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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Haploidentical vs. sibling, unrelated, or cord blood hematopoietic cell transplantation for acute lymphoblastic leukemia

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Matthew Wieduwilt (University of Oklahoma, Stephenson Cancer Center, United States) Leland Metheny (University Hospitals Cleveland Medical Center, United States) Mei-Jie Zhang (Medical College of Wisconsin, United States) Hai-Lin Wang (Everest Clinical Research Services, United States) Noel Estrada-Merly (CIBMTR, United States) David Marks (University Hospitals Bristol NHS Foundation Trust, United Kingdom) A. Al-Homsi (New York University Langone Medical Center, United States) Lori Muffly (Stanford University, United States) Nelson Chao (Duke University Medical Center, United States) David Rizzieri (Duke University Medical Center, United States) Robert Gale (Centre for Haematology Research, Department of Immunology and Inflammation, Imperial College London, London, UK, United States) Shahinaz Gadalla (National Cancer Institute, United States) Mitchell Cairo (IDIBELL-Institut Catala d'Oncologia, l'Hospitalet de Llobregat, Spain) Alberto Mussetti (IDIBELL-Institut Catala d'Oncologia, l'Hospitalet de Llobregat, Spain) Steven Gore (National Cancer Institute, United States) Vijaya Bhatt (University of Nebraska Medical Center, United States) Sagar Patel (Huntsman Cancer Institute, United States) Fotios Michelis (Princess Margaret Cancer Centre, Canada) Yoshihiro Inamoto (National Cancer Cancer Hospital, Japan) Sherif Badawy (Northwestern University Feinberg School of Medicine, United States) Edward Copelan (Northwestern University Feinberg School of Medicine, United States) Neil Palmisiano (Thomas Jefferson University, United States) Mohamed Kharfan-Dabaja (Mayo Clinic, United States) Hillard Lazarus (Case Western Reserve University, United States) Siddhartha Ganguly (Houston Methodist Hospital, United States) Christopher Bredeson (The Ottawa Hospital / University of Ottawa, Canada) Miguel Diaz Perez (Hospital Infantil Universitario Nino Jesus, Spain) Ryan Cassaday (University of Washington, United States) Bipin Savani (Vanderbilt University Medical Center, United States) Karen Ballen (University of Virginia, United States) Rodrigo Martino (Hospital de la Santa Creu i Sant Pau, Spain) Baldeep Wirk (Penn State Cancer Institute, United States) Ulrike Bacher (Inselspital, Universitatsspital Bern,) Mahmoud Aljurf (King Faisal Specialist Hospital, Saudi Arabia) Asad Bashey (Blood and Marrow Transplant Program at Northside Hospital, United States) Hemant Murthy (Mayo Clinic Florida, United States) Jean Yared (University of Maryland, Greenebaum Cancer Center, United States) Ibrahim Aldoss (City of Hope National Medical Center, United States) Nosha Farhadfar (University of Florida, United States) Hongtao Liu (The University of Chicago, United States) Hisham Abdel-Azim (Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital of Los Angeles, University of Southern California Keck School of Medicine, United States) Edmund Waller (Winship Cancer Institute, United States) Melhem Solh (The Blood and Marrow Transplant Program at Northside Hospital, United States) Matthew Seftel (University of British Columbia, Canada) Marjolein van der Poel (Maastricht University Medical Center, Netherlands) Michael Grunwald (Levine Cancer Institute, Atrium Health, United States) Jane Liesveld (University of Rochester Medical Center, United States) Rammurti Kamble (BCM, United States) Joseph McGuirk (University of Kansas Medical Center, United States) Reinhold Munker (University of Kentucky, United States) Jean-Yves Cahn (Centre Hospitalier Universitaire Grenoble Alpes, France) Jong Wook Lee (Seoul St. Mary's Hospital, The Catholic University of Korea, Korea, Republic of) Cesar Freytes (University of Texas Health Science Center, United States) Maxwell Krem (University of Kentucky College of Medicine, United States) Lena Winestone (University of California San Francisco Benioff Children's Hospitals, United States) Usama Gergis (Thomas Jefferson University, United States) Sunita Nathan (Rush University Medical Center, United States) Richard Olsson (Uppsala University, Sweden) Leo Verdonck (Isala Clinic, Netherlands) Akshay Sharma (St Jude Children's Research Hospital, United States) Olle Ringden (Uppsala University, Sweden) Brian Friend (Center for Cell and Gene Therapy, Baylor College of Medicine, United States) Jan Cerny (University of Massachusetts, United States) Hannah Choe (The Ohio State University, United States) Saurabh Chhabra (Medical College of Wisconsin, United States) Taiga Nishihori (Moffitt Cancer Center, United States) Sachiko Seo (Dokkyo Medical University, Japan) Biju George (Christian Medical College, India) Lee Ann Baxter-Lowe (Children's Hospital of Los Angeles, United States) Gerhard Hildebrandt (University of Kentucky, United States) Marcos de Lima (Ohio State Universithy, United States) Mark Litzow (Mayo Clinic, United States) Partow Kebriaei (University of Texas MD Anderson Cancer Center, United States) Christopher Hourigan (National Heart, Lung and Blood Institute, National Institutes of Health, United States) Muhammed Abid (Medical College of Wisconsin, United States) Daniel Weisdorf (University of Minnesota, United States) Wael Saber (Medical College of Wisconsin, United States)

Abstract:
The role of haploidentical hematopoietic cell transplantation (HCT) using post-transplant cyclophosphamide (PTCy) for acute lymphoblastic leukemia (ALL) is being defined. We performed a retrospective, multivariate analysis comparing outcomes of HCT approaches by donor for adults with ALL

in remission. The primary objective was to compare overall survival (OS) between haploidentical HCT using PTCy and HLA-matched sibling donor (MSD), 8/8 HLA-matched unrelated donor (MUD) , 7/8 HLA-matched UD, or umbilical cord blood (UCB) HCT. Comparing haploidentical to MSD HCT, OS, leukemia-free survival (LFS), non-relapse mortality (NRM), relapse, and acute graft-versus-host disease (aGVHD) were not different but chronic GVHD (cGVHD) was higher with MSD HCT. Compared to MUD HCT, OS, LFS, and relapse were not different but MUD HCT had increased NRM (HR 1.42, P=0.02), grade 3-4 aGVHD (HR 1.59, P=0.005), and cGVHD. Compared to 7/8 UD HCT, LFS and relapse were not different, but 7/8 UD HCT had worse OS (HR 1.38, P=0.01) and increased NRM (HR 2.13, P=<0.001), grade 3-4 aGVHD (HR 1.86, P=0.003), and cGVHD (HR 1.72, P=<0.001). Compared to UCB HCT, late OS , late LFS, relapse, and cGVHD were not different but UCB HCT had worse early OS ({less than or equal to}18 months, HR 1.93, P<0.001), worse early LFS (HR 1.40, P=0.007) and increased incidences of NRM (HR 2.08, P<0.001) and grade 3-4 aGVHD (HR 1.97, P<0.001). Haploidentical HCT using PTCy showed no difference in survival but less GVHD compared to traditional MSD and MUD HCT and is the preferred alternative donor HCT option for adults with ALL in CR.

Conflict of interest: COI declared - see note

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Dr. McGuirk reports other from AlloVir HCP, other from Juno Therapeutics, Inc, other from Gilead-Kite Pharmaceuticals, other from Magenta Therapeutics, outside the submitted work. Dr. Copelan reports other from Amgen Oncology Executive Advisory Council, outside the submitted work. Dr. Gale reports consultant to BeiGene Ltd., Kite Pharma Inc., Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Parmaceuticals Inc. and CStone Pharmaceuticals; Medical Director, FFF Enterprises Inc.; Partner, AZCA Inc.; Board of Directors, RakFond Foundation for Cancer Research Support; Scientific Advisory Board, Antegene Biotech LLC and StemRad Ltd. Dr. Hildebrandt reports other from Incyte, other from Jazz Pharmaceuticals, other from Morphosys, other from Alexion Pharmaceuticals, other from Karyopharm Therapeutics, other from Takeda, other from Jazz Pharmaceuticals, other from Pharmacyclics, other from Incyte, other from AstraZeneca, other from Jazz Pharmaceuticals, other from Astellas Pharma, other from Incyte, other from Falk Foundation, other from Takeda, outside the submitted work. Dr. Olsson reports personal fees from AstraZeneca, outside the submitted work. 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Authors

Matthew J. Wieduwilt[1], Leland Metheny III[2], Mei-Jie Zhang[3,4], Hai-Lin Wang[3], Noel Estrada-Merly[3], David I. Marks[5], A. Samer Al-Homsi[6], Lori Muffly[7], Nelson Chao[8], David Rizzieri[9], Robert Peter Gale[10], Shahinaz M. Gadalla[11], Mitchell Cairo[12], Alberto Mussetti[13,14,] Steven Gore[15], Vijaya Raj Bhatt[16], Sagar S. Patel[17], Fotios V. Michelis[18], Yoshihiro Inamoto[19], Sherif M. Badawy[20,21], Edward Copelan[22], Neil Palmisiano[23], Mohamed A. Kharfan-Dabaja[24], Hillard M. Lazarus[25], Siddhartha Ganguly[26], Christopher Bredeson[27], Miguel Angel Diaz Perez[28], Ryan Cassaday[29], Bipin N. Savani[30], Karen Ballen[31], Rodrigo Martino[32], Baldeep Wirk[33], Ulrike Bacher[34], Mahmoud Aljurf[35], Asad Bashey[36], Hemant S. Murthy[24], Jean A. Yared[37], Ibrahim Aldoss[38], Nosha Farhadfar[39], Hongtao Liu[40], Hisham Abdel-Azim[41], Edmund K. Waller[42], Melhem Solh[43], Matthew D. Seftel[44], Marjolein van der Poel[45], Michael R. Grunwald[22], Jane L. Liesveld[46], Rammurti T. Kamble[47], Joseph McGuirk[26], Reinhold Munker[48], Jean-Yves Cahn[49], Jong Wook Lee[50], César O. Freytes[51], Maxwell M. Krem[48], Lena E. Winestone[52], Usama Gergis[53], Sunita Nathan[54], Richard F. Olsson[55,56], Leo F. Verdonck[57], Akshay Sharma[58], Olle Ringdén[59],

Brian D. Friend[60], Jan Cerny[61], Hannah Choe[62], Saurabh Chhabra[3,63], Taiga Nishihori[64], Sachiko Seo[65], Biju George[66], Lee Ann Baxter-Lowe[67], Gerhard C. Hildebrandt[48], Marcos de Lima[68], Mark Litzow[69], Partow Kebriaei[70], Christopher S. Hourigan[71], Muhammad Bilal Abid[72], Daniel J. Weisdorf[73], and Wael Saber[3]

Affiliations

[1]University of Oklahoma, Stephenson Cancer Center, Oklahoma City, OK; [2]University Hospitals Seidman Cancer Center, Cleveland, OH; [3]CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [4]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI; [5]Adult Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, UK; [6]New York University Langone Health, New York, NY; [7]Division of Blood and Marrow Transplantation, Stanford University, Stanford, CA; [8]Division of Cell Therapy and Hematology, Department of Medicine, Duke University Medical Center, Durham, NC; [9]Division of Hematologic Malignancies and Cellular Therapy, Duke University, Durham, NC; [10]Haematology Research Centre, Department of Immunology and Inflammation, Imperial College London, London, UK; [11]Division of Cancer Epidemiology & Genetics, NIH-NCI Clinical Genetics Branch, Rockville, MD; [12]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Department of Pediatrics, New York Medical College, Valhalla, NY; [13]Hematology Department, Institut Catalá d'Oncologia - Hospitalet, Barcelona, Spain; [14]IDIBELL-Institut Català d'Oncologia, l'Hospitalet de Llobregat, El Prat de Llobregat,

Spain; [15]Yale New Haven Hospital, New Haven, CT; [16]The Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE; [17]Blood and Marrow Transplant Program, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [18]Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Centre, Toronto, Canada; [19]Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan; [20]Division of Hematology, Oncology and Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [21]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL; [22]Deparment of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC; [23]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; [24]Divsion of Hematology-Oncology, Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, FL; [25]University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH; [26]Division of Hematological Malignancies and Cellular Therapeutics, University of Kansas Health System, Kansas City, KS; [27]The Ottawa Hospital Transplant & Cellular Therapy Program, Ottawa, ON, Canada; [28]Department of Hematology/Oncology, Hospital Infantil Universitario Niño Jesus, Madrid, Spain; [29]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA; [30]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; [31]Division of Hematology/Oncology, University of Virginia Health System, Charlottesville, VA; [32]Division of Clinical Hematology, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; [33]Bone Marrow Transplant Program, Penn State Cancer Institute, Hershey, PA;

[34]Department of Hematology, Inselspital, Bern University Hospital, University of Bern, Switzerland; [35]Department of Oncology, King Faisal Specialist Hospital Center & Research, Riyadh, Saudi Arabia; [36]Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA; [37]Blood & Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD; [38]City of Hope Medical Center, Duarte, CA; [39]Division of Hematology/Oncology, University of Florida College of Medicine, Gainesville, FL; [40]Section of Hematology/Oncology, University of Chicago Medicine, Chicago, IL; [41]Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA; [42]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA; [43]The Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA; [44]Department of Medicine, University of British Columbia, Vancouver, Canada; [45]Maastricht University Medical Center, Maastricht, The Netherlands; [46]Department of Medicine, University of Rochester Medical Center, Rochester, NY; [47]Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX; [48]Markey Cancer Center, University of Kentucky, Lexington, KY; [49]Department of Hematology, CHU Grenoble Alpes, Université Grenoble Alpes, Grenoble, France; [50]Division of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [51]University of Texas Health Science Center at San Antonio, San Antonio, TX; [52]Division of Allergy, Immunology, and Blood & Marrow Transplant, University of California San

Francisco Benioff Children's Hospitals, San Francisco, CA; [53]Department of Medical Oncology, Division of Hematological Malignancies, Thomas Jefferson University, Philadelphia, PA; [54]Section of Bone Marrow Transplant and Cell Therapy, Rush University Medical Center, Chicago, IL; [55]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden; [56]Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden; [57]Department of Hematology/Oncology, Isala Clinic, Zwolle, The Netherlands; [58]Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, TN; [59]Translational Cell Therapy Group, CLINTEC (Clinical Science, Intervention and Technology), Karolinska Institutet, Stockholm, Sweden; [60]Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX; [61]Division of Hematology/Oncology, Department of Medicine, University of Massachusetts Medical Center, Worcester, MA; [62]The Ohio State University Wexner Medical Center, James Comprehensive Cancer Center, Columbus, OH; [63]Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [64]Department of Blood & Marrow Transplant and Cellular Immunotherapy (BMT CI), Moffitt Cancer Center, Tampa, FL; [65]Department of Hematology and Oncology, Dokkyo Medical University, Tochigi, Japan; [66]Christian Medical College, Vellore, India; [67]Children's Hospital Los Angeles, Los Angeles, CA; [68]Department of Medicine, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH; [69]Division of Hematology and Transplant Center, Mayo Clinic Rochester, Rochester, MN; [70]Department of Stem Cell Transplantation, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX;

[71]Laboratory of Myeloid Malignancies, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; [72]Divisions of Hematology/Oncology & Infectious Diseases, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [73]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN

Corresponding author information

Name: Matthew J. Wieduwilt, MD, PhD

Address: University of Oklahoma Health, Stephenson Cancer Center, 800 NE 10th Street Oklahoma City, OK 73104

Phone: 415-992-1972

Fax: 405-271-4776

Email: Matthew-Wieduwilt@ouhsc.edu

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Key points

Haploidentical hematopoietic cell transplantation is the preferred alternate donor approach for adults with acute lymphoblastic leukemia.

Haploidentical transplantation had similar survival compared to fully HLA-matched donor HCT but with reduced graft-versus-host disease.

Abstract

The role of haploidentical hematopoietic cell transplantation (HCT) using post-transplant cyclophosphamide (PTCy) for acute lymphoblastic leukemia (ALL) is being defined. We performed a retrospective, multivariate analysis comparing outcomes of HCT approaches by donor for adults with ALL in remission. The primary objective was to compare overall survival (OS) between haploidentical HCT using PTCy and HLA-matched sibling donor (MSD), 8/8 HLA-matched unrelated donor (MUD) , 7/8 HLA-matched UD, or umbilical cord blood (UCB) HCT. Comparing haploidentical to MSD HCT, OS, leukemia-free survival (LFS), non-relapse mortality (NRM), relapse, and acute graft-versus-host disease (aGVHD) were not different but chronic GVHD (cGVHD) was higher with MSD HCT. Compared to MUD HCT, OS, LFS, and relapse were not different but MUD HCT had increased NRM (HR 1.42, P=0.02), grade 3-4 aGVHD (HR 1.59, P=0.005), and cGVHD. Compared to 7/8 UD HCT, LFS and relapse were not different, but 7/8 UD HCT had worse OS (HR 1.38, P=0.01) and increased NRM (HR 2.13, P=<0.001), grade 3-4 aGVHD (HR 1.86, P=0.003), and cGVHD (HR 1.72, P=<0.001). Compared to UCB HCT, late OS , late LFS, relapse, and cGVHD were not different but UCB HCT had worse early OS (≤18 months, HR 1.93, P<0.001), worse early LFS (HR 1.40, P=0.007) and increased incidences of NRM (HR 2.08, P<0.001) and grade 3-4 aGVHD (HR 1.97, P<0.001). Haploidentical HCT using PTCy showed no difference in survival but less GVHD compared to traditional MSD and MUD HCT and is the preferred alternative donor HCT option for adults with ALL in CR.

Background

Allogeneic hematopoietic cell transplantation (HCT) is a curative therapy for acute lymphoblastic leukemia (ALL) and has been shown to be superior to intensive chemotherapy alone in some studies[1,2]. The MRC UK ALL XII/E2993 study compared an adult chemotherapy backbone or chemotherapy followed by myeloablative autologous HCT to myeloablative allogeneic HCT in patients with ALL aged 15-59 years. An overall survival (OS) benefit was seen in standard-risk ALL patients with a donor primarily due to higher rate of relapse in the no donor group that combined chemotherapy and autologous HCT groups[1]. A meta-analysis of 13 trials comparing allogeneic HCT to chemotherapy with or without autologous HCT concluded that the benefit of allogeneic HCT for ALL in first complete remission (CR) was limited to patients under the age of 35[3]. Recent studies have also shown that allogeneic HCT in first CR yields similar outcomes to pediatric-inspired chemotherapy in MRD-negative patients but improves outcomes for patients with MRD-positive disease[4]. For these MRD-positive patients, who benefit most from allogeneic HCT in first CR, donor availability is especially important as haploidentical HCT or umbilical cord blood (UCB) HCT may shorten the time to allogeneic HCT and promote the higher cure rates observed with traditional fully HLA-matched donor allogeneic HCT.

The optimal donor for allogeneic HCT based on existing data appears to be a matched sibling donor (MSD) or an 8/8 HLA-matched unrelated donor (MUD) if an MSD is

unavailable. A recently published CIBMTR study compared outcomes of traditional donor (MSD or MUD) HCT and 7/8 HLA-matched UD HCT for adults with ALL. Compared with MSD HCT, MUD HCT yielded similar survival outcomes whereas the alternative 7/8 HLA-matched UD HCT had inferior survival[5]. For patients without a related or unrelated donor, haploidentical HCT using post-transplant cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prophylaxis is now a common alternative transplant modality with demonstrated efficacy in ALL[6-8]. In addition, 7/8 HLA-matched UD, despite inferior outcomes to MSD and MUD HCT, and UCB HCT remain alternative graft sources for adult patients with ALL without a fully HLA-matched donor.

Although there are expanding comparative data supporting the use of haploidentical HCT as a reasonable alternative to traditional MSD and MUD allogeneic HCT for AML[9-13], for ALL comparative data is more limited. Recent retrospective, comparative studies using the European Society for Blood and Marrow Transplantation (EBMT) registry have found no differences in outcomes between haploidentical HCT using PTCy and MSD, MUD, and mismatched UD (MMUD) HCT[14,15]. Comparison of results of parallel Phase 2 studies of reduced-intensity conditioning haploidentical HCT using PTCy and UCB HCT in lymphoma and acute leukemia was addressed in the BMT-CTN 1101 study. The study found no difference in the primary endpoint of progression-free survival at 2 years but found increased non-relapse mortality (NRM) and decreased overall survival (OS) with UCB HCT compared to haploidentical HCT with PTCy[16]. Taken together, prior studies have shown no significant differences in OS when comparing haploidentical HCT to

MSD, MUD, or MMUD HCT and a superior alternative donor approach among haploidentical HCT with PTCy, 7/8 HLA-matched UD HCT, and UCB HCT for adult ALL specifically has not been established.

This retrospective, multivariate study was designed to compare OS, leukemia-free survival (LFS), relapse, and NRM between adult ALL patients undergoing post-remission therapy with haploidentical HCT using post-transplant cyclophosphamide (PTCy) compared to MSD HCT, MUD HCT, 7/8-HLA matched UD HCT, or umbilical cord blood (UCB) HCT. We hypothesized that haploidentical HCT using PTCy would result in similar OS compared with MSD, MUD, and UCB HCT and superior OS compared with 7/8 HLA-matched UD HCT in adults with ALL undergoing first allogeneic HCT in CR. Results from this study further define the role of haploidentical HCT for ALL in first or subsequent remission.

Methods

Patients

All patient data were generated from the Center for International Blood and Marrow Transplant Research (CIBMTR) patient registry. Eligible patients were 18 years of age or older with a diagnosis of ALL in first, second, or third or greater CR undergoing first allogeneic HCT from 2013 through 2017. Patients must have had an allogeneic HCT from a haploidentical, HLA-matched sibling, 8/8 HLA-matched unrelated, 7/8 HLA-matched unrelated, or cord blood donor[17]. Patients undergoing haploidentical HCT not employing PTCy-based GVHD prophylaxis were excluded as were those receiving *ex vivo* T-cell depletion or CD34 selection. Also excluded were patients without consent to research, from embargoed centers, with no follow-up forms, alive with <3 months of follow up, or receiving infrequently observed conditioning regimens. Minimal residual disease (MRD) testing methods and positivity was as reported from CIBMTR sites. MRD testing methods included flow cytometry (75%), molecular methods (76%), and cytogenetics (62%) with 74% of patients being evaluated with more than one method. Data on MRD testing methods was missing for 7% of patients. The study was approved by the National Marrow Donor Program's Institutional Review Board.

Study objectives

The primary objective was to compare OS after HCT between the following donor-transplant groups: (1) haploidentical HCT using PTCy, (2) MSD HCT, (3) MUD HCT, (4) 7/8 HLA-matched-UD HCT, and (5) UCB HCT. Secondary objectives included comparing the LFS, relapse, NRM, Grade 2-4 and Grade 3-4 acute GVHD (aGVHD) rates [18], and chronic GVHD (cGVHD) rates[19] between the groups. We also performed two planned sensitivity analyses restricting the analysis to (1) myeloablative conditioning[20] with peripheral blood as hematopoietic stem cell source for non-cord blood donor types and to (2) United States centers only. We also determined causes of death in each group.

Statistical analysis

This was a retrospective, five cohort, comparative study from the CIBMTR. Patient, disease and transplant-related factors were compared between the 5 transplant groups using Chi-square test for categorical and Mann-Whitney test for continuous variables. The outcomes that were analyzed were OS, LFS, cumulative incidence of relapse, cumulative incidence of NRM, rate of aGVHD, and rate of cGVHD. OS was the time from transplant to death from any cause with surviving patients censored at last time reported alive. LFS was the time to leukemia relapse or death from any cause with surviving patients censored at last time reported alive and leukemia-free. NRM was summarized by the cumulative incidence estimate of death in CR with relapse as a competing risk. Relapse was summarized by the cumulative incidence estimate with treatment related mortality as a competing risk. Probabilities of OS and LFS were

calculated using the Kaplan-Meier estimator. Cumulative incidence curves were made to present relapse and NRM with time to relapse and time to NRM as competing risks.

To adjust for the differences in baseline characteristics, Cox proportional hazards regression were used to compare the main treatment groups. First, variables to be considered in the multivariate models were selected. Variables considered were donor type, recipient age, Karnofsky performance status, gender, HCT-CI score[21], race, ALL lineage, Philadelphia chromosome/*BCR-ABL1* status, cytogenetic risk, remission status, MRD status for CR1, time from diagnosis to HCT for CR1, conditioning intensity, donor/recipient sex match, donor/recipient CMV serostatus, year of transplant, and transplant center. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. When the test indicated differential effects over time (non-proportional hazards), models were constructed breaking the post-transplant time course into two periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions were further tested. A backward stepwise model selection approach was used to identify all significant risk factors. Each step of model building contained the main effect for treatment groups. Factors which were significant at a 5% level were kept in the final model. The potential interactions between main effect and all significant risk factors were tested. Adjusted probabilities of LFS and OS, and adjusted cumulative incidence estimates were generated from the final regression models stratified on treatment and weighted averages of covariate values using the pooled sample proportion as the weight

function. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors. With haploidentical HCT using PTCy as the baseline comparison group (independent testing, no multiple testing considered, no differences in patient characteristics adjusted, assuming all subjects had at least 2-year follow-up), power test for 2-year OS probability based on two-sided test with significance level of 5%: haploidentical HCT using PTCy vs MSD HCT, 80% power to detect at least difference of 8%; haploidentical HCT using PTCy vs MUD HCT, 80% power to detect at least difference of 8%; haploidentical HCT using PTCy vs 7/8 HLA-matched UD HCT, 80% power to detect at least difference of 11%; haploidentical HCT using PTCy vs UCB HCT, 80% power to detect at least difference of 10%.

Results

Patients

Between 2013 and 2017, a total of 4201 patients in 5 HCT cohorts were eligible: 393 haploidentical HCT using PTCy, 1627 MSD HCT, 1646 MUD HCT, 230 7/8 HLA-matched UD HCT, and 305 UCB HCT. Cohorts were well matched for age, sex, Karnofsky performance status, HCT-CI, immunophenotype, cytogenetic risk, Philadelphia chromosome/*BCR-ABL1* status, disease status, MRD status at transplantation, and recipient CMV serostatus. Notable differences between groups included race, time from diagnosis to HCT (CR1 only), conditioning regimen intensity, donor age, graft source for

non-cord (peripheral blood or bone marrow), GVHD prophylaxis modality, and the use of *in vivo* T-cell depletion. PTCy-based GVHD prophylaxis was used in 5% of MSD HCT, 4% of MUD HCT, and 13% of 7/8 HLA-matched UD HCT. Compared to other groups, haploidentical HCT using PTCy had the lowest percentage of non-Hispanic white patients (43% vs. 49-74%), was more likely to use reduced-intensity conditioning (42% vs 17-25%) and was more likely to use bone marrow as the graft source (41% vs. 14-29%). See **Table 1** for details.

Overall and Leukemia-free Survival

In multivariate analysis, compared to haploidentical HCT, MSD HCT and MUD HCT had similar OS (HR 1.13, P=0.18 and HR 1.17, P=0.11, respectively) and LFS (HR 1.03, P=0.71 and HR 1.03, P=0.73 respectively). In contrast, 7/8 HLA-matched UD HCT had inferior OS and similar LFS when compared to haploidentical HCT (OS, HR 1.38, P=0.01; LFS, HR 1.21, P=0.12). UCB HCT had inferior OS prior to 18 months (HR 1.93, P=<0.001) and similar OS after 18 months (HR 0.68, P=0.19) when compared to haploidentical HCT. In addition, LFS prior to 18 months was inferior with UCB HCT (HR 1.40, P=0.007) and similar after 18 months (HR 0.58, P=0.08). Other multivariate factors associated with decreased OS included HCT in CR2+, older age, female donor to male recipient, Ph/*BCR-ABL1* negativity, and CMV-seronegative donor to CMV-seropositive recipient for MSD HCT vs. haploidentical HCT; CR2+, older age, non-Asian race, HCT-CI 3+, and Ph/*BCR-ABL1* negativity for MUD HCT vs. haploidentical HCT; CR2+ for 7/8 HLA-matched UD HCT

vs. haploidentical HCT; and CR2+ and myeloablative chemotherapy (vs. myeloablative TBI) for UCB HCT vs. haploidentical HCT. Multivariate survival outcomes are summarized in **Tables 2-5** and **Figure 1**. Univariate outcomes are summarized in **Supplemental Table 3**.

Relapse and Non-relapse Mortality

In multivariate analysis, MSD HCT had similar relapse (HR 0.99, P=0.93) and NRM (HR 1.06, P=0.66) compared to haploidentical HCT. Compared to haploidentical HCT, relapse was not significantly different with MUD HCT (HR 0.83, P=0.09), 7/8 HLA-matched UD HCT (HR 0.81, P=0.22), or UCB HCT (HR 0.83, P=0.23). NRM, however, was significantly higher with MUD HCT (HR 1.42, P=0.02), 7/8 HLA-matched UD HCT (HR 2.13, P=<0.001), or UCB HCT (HR 2.08, P=<0.001) compared to haploidentical HCT. Notably, myeloablative conditioning using total body irradiation significantly reduced the risk of relapse across all donor HCT cohorts. Multivariate relapse and NRM analyses are summarized in **Tables 2-5** and **Figure 1**. Univariate analyses are summarized in **Supplemental Table 3**.

Graft-versus-host Disease

Multivariate analysis revealed either reduced or similar rates of severe acute GVHD and chronic GVHD with haploidentical HCT using PTCy relative to other HCT cohorts. Compared to haploidentical HCT, MSD HCT had similar cumulative incidences of grade 2-4 and grade 3-4 acute GVHD (HR 0.92, P=0.40 and HR 1.09, P=0.59, respectively) but increased cumulative incidence of chronic GVHD (HR 2.59, P<0.001 for female/male donor/recipient sex match; HR 1.37, P=0.003 for other donor/recipient sex match). MUD HCT had a similar cumulative incidence of grade 2-4 acute GVHD (HR 1.17, P=0.09), an increased cumulative incidence of grade 3-4 acute GVHD (HR 1.59, P=0.005), and an increased cumulative incidence of chronic GVHD (HR 1.38, P=0.001). 7/8 HLA-matched UD HCT had an increased cumulative incidence of Grade 2-4 acute GVHD (HR 1.33, P=0.04), Grade 3-4 acute GVHD (HR 1.86, P=0.003), and chronic GVHD (HR 1.72, P<0.001). UCB HCT was associated with an increased cumulative incidence of grade 2-4 and grade 3-4 acute GVHD (HR 1.83, P<0.001 and HR 1.97, P<0.001, respectively) with a similar cumulative incidence of chronic GVHD (HR 1.13, P=0.38). Multivariate GVHD analyses are summarized in **Tables 2-5**.

Causes of Death

Death from acute lymphoblastic leukemia was more common with haploidentical HCT (48%) and HLA-identical sibling HCT (52%) relative to other HCT cohorts (31-38%). Death from graft-versus-host disease accounted for 5% of deaths after haploidentical HCT compared to 12-24% in other HCT cohorts. Similar rates of death from infection were

observed comparing haploidentical HCT (21%) to other HCT cohorts (17-23%). Other causes of death were also similar among the cohorts. See **Table 6** for detailed summary.

Sensitivity Analyses

To address two potential sources of bias, we performed two sensitivity analyses for OS, LFS, relapse, and NRM restricting the study population to either the most common modalities of myeloablative conditioning with peripheral blood as hematopoietic stem cell source or to United States centers for better completion of follow up at 2 years. When restricted to myeloablative conditioning and peripheral blood stem cell source, outcomes were similar to the full population except decreased overall survival with 7/8 HLA-matched UD compared to haploidentical HCT was no longer statistically significant (HR 1.39, P=0.07; **Supplemental Tables 1, 4, 6-9, Supplemental Figures 1-4**). When restricted to United States centers only, outcomes were also similar except with a decreased risk of relapse (HR 0.76, P=0.02) but inferior overall survival (HR 1.23, 95% CI 1.00-1.50, P=0.05) with MUD compared to haploidentical HCT See **Supplemental Tables 2, 5, 10-13** and **Supplemental Figures 1-4.**

Discussion

Haploidentical HCT is a growing allogeneic HCT modality for ALL that has expanded allogeneic HCT to patients without traditional HLA-matched related or unrelated donors,

especially those of mixed race or ethnicity. The choice of alternative donors for allogeneic HCT in ALL is an area of ongoing research, debate and clinical interest. In addition, the relative benefits of haploidentical HCT compared to traditional MSDs and MUDs is just being defined. In this study, we demonstrated that haploidentical HCT using PTCy resulted in similar OS to traditional MSDs and MUDs allogeneic HCT but with less GVHD. In addition, we found superior OS compared to alternative 7/8 HLA-matched UD and UCB HCT. The superior survival seen with haploidentical HCT using PTCy compared with 7/8 HLA-matched UD HCT and UCB HCT was likely due to reduced NRM related to reduced GVHD with haploidentical HCT. Notably, rates of infection were similar among the 5 cohorts suggesting that delayed immune reconstitution with haploidentical HCT in the adult ALL population did not translate into increased infection-related mortality.

Prior smaller retrospective studies comparing haploidentical HCT to MSD, MUD, and MMUD HCT found no differences in DFS, relapse, NRM, aGVHD or cGVHD. Recently, Shem-Tov et al. performed a retrospective multi-institution comparison of 136 ALL patients undergoing haploidentical HCT to 809 ALL patients getting MUD HCT and 289 ALL patients getting 9/10 HLA-matched UD HCT. This smaller study found no differences in OS, LFS, relapse, NRM, aGVHD, or cGVHD between the groups.[14] Similarly, a larger study comparing 487 haploidentical HCTs to 974 MUD HCTs for ALL found no difference in any outcome including aGVHD and cGVHD.[15] Our study expands on and contrasts these studies with a large contemporary population showing significant differences in

major outcomes between haploidentical HCT using PTCy to all other major donor sources. This study helps clarify the role of haploidentical HCT in adult ALL and expands our knowledge of the expected benefits of haploidentical HCT relative to other donor HCT approaches. Importantly, our study supports haploidentical HCT with PTCy as the preferred HCT approach for patients lacking an MSD or MUD donor.

Similar to prior studies[22-25], we found that myeloablative conditioning using TBI compared with myeloablative chemotherapy or reduced-intensity/non-myeloablative conditioning significantly reduced the risk of relapse and improved LFS across all donor HCT cohorts. The recently published Phase III FORUM study randomized 417 children and young adults ages 4-21 years with ALL to either myeloablative TBI-based or myeloablative chemotherapy-based conditioning prior to MSD, MUD, or MMUD allogeneic HCT. Patients in the TBI arm had improved OS, improved event-free survival, less relapse, and improved NRM[23]. In adults with ALL, a retrospective EBMT registry study comparing TBI-based to chemotherapy-myeloablative conditioning for MSD< MUD, or MMUD allogeneic HCT found better OS, LFS, and relapse incidence with TBI-based conditioning[24], although the OS benefit in adults has not been seen across all retrospective studies[22,25]. In this study, the benefit of myeloablative conditioning using total body irradiation on reducing relapse only improved OS in haploidentical HCT and UCB HCT comparison, suggesting these modalities may derive more benefit from TBI. Overall, our study supports current recommendations[26] for the use of myeloablative TBI for conditioning in allogeneic HCT for adult ALL due to reduced relapse risk with similar

or improved OS, but further study is warranted on optimal conditioning regimens across donor HCT types for adult ALL.

The primary reason for decreased NRM with haploidentical HCT compared to MUD HCT, 7/8 MMUD HCT, and UCB HCT appears to be significantly decreased rates of severe acute and chronic GVHD with haploidentical HCT using PTCy. Death from GVHD was substantially higher in the non-haploidentical HCT cohorts and reduced quality of life from GVHD-related complications, although not assessed in this study, with other donor sources may be an additional reason to pursue haploidentical HCT with PTCy in the ALL population. Based on its success in haploidentical HCT, PTCy GVHD prophylaxis is being studied in MSD, MUD, and MMUD HCT. Existing studies evaluating alternative GVHD prophylaxis with PTCy for MSD and UD HCT[27-30] have consistently found low rates of cGVHD and these approaches may produce similar relative benefits seen with haploidentical HCT in this study for reducing GVHD and NRM. However, the impact of these approaches on relapse in the setting of fully HLA-matched donor HCT will need to be closely evaluated.

Although hazard ratios for relapse favored non-haploidentical HCT modalities except HLA-identical sibling (HRs 0.81-0.83), this finding was not statistically significant and did not lead to inferior OS or LFS with haploidentical HCT using PTCy. When restricted to United Stated sites only, relapse was significantly higher with haploidentical HCT using PTCy compared with MUD HCT (HR 0.76, 95% CI 0.61-0.96, P=0.02) raising some concern

that relapse may be higher in some settings with haploidentical HCT although in the same comparison haploidentical HCT showed significantly better OS due to substantially lower NRM. A larger future study and longer follow up are needed to evaluate if the large and significant reduction in acute and chronic GVHD and death from GVHD with haploidentical HCT may be associated with a small increased risk of relapse after HCT. Non-severe acute and chronic GVHD have been previously associated with reduced relapse[31] and this study suggests that reducing GVHD with haploidentical HCT may impact relapse. Consistent with this, MSD HCT and haploidentical HCT had similar rates of acute GVHD and nearly identical risk of relapse (HR 0.99).

A strength of this study is the large number patients and international centers allowing generalization the results, especially to United States centers. In addition, the large sample size in each cohort allowed adequate power to detect meaningful differences in outcomes between the HCT approaches. One limitation of this study is that it is retrospective and a prospective randomized study to better control for numerous variables would be needed to confirm our findings and address some limitations. For instance, the impact on outcomes from large centers favoring certain donor HCT modalities could influence the results. Another limitation is lack of standardized testing and definitions for MRD in data collected from sites. We found no differences in overall survival based on the CIBMTR definitions of MRD prior to HCT in contrast to a recent EBMT registry report[24]. However, well-defined MRD positivity prior to allogeneic HCT has been shown to predict poor outcomes with increased relapse and reduced survival

after allogeneic HCT for ALL[32-40]. Reasons for our findings could be heterogeneity in testing, definitions of MRD used at different CIBMTR sites, and possibly a lack of sensitivity of MRD for predicting outcomes in a real-world setting. Another limitation of our study was an inability to evaluate the impact of central nervous system and extramedullary ALL on outcomes as this data was not reported from centers. Follow up for this study was also relatively short given that haploidentical HCT has only come into widespread use in the last 5 years. Lastly, our analysis is restricted to patients undergoing haploidentical HCT employing PTCy and our conclusions may not extend to alternate haploidentical HCT approaches. Approaches utilizing *in vivo* T-cell depletion or *in vitro* T-cell depletion/CD34+ cell selection have shown promising outcomes in ALL that appear comparable or possibly superior to MSD and MUD allogeneic HCT.[41-48] High-quality comparative studies are needed that compare well-matched populations undergoing T-cell replete haploidentical HCT using PTCy with approaches using *in vivo* T-cell depletion or *in vitro* T-cell depletion/CD34+ cell selection.

Our findings support haploidentical HCT using PTCy as the preferred alternative donor HCT for ALL given the superior OS seen relative to 7/8 HLA-matched UD and UCB HCT. Our data also suggest that OS is not different with haploidentical HCT using PTCy compared with traditional MSD and MUD HCT, but with a reduced risk of GVHD. Although longer follow up and confirmatory studies are needed, from this analysis haploidentical HCT appears to be an acceptable HCT option for all adult patients with ALL in remission lacking anti-donor specific HLA antibodies. To overcome the major

causes of failure of haploidentical HCT uncovered in this study, future studies aiming to prevent relapse and reduce infectious death may further improve outcomes after haploidentical HCT. Future studies with longer follow-up will also be needed to definitively establish the role of haploidentical HCT using PTCy at different stages of ALL remission, particularly in the era of effective salvage treatments such as bispecific T-cell engagers, antibody-drug conjugates, and cellular therapies.

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Author contributions:
Conception and design: Matthew Wieduwilt and Leland Metheny
Financial support: CIBMTR
Collection and assembly of data: CIBMTR
Data analysis: Matthew Wieduwilt, Leland Metheny, Marcos de Lima, Wael Saber, Mei-Jie Zhang, Noel Estrada-Merly
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Dr. Hildebrandt reports other from Incyte, other from Jazz Pharmaceuticals, other from Morphosys, other from Alexion Pharmaceuticals, other from Karyopharm Therapeutics, other from Takeda, other from Jazz Pharmaceuticals, other from Pharmacyclics, other from Incyte, other from AstraZeneca, other from Jazz Pharmaceuticals, other from Astellas Pharma, other from Incyte, other from Falk Foundation, other from Takeda, outside the submitted work.
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Figure legend

Figure 1. Overall survival, leukemia-free survival, cumulative incidence or relapse, and cumulative incidence of non-relapse mortality comparing haploidentical hematopoietic cell transplantation (HCT) with post-transplant cyclophosphamide to matched sibling, 8/8 HLA-matched unrelated, 7/8 HLA-matched unrelated, or umbilical cord blood HCT.

Table 1. Patient characteristics

Characteristic	Donor/HCT group				
	Haploidentical	Matched sibling	8/8-HLA MUD	7/8-HLA MUD	Umbilical cord blood
Number of patients	393	1627	1646	230	305
Number of centers	92	206	181	90	79
Median follow-up, months (range)	24 (3-67)	26 (3-72)	35 (3-74)	35 (3-64)	35 (3-64)
Recipient age, median, years (range)	41 (18-74)	42 (18-75)	43 (18-77)	38 (18-70)	37 (18-70)
Karnofsky performance status score					
≥90%	233 (59)	1046 (64)	995 (60)	163 (71)	196 (64)
<90%	152 (39)	542 (33)	629 (38)	65 (28)	107 (35)
Missing	8 (2)	39 (2)	22 (1)	2 (<1)	2 (<1)
Recipient gender					
Male	214 (54)	969 (60)	976 (59)	134 (58)	176 (58)
HCT-CI score					
0	81 (21)	592 (36)	405 (25)	53 (23)	89 (29)
1	57 (15)	221 (14)	224 (14)	35 (15)	42 (14)
2	61 (16)	228 (14)	266 (16)	37 (16)	46 (15)
3+	194 (49)	552 (34)	745 (45)	104 (45)	125 (41)
Missing	0	34 (2)	6 (<1)	1 (<1)	3 (<1)
Race[a]					
Hispanic white	87 (22)	246 (15)	136 (8)	42 (18)	64 (21)
Non-Hispanic white	170 (43)	846 (52)	1226 (74)	113 (49)	150 (49)
Black	59 (15)	74 (5)	53 (3)	19 (8)	27 (9)
Asian	22 (6)	111 (7)	64 (4)	10 (4)	22 (7)
Other/Not specified	55 (14)	350 (22)	167 (10)	46 (20)	42 (14)
Immunophenotype					
T-cell	25 (6)	201 (12)	186 (11)	27 (12)	36 (12)
B-cell	330 (84)	1316 (81)	1319 (80)	185 (80)	246 (81)
Not specified	38 (10)	110 (7)	141 (9)	18 (8)	23 (8)
Cytogenetic risk score[b]					
Normal	91 (23)	320 (20)	335 (20)	52 (23)	63 (21)
Poor	222 (56)	750 (46)	855 (52)	101 (44)	154 (50)
Missing/Not tested/Other	80 (21)	557 (34)	456 (28)	77 (33)	88 (29)
Philadelphia chromosome/*BCR-ABL1* status					
Yes	152 (46)	562 (43)	614 (47)	80 (43)	122 (50)
Remission status					
CR1- MRD positive	112 (28)	513 (32)	509 (31)	58 (25)	78 (26)
CR1- MRD negative	143 (36)	644 (40)	697 (42)	85 (37)	124 (41)
CR1- MRD missing	14 (4)	145 (9)	59 (4)	6 (3)	10 (3)
CR2	105 (27)	296 (18)	334 (20)	62 (27)	74 (24)
≥ CR3	19 (5)	29 (2)	47 (3)	19 (8)	19 (6)
Time from diagnosis to HCT (CR1-only)					
0-5 months	130 (48)	842 (65)	744 (59)	56 (38)	93 (44)
6-11 months	115 (43)	388 (30)	463 (37)	81 (54)	102 (48)
≥ 12 months	24 (9)	72 (6)	58 (5)	12 (8)	17 (8)
Conditioning regimen					
MAC, TBI-based	163 (41)	984 (60)	950 (58)	139 (60)	217 (71)
MAC, Chemotherapy-based	63 (16)	323 (20)	312 (19)	51 (22)	11 (4)

RIC/NMA	167 (42)	316 (19)	383 (23)	39 (17)	76 (25)
Missing	0	4 (<1)	1 (<1)	1 (<1)	1 (<1)
Donor/recipient gender					
F-M	82 (21)	415 (26)	244 (15)	42 (18)	161 (53)
Other	311 (79)	1212 (74)	1396 (85)	188 (82)	137 (45)
Missing	0	0	6 (<1)	0	7 (2)
Donor/recipient CMV serostatus					
+/+	206 (52)	859 (53)	506 (31)	90 (39)	0
+/-	31 (8)	144 (9)	197 (12)	25 (11)	0
-/+	83 (21)	287 (18)	553 (34)	64 (28)	0
-/-	72 (18)	306 (19)	382 (23)	50 (22)	0
UCB – Recipient +	0	0	0	0	200 (66)
UCB – Recipient -	0	0	0	0	100 (33)
Missing	1 (<1)	31 (2)	8 (<1)	1 (<1)	5 (2)
Donor age, median, years (range)	35 (10-74)	41 (9-75)	28 (18-60)	31 (19-60)	Not applicable
Graft source					
Bone marrow	160 (41)	230 (14)	316 (19)	67 (29)	-
Peripheral blood	233 (59)	1397 (86)	1330 (81)	163 (71)	-
GVHD prophylaxis					
CNI + MTX ± others	0	1107 (68)	1165 (71)	162 (70)	7 (2)
CNI + MMF ± others	0	236 (15)	191 (12)	18 (8)	265 (87)
CNI + others	0	118 (7)	141 (9)	13 (6)	6 (2)
CNI alone	0	66 (4)	58 (4)	5 (2)	14 (5)
PTCy + CNI ± MMF	393	75 (5)	73 (4)	29 (13)	2 (<1)
Other prophylaxis	0	17 (1)	13 (<1)	2 (<1)	10 (3)
Missing	0	8 (<1)	5 (<1)	1 (<1)	1 (<1)
***In vivo* T-cell depletion**					
Anti-thymocyte globulin	5 (1)	76 (5)	561 (34)	116 (50)	39 (13)
Alemtuzumab	0	33 (2)	62 (4)	6 (3)	0
None	388 (99)	1505 (93)	1010 (61)	105 (46)	265 (87)
Missing	0	13 (<1)	13 (<1)	3 (1)	1 (<1)

Abbreviations: HLA, human leukocyte antigen; MUD, matched unrelated donor; HCT-CI, hematopoietic cell transplant comorbidity index; CR, complete remission; MRD, minimal residual disease; MAC, myeloablative conditioning; TBI, total body irradiation; RIC, reduced-intensity conditioning; NMA, non-myeloablative; F, female; M, male; CMV, cytomegalovirus; UCB, umbilical cord blood; CNI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide

[a]Other/ not specified: Native American (n=30), Pacific Islander (n=20), Non-resident of the US (n=291), not specified (n= 156), Hispanic – excluding white Hispanic (n= 213)

[b]CIBMTR cytogenetics criteria definition: Poor: Ph+/t(9:22)/*BCR-ABL1*, t(4:11), 11q23/MLL/KMT2A, hypodiploid (<45), t(8:14), complex(≥ 3 abnormalities), iAMP21; Normal: without any abnormality; Other: abnormality count 1 or 2 abnormalities.

[c]Donor age is not reported for cord bloods.

[d]Cord Blood type: Double CB, worst HLA-match was selected

Table 2. Multivariate analysis for HLA-matched sibling donor (MSD) HCT vs. haploidentical HCT, 2013-2017

Covariate	N	HR (95% CI)	p-value
Overall survival			
Main effect			
Haploidentical HCT	393	Reference	
MSD HCT	1627	1.13 (0.94-1.36)	0.18
Remission status			
CR1	1571	Reference	
CR2+	449	1.86 (1.58-2.19)	< 0.001
Age (years)			< 0.001
18-29	572	Reference	
30-39	367	0.97 (0.77-1.22)	0.78
40-49	432	1.30 (1.05-1.60)	0.02
50-59	417	1.49 (1.21-1.85)	< 0.001
60-69	232	2.07 (1.63-2.63)	< 0.001
Donor/recipient sex match			
Other than F/M	1523	Reference	
F/M	497	1.29 (1.10-1.51)	0.002
Ph chromosome/*BCR-ABL1* status			0.007
Negative	932	Reference	
Positive	714	0.78 (0.66-0.92)	0.003
T-ALL/ Unspecified subtype	374	1.02 (0.84-1.24)	0.83
D/R CMV serostatus			0.02
+/+	1065	Reference	
+/-	175	0.81 (0.62-1.05)	0.11
-/+	370	0.76 (0.62-0.93)	0.007
-/-	378	0.84 (0.69-1.01)	0.07
Leukemia-free survival			
Main effect			
Haploidentical HCT	381	Reference	
MSD HCT	1583	1.03 (0.88-1.22)	0.71
Disease status			
CR1	1528	Reference	
CR2+	436	1.93 (1.67-2.23)	< 0.001
Conditioning regimen			
MAC-TBI	1116	Reference	
MAC-Chemotherapy	376	1.35 (1.15-1.60)	< 0.001
RIC/NMA	470	1.50 (1.28-1.76)	< 0.001
Non-relapse mortality			
Main effect			

Covariate	N	HR (95% CI)	p-value
Haploidentical HCT	381	Reference	
MSD HCT	1583	1.06 (0.81-1.41)	0.66
Remission status			
CR1	1528	Reference	
CR2+	436	1.52 (1.17-1.98)	0.002
Age (years)			< 0.001
18-29	553	Reference	
30-39	353	0.66 (0.44-0.99)	0.04
40-49	422	1.19 (0.86-1.65)	0.28
50-59	411	1.59 (1.17-2.16)	0.003
60-69	225	2.10 (1.49-2.96)	< 0.001
D/R sex match			
Other than F/M	1479	Reference	
F/M	485	1.54 (1.22-1.94)	< 0.001
Relapse			
Main effect			
Haploidentical HCT	381	Reference	
MSD HCT	1583	0.99 (0.81-1.21)	0.93
Remission status			
CR1	1528	Reference	
CR2+	436	2.25 (1.89-2.68)	< 0.001
Conditioning regimen			
MAC-TBI	1116	Reference	
MAC-Chemotherapy	376	1.40 (1.14-1.72)	0.001
RIC/NMA	470	1.53 (1.26-1.87)	< 0.001
Acute GVHD, Grade 2-4			
Main effect			
Haploidentical HCT	376	Reference	
MSD HCT	1545	0.92 (0.77-1.11)	0.40
Acute GVHD, Grade 3-4			
Main effect			
Haploidentical HCT	376	Reference	
MSD HCT	1545	1.09 (0.79-1.50)	0.59
Chronic GVHD			
MSD vs. haploidentical HCT for D/R sex match = other		1.37 (1.12-1.69)	0.003
MSD vs. haploidentical HCT for D/R sex match = F/M		2.59 (1.68-3.99)	< 0.001
Age (years)			0.002
18-29	563	Reference	
30-39	361	1.13 (0.93-1.37)	0.24
40-49	428	1.37 (1.14-1.64)	< 0.001
50-59	413	1.17 (0.95-1.43)	0.14
60-69	228	1.57 (1.21-2.03)	< 0.001
Race			
White Hispanic	333	Reference	

Covariate	N	HR (95% CI)	p-value
White non-Hispanic	1006	0.75 (0.63-0.89)	0.001
Black	132	0.93 (0.70-1.23)	0.61
Asian	130	0.79 (0.59-1.07)	0.13
Other/not specified	392	0.66 (0.53-0.82)	< 0.001
D/R sex match			
Other than F/M	1501	Reference	
F/M	492	0.73 (0.47-1.14)	0.17
Conditioning regimen			
MAC-TBI	1132	Reference	
MAC-Chemotherapy	380	0.94 (0.79-1.11)	0.46
RIC/NMA	478	0.74 (0.61-0.90)	0.002

Abbreviations: HLA, human leukocyte antigen; HCT, hematopoietic cell transplantation; N, number; HR, hazard ratio; CI, confidence interval; CR, complete remission; F, female; M, male; Ph, Philadelphia; BCR-ABL, breakpoint cluster region-Abelson murine leukemia; ALL, acute lymphoblastic leukemia; D, donor; R, recipient; CMV, cytomegalovirus; MAC, myeloablative; TBI, total body irradiation; RIC, reduced intensity; NMA, nonmyeloablative; GVHD, graft-versus-host disease; MSD, matched sibling donor

Table 3. Multivariate analysis for 8/8 HLA-matched-unrelated donor (MUD) HCT vs. haploidentical HCT, 2013-2017

Covariates	N	HR (95% CI)	p-value
Overall survival			
Main effect			
Haploidentical HCT	393	Reference	
MUD HCT	1646	1.17 (0.96-1.41)	0.11
Remission status			
CR1	1534	Reference	
CR2+	505	1.79 (1.53-2.10)	< 0.001
Age (years)			< 0.001
18-29	545	Reference	
30-39	364	1.03 (0.81-1.30)	0.82
40-49	391	1.38 (1.11-1.71)	0.004
50-59	382	1.55 (1.24-1.93)	< 0.001
60-69	357	1.85 (1.48-2.31)	< 0.001
Race			
White Hispanic	223	Reference	
White non-Hispanic	1396	0.95 (0.75-1.21)	0.68
Black	112	1.33 (0.94-1.87)	0.11
Asian	86	0.44 (0.26-0.75)	0.002
Other/not specified	222	1.02 (0.74-1.39)	0.92
HCT-CI			0.01
0	486	Reference	
1	281	1.01 (0.79-1.30)	0.91
2	327	1.03 (0.81-1.30)	0.84
3+	939	1.25 (1.04-1.50)	0.02
Ph chromosome/*BCR-ABL1* status			
Negative	883	Reference	
Positive	766	0.82 (0.70-0.96)	0.02
T-ALL/ Unspecified subtype	390	1.03 (0.85-1.24)	0.77
Leukemia-free survival			
Main effect			
Haploidentical HCT	381	Reference	
MUD HCT	1618	1.03 (0.87-1.22)	0.73
Remission status			
CR1	1509	Reference	
CR2+	490	1.74 (1.51-1.99)	< 0.001
Race			
White Hispanic	217	Reference	
White non-Hispanic	1379	0.97 (0.78-1.19)	0.76
Black	105	1.33 (0.98-1.82)	0.07
Asian	84	0.57 (0.37-0.87)	0.010
Other/not specified	214	0.94 (0.71-1.24)	0.67

Covariates	N	HR (95% CI)	p-value
Conditioning regimen			
MAC-TBI	1097	Reference	
MAC-Chemotherapy	363	1.46 (1.24-1.73)	< 0.001
RIC/NMA	539	1.61 (1.39-1.87)	< 0.001
Non-relapse mortality			
Main effect			
Haploidentical HCT	381	Reference	
MUD HCT	1618	1.42 (1.07-1.89)	0.02
Remission status			
CR1	1509	Reference	
CR2+	490	1.33 (1.06-1.67)	0.01
Age (years)			< 0.001
18-29	539	Reference	
30-39	356	0.86 (0.62-1.20)	0.37
40-49	382	1.30 (0.97-1.76)	0.08
50-59	372	1.61 (1.20-2.15)	0.001
60-69	350	1.82 (1.36-2.44)	< 0.001
Race			
White Hispanic	217	Reference	
White non-Hispanic	1379	0.79 (0.58-1.09)	0.15
Black	105	1.04 (0.63-1.73)	0.87
Asian	84	0.35 (0.16-0.74)	0.006
Other/not specified	214	0.98 (0.66-1.47)	0.93
Relapse			
Main effect			
Haploidentical HCT	381	Reference	
MUD HCT	1618	0.83 (0.67-1.03)	0.09
Remission status			
CR1	1509	Reference	
CR2+	490	2.20 (1.84-2.64)	< 0.001
Gender			
Male	1168	Reference	
Female	831	0.81 (0.68-0.97)	0.02
Race			
White Hispanic	217	Reference	
White non-Hispanic	1379	1.04 (0.78-1.39)	0.77
Black	105	1.59 (1.06-2.37)	0.02
Asian	84	0.75 (0.44-1.26)	0.27
Other/not specified	214	0.88 (0.60-1.29)	0.52
Conditioning regimen			
MAC-TBI	1097	Reference	
MAC-Chemotherapy	363	1.57 (1.25-1.98)	< 0.001
RIC/NMA	539	1.83 (1.50-2.23)	< 0.001
Acute GVHD, Grade 2-4			

Covariates	N	HR (95% CI)	p-value
Main effect			
Haploidentical HCT	376	Reference	
MUD HCT	1553	1.17 (0.98-1.41)	0.09
Conditioning regimen			
MAC-TBI	1042	Reference	
MAC-Chemotherapy	367	0.86 (0.72-1.04)	0.11
RIC/NMA	519	0.81 (0.68-0.95)	0.01
Acute GVHD, Grade 3-4			
Main effect			
Haploidentical HCT	376	Reference	
MUD HCT	1553	1.59 (1.15-2.20)	0.005
Race			
White Hispanic	217	Reference	
White non-Hispanic	1318	0.65 (0.47-0.90)	0.009
Black	109	0.90 (0.53-1.53)	0.69
Asian	80	0.29 (0.12-0.68)	0.005
Other/not specified	205	0.67 (0.43-1.06)	0.08
Chronic GVHD			
MUD vs. haploidentical for D/R sex match = other		1.38 (1.14-1.68)	0.001
MUD vs. haploidentical for D/R sex match = F/M		2.91 (1.87-4.52)	< 0.001
Remission status			
CR1	1528	Reference	
CR2+	501	0.81 (0.69-0.95)	0.009
D/R sex match			
Other than F/M	1707	Reference	
F/M	322	0.69 (0.44-1.08)	0.10

Abbreviations: HLA, human leukocyte antigen; HCT, hematopoietic cell transplantation; N, number; HR, hazard ratio; CI, confidence interval; CR, complete remission; F, female; M, male; Ph, Philadelphia; BCR-ABL, breakpoint cluster region-Abelson murine leukemia; ALL, acute lymphoblastic leukemia; D, donor; R, recipient; CMV, cytomegalovirus; MAC, myeloablative conditioning; TBI, total body irradiation; RIC, reduced intensity conditioning; NMA, nonmyeloablative; GVHD, graft-versus-host disease; MUD, matched unrelated donor

Table 4. Multivariate analysis for 7/8 HLA-matched-unrelated donor HCT vs. haploidentical HCT, 2013-2017

Covariates	N	HR (95% CI)	p-value
Overall survival			
Main effect			
Haploidentical HCT	393	Reference	
7/8 HLA-matched UD HCT	230	1.38 (1.08-1.78)	0.01
Remission status			
CR1	418	Reference	
CR2+	205	1.82 (1.41-2.34)	< 0.001
Leukemia-free survival			
Main effect			
Haploidentical HCT	381	Reference	
7/8 HLA-matched UD	227	1.21 (0.95-1.54)	0.12
Remission status			
CR1	414	Reference	
CR2+	194	1.84 (1.46-2.33)	< 0.001
Race			
White Hispanic	124	Reference	
White non-Hispanic	277	0.95 (0.71-1.28)	0.73
Black	75	1.33 (0.92-1.94)	0.13
Asian	32	0.50 (0.25-0.97)	0.04
Other/not specified	100	0.70 (0.48-1.03)	0.07
Conditioning regimen			
MAC-TBI	295	Reference	
MAC-Chemotherapy	111	1.29 (0.94-1.75)	0.11
RIC/NMA	201	1.46 (1.12-1.89)	0.005
Non-relapse mortality			
Main effect			
Haploidentical HCT	381	Reference	
7/8 HLA-matched UD HCT	227	2.13 (1.50-3.01)	< 0.001
Donor/recipient CMV serostatus			
+/+	287	Reference	
+/-	55	0.40 (0.18-0.86)	0.02
-/+	143	0.78 (0.51-1.19)	0.25
-/-	121	0.56 (0.34-0.92)	0.02
Relapse			
Main effect			
Haploidentical HCT	381	Reference	
7/8 HLA-matched UD HCT	227	0.81 (0.57-1.13)	0.22
Remission status			
CR1	414	Reference	
CR2+	194	2.39 (1.76-3.25)	< 0.001

Covariates	N	HR (95% CI)	p-value
Race			
White Hispanic	124	Reference	
White non-Hispanic	277	0.94 (0.64-1.39)	0.76
Black	75	1.24 (0.76-2.02)	0.38
Asian	32	0.36 (0.14-0.93)	0.03
Other/not specified	100	0.58 (0.34-0.99)	0.05
Conditioning regimen			
MAC-TBI	295	Reference	
MAC-Chemotherapy	111	1.60 (1.05-2.44)	0.03
RIC/NMA	201	2.09 (1.49-2.95)	< 0.001
Acute GVHD, Grade 2-4			
Main effect			
Haploidentical HCT	376	Reference	
7/8 HLA-matched UD HCT	216	1.33 (1.02-1.73)	0.04
Conditioning regimen			
MAC-TBI	288	Reference	
MAC-Chemotherapy	107	0.68 (0.47-0.98)	0.04
RIC/NMA	196	0.68 (0.51-0.92)	0.01
Acute GVHD, Grade 3-4			
Main effect			
Haploidentical HCT	376	Reference	
7/8 HLA-matched UD HCT	216	1.86 (1.23-2.80)	0.003
Chronic GVHD			
Main effect			
Haploidentical HCT	393	Reference	
7/8 HLA-matched UD HCT	230	1.72 (1.34-2.20)	< 0.001

Abbreviations: HLA, human leukocyte antigen; HCT, hematopoietic cell transplantation; N, number; HR, hazard ratio; CI, confidence interval; CR, complete remission; F, female; M, male; Ph, Philadelphia; BCR-ABL, breakpoint cluster region-Abelson murine leukemia; ALL, acute lymphoblastic leukemia; D, donor; R, recipient; CMV, cytomegalovirus; MAC, myeloablative conditioning; TBI, total body irradiation; RIC, reduced intensity conditioning; NMA, nonmyeloablative; GVHD, graft-versus-host disease; UD, unrelated donor

Table 5. Multivariate analysis for umbilical cord blood (UCB) HCT vs. haploidentical HCT, 2013-2017

Covariates	N	HR (95% CI)	p-value
Overall survival			
UCB HCT vs. haploidentical HCT <=18 months		1.93 (1.45-2.56)	< 0.001
UCB HCT vs. haploidentical HCT >18 months		0.68 (0.38-1.21)	0.19
Remission status			
CR1	481	Reference	
CR2+	217	1.62 (1.27-2.07)	< 0.001
Karnofsky score			
<90%	259	Reference	
>=90%	429	0.81 (0.64-1.04)	0.10
Conditioning regimen			
MAC-TBI	380	Reference	
MAC-Chemotherapy	74	2.14 (1.45-3.14)	< 0.001
RIC/NMA	243	1.22 (0.93-1.59)	0.15
Leukemia-free survival			
UCB HCT vs. haploidentical HCT <=18 months		1.40 (1.09-1.79)	0.007
UCB HCT vs. haploidentical HCT >18 months		0.58 (0.31-1.07)	0.08
Remission status			
CR1	469	Reference	
CR2+	203	1.59 (1.27-1.99)	< 0.001
Race			
White Hispanic	144	Reference	
White non-Hispanic	310	0.86 (0.65-1.13)	0.27
Black	83	1.33 (0.93-1.89)	0.12
Asian	41	0.55 (0.31-0.97)	0.04
Other/not specified	94	0.94 (0.65-1.36)	0.74
Conditioning regimen			
MAC-TBI	364	Reference	
MAC-Chemotherapy	72	1.77 (1.23-2.55)	0.002
RIC/NMA	235	1.51 (1.19-1.91)	< 0.001
Non-relapse mortality			
Main effect			
Haploidentical HCT	381	Reference	
UCB HCT	291	2.08 (1.45-2.99)	< 0.001
Karnofsky score			
<90%	247	Reference	
>=90%	416	0.65 (0.46-0.90)	0.01
Conditioning regimen			
MAC-TBI	364	Reference	
MAC-Chemotherapy	72	1.96 (1.16-3.32)	0.01
RIC/NMA	235	0.88 (0.59-1.29)	0.51

Covariates	N	HR (95% CI)	p-value
Relapse			
Main effect			
Haploidentical HCT	381	Reference	
UCB HCT	291	0.83 (0.60-1.13)	0.23
Remission status			
CR1	469	Reference	
CR2+	203	1.88 (1.40-2.53)	< 0.001
Race			
White Hispanic	144	Reference	
White non-Hispanic	310	0.99 (0.68-1.45)	0.98
Black	83	1.51 (0.95-2.39)	0.08
Asian	41	0.55 (0.26-1.19)	0.13
Other/not specified	94	0.73 (0.43-1.25)	0.25
Conditioning regimen			
MAC-TBI	364	Reference	
MAC-Chemotherapy	72	1.64 (0.99-2.71)	0.05
RIC/NMA	235	2.01 (1.47-2.74)	< 0.001
Acute GVHD, Grade 2-4			
Main effect			
Haploidentical HCT	376	Reference	
UCB HCT	285	1.83 (1.46-2.30)	< 0.001
Acute GVHD, Grade 3-4			
Main effect			
Haploidentical HCT	376	Reference	
UCB HCT	285	1.97 (1.35-2.88)	< 0.001
Chronic GVHD			
Main effect			
Haploidentical HCT	393	Reference	
UCB HCT	297	1.13 (0.86-1.47)	0.38
Conditioning regimen			
MAC-TBI	375	Reference	
MAC-Chemotherapy	71	1.11 (0.72-1.72)	0.64
RIC/NMA	243	0.65 (0.49-0.87)	0.003
HCT-CI			0.05
0	169	Reference	
1	98	0.60 (0.39-0.92)	0.02
2	105	0.91 (0.63-1.31)	0.60
3+	317	0.68 (0.50-0.91)	0.01

Abbreviations: HLA, human leukocyte antigen; HCT, hematopoietic cell transplantation; N, number; HR, hazard ratio; CI, confidence interval; CR, complete remission; F, female; M, male; Ph, Philadelphia; BCR-ABL, breakpoint cluster region-Abelson murine leukemia; ALL, acute lymphoblastic leukemia; D, donor; R, recipient; CMV, cytomegalovirus; MAC, myeloablative conditioning; TBI, total body irradiation; RIC, reduced intensity conditioning; NMA, nonmyeloablative; GVHD, graft-versus-host disease; UCB, umbilical cord blood

Table 6. Causes of death by cohort

Characteristic	Haploidentical	MSD	MUD	7/8 UD	UCB
Number of deaths	132	564	625	103	130
Cause of death					
Acute lymphoblastic leukemia	64 (48)	293 (52)	240 (38)	33 (32)	40 (31)
Graft failure	1 (<1)	4 (<1)	1 (<1)	3 (3)	3 (2)
Graft-versus-host disease	7 (5)	81 (14)	126 (20)	25 (24)	16 (12)
Infection	28 (21)	98 (17)	126 (20)	21 (20)	30 (23)
Idiopathic pneumonia	4 (3)	5 (<1)	7 (1)	0	5 (4)
Acute respiratory distress syndrome	3 (2)	7 (1)	9 (1)	0	4 (3)
Organ failure	8 (6)	31 (5)	53 (8)	9 (9)	19 (15)
Organ toxicity	0	4 (<1)	1 (<1)	2 (2)	0
Secondary malignancy	2 (2)	4 (<1)	4 (<1)	2 (2)	2 (2)
Hemorrhage	3 (2)	4 (<1)	4 (<1)	1 (<1)	2 (2)
Accident/suicide	0	0	3 (<1)	0	0
Vascular	0	2 (<1)	1 (<1)	0	2 (2)
Other known	11 (8)	23 (4)	39 (6)	7 (7)	6 (5)
Unknown	1 (<1)	8 (1)	11 (2)	0	1 (<1)

Abbreviations: MSD, matched sibling donor; MUD, matched unrelated donor; 7/8 UD, 7/8 HLA-matched unrelated donor; UCB, umbilical cord blood

Figure 1