *(RSS)* that flank V(D)J gene segments and introduce site-specific DNA-dsbs. **C,** The phosphorylated blunt signal ends and the covalently sealed hairpin intermediate of the coding end are held together by the RAG complex. **D,** The MRN complex binds the broken DNA ends and activates ATM, which initiates cell-cycle arrest and attraction of the repair proteins. H2AX, 53BP1, and RNF168, with other proteins, stabilize the damaged chromatin. **E,** *i*, The Ku70/Ku80 heterodimer binds the coding ends and recruits DNA protein kinase catalytic subunit *(DNA-PKcs)* and Artemis, which is required to open the hairpin intermediates. The covalently sealed hairpin intermediate is randomly nicked by the DNA-PKcs/Artemis complex, which generates a single-strand break with 3′ or 5′ overhangs. *ii*, XRCC4, LIG4, and cernunnos-XLF coassociate and are recruited to the ends. The signal ends are directly ligated by the XRCC4/DNA-LIG4/cernunnos-XLF complex. The opened hairpin intermediate is modified by polymerases, exonucleases, and the lymphoid-specific terminal deoxynucleotidyl transferase *(TdT)*. *iii*, Repair and ligation by the XRCC4/DNA-LIG4/cernunnos-XLF complex. Reproduced with permission from Ussowicz et al.[E17]

TABLE E1. Characteristics of patients with LIG4[E1-E8]

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	aGvHD	Complications	Follow-up (mo)	Outcome
New cases								
1								
Transplant 1	5/M	Infection	MUD	Alemtuzumab, 1 mg/kg	Nil	Initial graft failure, chronic lung disease	—	Alive
Transplant 2	9/M	Graft failure	CB MUD BM	Flu, 150 mg/m^2* Melph, 70 mg/m^2 Alemtuzumab, 1 mg/kg	Nil	EBV viremia and colitis, hypothyroidism, bronchiolitis obliterans	83	Alive
2	8/F	Autoimmunity Omenn phenotype	MMUD 5/6 CB	Flu 150 mg/m^2† Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Grade 2, skin and liver	Nil	48	Alive
3	17/M	Pre-emptive	MUD BM	Flu, 150 mg/m^2* Melph, 70 mg/m^2 Alemtuzumab, 1 mg/kg	Grade 3, skin and gut	cGvHD, EBV, and adenovirus viremia colitis, HTN, cholecystitis	36	Alive
4	18/M	Infection	MUD PBSC CD34$^+$ selected	Flu, 150 mg/m^2* Melph, 140 mg/m^2 ATG (dose NA)	Nil	Dilated cardiomyopathy	83	Alive
5	18/M	NA	MUD 8/8 BM	Flu, 150 mg/m^2* Melph, 70 mg/m^2 Alemtuzumab, 1 mg/kg	Grade 3	NA	24	Alive
6								
Transplant 1	21/M	Infection	MMFD BM	Nil	Nil	Graft failure	143	Alive
Transplant 2	23/M	Graft failure	MMFD BM	Bu, 12.9 mg/kg* Flu, 120 mg/m^2 Alemtuzumab, 0.3 mg/kg		Mucositis, left arytenoid cartilage fracture, synechia of anterior vocal cord		Alive
7	20/F	Infection SCID phenotype	MFD BM	Flu, 150 mg/m^2† Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Nil	Sepsis	2	Alive
8	28/M	BMF	MUD BM	Flu, 150 mg/m^2* Melph, 70 mg/m^2 Alemtuzumab, 1 mg/kg	Nil	Nil	46	Alive
9	28/F	NA	MUD 8/8 BM	Flu, 150 mg/m^2* Melph, 70 mg/m^2 Alemtuzumab, 1 mg/kg	Nil	NA	36	Alive
10	31/F	Infection	MMFD BM	Nil	Grade 3, skin, gut	Developmental delay	142	Alive
11	43/F	BMF	MUD BM, buffy coat enrichment, plasma reduction	Flu, 150 mg/m^2† Cy, 40 mg/kg Alemtuzumab, 1 mg/kg	Nil	Nil	24	Alive
12	47/M	Infection	MFD BM	Flu, 150 mg/m^2† Cy, 20 mg/kg ATG, 30 mg/kg	Nil	Nil	15	Alive
13	52/F	Infection	MMFD 9/10 BM	Flu, 150 mg/m^2† Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Nil	CMV viremia, EBV-PTLD	50	Alive

(Continued)

TABLE E1. *(Continued)*

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	aGvHD	Complications	Follow-up (mo)	Outcome
14	54/M	Infection Autoimmunity BMF	MSD BM	Flu, 150 mg/m^2† Cy, 40 mg/kg ATG, 7.5 mg/kg	Grade 1, skin	Limited cGvHD (resolved) Autoimmune hypothyroidism	45	Alive
15	75/F	BMF	MUD 9/10 BM	Bu, 2.4 mg/kg† Flu, 180 mg/m^2 Cy, 40 mg/kg Alemtuzumab, 1.5 mg/kg	Nil	Nil	22	Alive
16	83/F	BMF	MUD PBSC	Flu, 150 mg/m^2† Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Nil	Nil	21	Alive
17	116/F	BMF	MMUD 5/6 BM	Flu, 150 mg/m^2† Cy, 40 mg/kg ATG, 10 mg/kg	Grade 1, skin	PRES cGvHD, skin and mucosa Mixed chimerism	12	Alive
18	120/M	Infection	MSD BM	Flu, 40 mg/m^2† Cy, 24 mg/kg ATG, 3 mg/kg	Nil	Nil	22	Alive
19	11/M	Infection SCID phenotype	MUD CB	Flu, 90 mg/m^2* Melph, 114 mg/m^2	Nil	MOF	2	Dead
20	22/F	Infection	MRD BM	Bu, 4 mg/kg* Flu, 120 mg/m^2 Melph, 140 mg/m^2	Nil	Heart failure, multiorgan failure from D+1	5 d	Dead
21	33/M	Infection	MUDBM	Flu, 150 mg/m^2* Melph, 140 mg/m^2 ATG (dose NA)	Grade 2, skin and gut	VOD, mucositis, died MOF, GI bleeding	NA	Dead
22	49/F	Infection BMF	MMUD CB	Flu, 150 mg/m^2† Cy, 40 mg/kg ATG, 10 mg/kg	Grade 3, gut	Pericardial effusion, SVT, MAS	7	Dead
23	8/M	Pre-emptive	MUD BM	Treo, 42 g/m^2‡ Flu, 150 mg/m^2 ATG, 10 mg/kg	Grade 3, skin and gut	Norovirus, TPN dependence, graft failure, osteopenic fractures, HTN, rhinovirus, MOF	8	Dead
24	10/F	Infection	Paternal haploidentical PBSC CD34$^+$ selected	Flu, 120 mg/m^2‡ Melph, 140 mg/m^2 TT, 10 mg/kg	Grade 1, skin	GI and pulmonary hemorrhage	1	Dead
25	13/M	Infection SCID phenotype	MMUD 9/10 BM	Flu, 150 mg/m^2‡ TT, 15 mg/kg ATG, 10 mg/kg	Grade 3, skin, gut, and liver	*Pseudomonas aeruginosa*, RSV, EBV, CMV, capillary leak syndrome Pneumopathy	5	Dead
26	60/M	BMF	Maternal CD34$^+$ haploidentical	Flu, 200 mg/m‡ Cy, 20 mg/kg TT, 5 mg/kg ATG, 3 mg/kg	Nil	Rejection Fungal pneumonia	6	Dead

(Continued)

TABLE E1. *(Continued)*

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	aGvHD	Complications	Follow-up (mo)	Outcome
Updated cases								
27[E7]	49/M	Infection	MUD PBSC	Flu, 150 mg/m^2† Cy, 40 mg/mg Alemtuzumab, 0.6 mg/kg YTH24/54, 1.6 mg/kg	Grade 2, skin and gut	Autoimmune hypothyroidism	93	Alive
28[E6]	6/F	Infection SCID phenotype	MUD BM	Bu, 16 mg/kg‡ Cy, 200 mg/kg	Grade 4, skin and gut	cGvHD respiratory failure, cardiac hypertrophy, renal failure, EBV, developmental delay, increased ICP, tube feed, optic neuritis	103	Alive
29[E1]	552/M	BMF MDS	MSD BM	Bu, 12.8 mg/kg‡ Cy, 120 mg/kg	Nil	Severe mucositis, CMV cGvHD	?	Alive
30[E2]	19/F	Infection SCID phenotype	MMUD BM (TCD)	Bu, 16 mg/kg‡ Cy, 200 mg/kg ATG, 10 mg/kg	Nil	EBV-PTLD	2	Dead
31[E2]	2.5/F	Pre-emptive SCID phenotype	MMUD BM 3/6 TCD	Bu, 15 mg/kg‡ Cy, 200 mg/kg ATG, 10 mg/kg	Nil	VOD Pneumopathy	1.5	Dead
32[E8]	212/M	BMF	TCRα/β PBSC haploidentical mother	Flu, 180 mg/m^2* Cy, 60 mg/kg ATG, 2.5 mg/kg	Grade 3, GI	Poor immunoreconstitution, BK viral infection acute renal failure	12	Dead
Published								
33[E5]	132/F	BMF	MSD BM	Flu, 120 mg/m^2† Cy, 40 mg/kg ATG, 60 mg/kg	Nil	Delayed puberty	60	Alive
34[E3]	4/F	SCID phenotype	MUD BM	Flu (dose NA)‡ TT (dose NA)	Nil	Severe HUS, with renal impairment	8	Alive
35[E4]	18/F	Infection	MSD cord	Bu, 20 mg/kg‡ Cy, 200 mg/kg	Nil	Died before HSCT, VOD, respiratory arrest	–	Dead
36[E3]	24/F	Infection Autoimmunity Malignancy		Myeloablative‡ No details available		Died during conditioning MOF Aspergillosis	—	Dead

ATG, Anti-thymocyte globulin; *BM*, bone marrow; *BMF*, bone marrow failure; *Bu*, busulphan; *CB*, cord blood; *CMV*, cytomegalovirus; *Cy*, cyclophosphamide; *Flu*, fludarabine; *GI*, gastrointestinal; *HSCT*, hematopoietic stem cell transplant; *HTN*, hypertension; *HUS*, hemolytic uremic syndrome; *ICP*, intracranial pressure; *MAS*, macrophage activation syndrome; *Melph*, melphalan; *MFD*, matched family donor; *MMFD*, mismatched family donor; *MOF*, multiorgan failure; *MUD*, matched unrelated donor; *NA*, not available; *PBSC*, peripheral blood stem cells; *PRES*, posterior reversible encephalopathy syndrome; *RSV*, respiratory syncytial virus; *SVT*, supraventricular tachycardia; *TCD*, T cell depleted; *TCRα/β*, T-cell receptor alpha/beta depletion; *TPN*, total parenteral nutrition; *Treo*, treosulfan; *TT*, thiotepa; *VOD*, veno-occlusive disease; *YTH24/54*, anti-CD45 mAbs.

*RIC regimen.

†Fanconi or modified Fanconi regimen.

‡MAC regimen.

TABLE E2. Characteristics of patients with defects in *NBN*[E9-E12]

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	aGvHD	Complications	Follow-up (mo)	Outcome
New cases								
37	45/F	Autoimmunity	MSD BM	Alemtuzumab,† 1 mg/kg Flu, 150 mg/m^2 Cy, 20 mg/kg	Grade 2, skin	AIHA	14	Alive
38	69/M	Malignancy	TCRα/β PBSC MUD 9/10	Bu, 4 mg/kg* Flu, 150 mg/m^2 Cy, 30 mg/kg ATG, 5 mg/kg Rituximab, 100 mg/m^2	Nil	Hepatitis CMV viremia	5	Alive
39	71/M	Infection	TCRα/β PBSC 9/10 sibling donor	Bu, 4 mg/kg* Flu, 150 mg/m^2 Cy, 20 mg/kg ATG, 5 mg/kg Rituximab, 100 mg/m^2	Nil	Nil	2	Alive
40	90/M	Malignancy	TCRα/β PBSC MUD 10/10	Bu, 4 mg/kg* Flu, 150 mg/m^2 Cy, 40 mg/kg ATG, 5 mg/kg Rituximab, 100 mg/m^2	Nil	Hepatitis	6	Alive
41	107/F	Pre-emptive	MUD 9/10 PBSC CD34+ with T-cell add-back 1 × 10^8/kg	Bu, 2 mg/kg† Flu, 180 mg/kg Cy, 20 mg/kg Alemtuzumab, 0.5 mg/kg	Nil	Secondary graft loss	14	Alive with disease
42	144/M	Malignancy	MSD BM	Bu, 4 mg/kg* Flu, 150 mg/m^2 Cy, 20 mg/kg ATG, 5 mg/kg	Grade 1, skin	Norovirus, adenovirus enterocolitis	16	Alive
43	205/F	EBV-associated LPD	MSD BM	Bu, 4 mg/kg* Flu, 150 mg/m^2 Cy, 30 mg/kg ATG, rituximab	Nil	EBV-PTLD	6	Alive
44	228/M	NA	MUD 8/8 PBSC	TBI (2 Gy)‡ Flu, 150 mg/m^2	Grade 2	cGvHD	59	Alive
45	60/F	Malignancy	MUD PBSC TCRα/β	Bu, 4 mg/kg* Flu, 150 mg/m^2 Cy, 40 mg/kg ATG, 5 mg/kg Rituximab, 100 mg/m^2	Grade 1, skin	Mucositis grade 2, relapse PTCL	3	Dead
46	136/F	Malignancy	MMFD PBSC	Melph, 140 mg/m^2* Flu, 120 mg/m^2 Alemtuzumab, 1 mg/kg	Nil	VOD, MOF, sepsis	2	Dead
47	204/F	BMF	MUD PBSC TCRα/β	Bu, 4 mg/kg* Flu, 150 mg/m^2 Cy, 40 mg/kg ATG, 5 mg/kg Rituximab, 100 mg/m^2	Nil	Rejected 10 mo Developed T-cell lymphoma	16	Dead

(Continued)

TABLE E2. *(Continued)*

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	aGvHD	Complications	Follow-up (mo)	Outcome
Updated cases								
48[E9,E11]	27/F	Infection	MSD BM	Alemtuzumab,† 1 mg/kg Flu, 150 mg/m^2 Cy, 20 mg/kg	Nil	Autoimmune hyperthyroidism	102	Alive
49[E9,E11]	42/M	Pre-emptive	MFD 10/10 BM	Thoracoabdominal‡ irradiation, 5 Gy Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Nil	ADV, CMV Mucositis Mixed chimerism	150	Alive
50[E11]	77/F	Malignancy	MUD BM	Flu, 150 mg/m^2† Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Grade 1, skin	Nil	29	Alive
51[E11]	110/M	Malignancy	MFD BM	Flu, 150 mg/m^2† Cy, 40 mg/kg ATG, 70 mg/kg Rituximab, 750 mg/m^2	Grade 3, skin	cGvHD skin, liver CMV reactivation	48	Alive
52[E9]	240/M	Malignancy	MUD PBSC	Melph, 140 mg/m^2* Flu, 125 mg/m^2 ATG, 60 mg/kg	Grade 1, skin	Nil	99	Alive
53[E12]	185/M	Malignancy	MSD BM	Melph, 140 mg/m^2* Flu, 150 mg/m^2 Alemtuzumab, 1 mg/kg	Grade 1, skin and gut	Toxoplasmosis	1	Dead
Published cases								
54[E10]	19/F	Infection	MUD CB	ATG, 10 mg/kg† Flu, 150 mg/m^2 Cy, 20 mg/kg	Nil	Nil	34	Alive
55[E11]	46/F	Infection	MUD PBSC	Flu, 150 mg/m^2† Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Grade 2, skin and gut	Nil	48	Alive
56[E11]	72/F	Malignancy	MUD PBSC	Bu, 2 mg/kg† Flu, 150 mg/m^2 ATG, 7.5 mg/kg	Nil	Nil	17	Alive
57[E9,E11]	165/M	Malignancy	MUD PBSC	Bu, 2 mg/kg† Flu, 150 mg/m^2 ATG, 60 mg/kg	Grade 2, skin	cGvHD Mild hemorrhagic cystitis	81	Alive
58[E9]	174/M	Malignancy	MMFD TCD PBSC	Flu, 160 mg/m^2‡ TT, 10 mg/kg Melph, 70 mg/m^2	Nil	Mucositis, ITP, sepsis, adeno cryptosporidiosis	24	Alive
59[E11]	102/M 113	Malignancy Malignancy relapse	MSD BM MSD BM	Flu (dose NA)* Cy (dose NA) Bu, 12 mg/kg‡ Cy, 120 mg/kg	Nil Gut	Rejected Sepsis	11 3	Alive Dead
60[E11]	110/F	Malignancy	MSD BM	Bu, 2 mg/kg† Flu, 150 mg/m^2 ATG (dose NA)	Nil	Lymphoma relapse	2	Dead

(Continued)

TABLE E2. *(Continued)*

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	aGvHD	Complications	Follow-up (mo)	Outcome
61[E9,E11]	192/M	Malignancy	MSD PBSC	Bu, 10 mg/kg‡ Cy, 120 mg/kg TT, 25 mg/kg	Nil	Nil	Sepsis D+5	Dead
62[E11]	218/M	Malignancy	MUD PBSC	Flu, 150 mg/m^2* Melph, 140 mg/m^2 ATG (dose NA)	Nil	Sepsis	6	Dead

ADV, Adenovirus; *AIHA*, autoimmune hemolytic anemia; *ATG*, anti-thymocyte globulin; *BM*, bone marrow; *BMF*, bone marrow failure; *Bu*, busulphan; *CB*, cord blood; *CMV*, cytomegalovirus; *Cy*, cyclophosphamide; *Flu*, fludarabine; *GI*, gastrointestinal; *HSCT*, hematopoietic stem cell transplantation; *ITP*, idiopathic thrombocytopenia; *LPD*, lymphoproliferative disease; *Melph*, melphalan; *MFD*, matched family donor; *MMFD*, mismatched family donor; *MOF*, multiorgan failure; *MUD*, matched unrelated donor; *NA*, not available; *PBSC*, peripheral blood stem cells; *TBI*, total-body irradiation; *TCD*, T cell depleted; *TCRα/β*, T-cell receptor α/β depletion; *TT*, thiotepa; *VOD*, veno-occlusive disease.

*RIC regimen.

†Fanconi or modified Fanconi regimen.

‡MAC regimen.

TABLE E3. Characteristics of patients with defects in *NHEJ1*[E13-E15]

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	GvHD	Complications	Follow-up (mon)	Outcome
New cases								
63	5/M	Infection	MUD PBSC	Flu, 150 mg/m^2* Cy, 20 mg/kg Alemtuzumab, 1 mg/kg	Grade 4, skin	ADV	10	Alive
64	10/M	Infection	MSD BM	Flu, 150 mg/m^2* Cy, 20 mg/kg	Nil	CMV	3	Alive
65	12/F	SCID-like infection	MSD BM	Nil	Grade 1 aGvHD, skin	Nil	76	Alive
66	17/M	Infection	MSD BM	Cy, 200 mg/kg* ATG, 60 mg/kg	Nil	Nil	168	Alive
67	28/M	Infection	MSD BM	Cy, 200 mg/kg* ATG, 60 mg/kg	Nil	Idiopathic pneumonitis	166	Alive
68	48/F	Infection	MMUD CB	Flu, 150 mg/m^2† Cy, 40 mg/kg ATG, 60 mg/kg	Grade 2, skin	CMV reactivation	24	Alive
69	100/F	BMF	MUD 6/6 PBSC	Flu, 150 mg/m^2† Cy, 4 mg/kg ATG, 7.5 mg/kg	Grade 2, skin	Severe skin cGvHD with scleroderma and joint deformation Cachexia, esophageal stenosis	86	Alive
70	112/F	Infection, cytopenia	MSD BM	Flu, 150 mg/m^2† Cy, 40 mg/kg ATG, 60 mg/kg	Grade 1 aGvHD, skin	Lung cGvHD obstructive lung disease	39	Alive
71	172/M	Infection BMF	MUD 10/10 BM	ATG, 15 mg/kg‡ Treo, 42 mg/m^2 Flu, 160 mg/m^2	Nil	Nil	7	Alive
72	15/M	Autoimmune (AIHA)	MUD CB	Bu, 6.4 mg/kg* Flu, 120 mg/m^2 ATG, 10 mg/kg	Grade 2, skin	Sepsis, EBV, myocarditis	5	Dead
73	41/M	Infection	MUD BM	Flu, 150 mg/m^2† Cy, 40 mg/kg Alemtuzumab, 1 mg/kg	Grade 3, skin and gut	Pancreatitis, CMV, renal failure, HTN, seizures, myelofibrosis, hyperglycemia	12	Dead
74	108/F	BMF	MUD 4/6 CB ×2	Flu, 150 mg/m^2* Melph, 140 mg/m^2 Alemtuzumab, 1.5 mg/kg	Grade 3, gut	cGvHD EBV, ADV	13	Dead
Published cases								
75[E14]	10/M	Infection	MMUD PBSC	Flu, 120 mg/m^2† Cy, 40 mg/kg ATG, 15 mg/kg	Grade 2 aGvHD, skin	cGvHD EBV-PTLD	26	Alive
76[E15]	15/F	Infection AIHA	MSD BM	Nil	Nil	Nil	83	Alive
77[E15]	18/F	Infection	MSD BM	Nil	Grade 4, gut	Nil	6	Alive
78[E13]	22/F	Infection	BM	NA	NA	NA	NA	NA
79[E13]	101/M	Infection	BM	NA	NA	NA	NA	NA

ADV, Adenovirus; *AIHA*, autoimmune hemolytic anemia; *ATG*, anti-thymocyte globulin; *BM*, bone marrow; *BMF*, bone marrow failure; *Bu*, busulphan; *CB*, cord blood; *CMV*, cytomegalovirus; *Cy*, cyclophosphamide; *Flu*, fludarabine; *HTN*, hypertension; *Melph*, melphalan; *MFD*, matched family donor; *MOF*, multiorgan failure; *MUD*, matched unrelated donor; *MMUD*, mismatched unrelated donor; *NA*, not available; *PBSC*, peripheral blood stem cells; *Treo*, treosulfan.

*RIC regimen.

†Fanconi or modified Fanconi regimen.

‡MAC regimen.

TABLE E4. Characteristics of patients with AT[E16,E17]

Patient	Age (mo) at HSCT/sex	Indication	Donor/stem cell source	Conditioning	aGvHD	Complications	Follow-up (mo)	Outcome
New cases								
80	156/M	Malignancy	MSD BM	Bu, 1.6 mg/kg† Flu, 180 mg/m^2 Cy, 40 mg/kg Rituximab (dose NA)	Nil	Hemorrhagic cystitis, VOD, septicemia, GI bleed	27	Alive
81	8/M	Infection	MUD BM	Treo, 36 mg/m^2‡ Flu, 150 mg/m^2 Alemtuzumab, 1 mg/kg	Grade 1-2, skin	EBV-PTLD	6	Dead
82	22/F	BMF	MFD BM	Treo, 46 g/m^2‡ Flu, 150 mg/m^2	Grade 3, liver and skin	PTLD, hepatic failure	20	Dead
83	101/F	NA	MSD NA	Bu (dose NA)‡ Cy, (dose NA)	Grade 2, skin and gut	MOF	4	Dead
84	138/M	Malignancy	MFD PBSC	Flu, 150 mg/m^2† Cy, 0.3 mg/kg	Grade (NA), skin	Extensive cGvHD skin Interstitial pneumonitis	11	Dead
85	144/M	Malignancy	MSD BM	Bu (dose NA)‡ Cy, (dose NA)	Grade 2, skin	Pericardial effusion Hemorrhagic cystitis	3	Dead
Updated publication								
86[E16]	54/M	ALL-T	MSD BM	Bu, 2 mg/kg† Flu, 150 mg/m^2 ATG, 80 mg/kg OKT3 (dose NA)*	Nil	Hemorrhagic cystitis, CMV reactivation	48	Alive
87[E17]	22/M	Infection	MFD BM	Treo, 36 g/m^2‡ Flu, 150 mg/m^2 ATG, 60 mg/kg	Grade 3, skin and liver	Fulminant hepatic failure, gammopathy, EBV reactivation, encephalopathy	10	Dead

ALL-T, T-cell acute lymphoblastic leukemia; *ATG*, Anti-thymocyte globulin; *BM*, bone marrow; *BMF*, bone marrow failure; *Bu*, busulphan; *CMV*, cytomegalovirus; *Cy*, cyclophosphamide; *Flu*, fludarabine; *GI*, gastrointestinal; *MFD*, matched family donor; *MMFD*, mismatched family donor; *MOF*, multiorgan failure; *MUD*, matched unrelated donor; *NA*, not available; *OKT3*, Muromonab-CD3; *PBSC*, peripheral blood stem cells; *Treo*, treosulfan; *VOD*, veno-occlusive disease.

*RIC regimen.

†Fanconi or modified Fanconi regimen.

‡MAC regimen.