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A G E N D A
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Orlando, Florida
Thursday, February 20, 2020, 2:45 – 4:45 pm

Co-Chair:	**Minoo Battiwalla, MD, MS, Sarah Cannon Research Institute, Nashville, TN; Phone: 301-742-7782; E-mail: minoo.battiwalla@hcahealthcare.com**
Co-Chair:	**David Buchbinder, MD, CHOC Children's Hospital, Orange, CA; Phone: 714-509-8744; E-mail: dbuchbinder@choc.org**
Co-Chair:	**Betty Hamilton, MD, Cleveland Clinic Foundation, Cleveland, OH; Telephone: 216-445-7580; E-mail: hamiltb2@ccf.org**
Scientific Director:	**Bronwen Shaw, MBChB, MRCP, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0700; E-mail: beshaw@mcw.edu**
Assistant Scientific Director:	**Rachel Phelan, MD, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4153; E-mail: rphelan@mcw.edu**
Statistical Director:	**Ruta Brazauskas, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-456-8687; E-mail: ruta@mcw.edu**
Statistician:	**Stephanie Bo-Subait, MPH, CIBMTR Statistical Center, Minneapolis, MN; Telephone: 763-406-8515; E-mail: sbosuba2@nmdp.org**

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1. Introduction

a. Minutes and Overview Plan from February 2019 meeting (Attachment 1)

b. Introduction of incoming Co-Chair:

Hélène Schoemans, MD, PhD, EBMT, University Hospitals Leuven and KU Leuven; Leuven, Belgium;

Telephone: 32 16 34 68 80; Email: helene.schoemans@uzleuven.be

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

a. **LE13-02** Herr MM, Curtis RE, Tucker MA, Tecca HR, Engels EA, Cahoon EK, Battiwalla M, Buchbinder D, Flowers ME, Brazauskas R, Shaw BE, Morton LM. Risk factors for the development of cutaneous melanoma after allogeneic hematopoietic cell transplantation***. Journal of the American Academy of Dermatology. doi:10.1016/j.jaad.2019.10.034. Epub 2019 Oct 22.***

b. **LE16-02** Kahn JM, Brazauskas R, Tecca HR, Bo-Subait S, Buchbinder D, Battiwalla M, Flowers MED, Savani BN, Phelan R, Broglie L, Abraham AA, Keating AK, Daly A, Wirk B, George B, Alter BP, Ustun C, Freytes CO, Beitinjaneh AM, Duncan C, Copelan E, Hildebrandt GC, Murthy HS, Lazarus HM, Auletta JJ, Myers KC, Williams KM, Page KM, Vrooman LM, Norkin M, Byrne M, Diaz MA, Kamani N, Bhatt NS, Rezvani A, Farhadfar N, Mehta PA, Hematti P, Shaw PJ, Kamble RT, Schears R, Olsson RF, Hayashi RJ, Gale RP, Mayo SJ, Chhabra S, Rotz SJ, Badawy SM, Ganguly S, Pavletic S, Nishihori T, Prestidge T, Agrawal V, Hogan WJ, Inamoto Y, Shaw BE, Satwani P. Subsequent Neoplasms and Late Mortality in

Children Undergoing Allogeneic Transplantation for Non-Malignant Diseases. ***Submitted.***

c. **LE17-02** *Lee CJ, Kim S, Tecca HR, Bo-Subait S, Phelan R, Brazauskas R, Buchbinder D, Hamilton BK, Battiwalla M, Majhail NS, Lazarus H, Shaw P, Marks D, Litzow MR, Chhabra S, Inamoto Y, DeFilipp Z, Hildebrandt G, Olsson R, Kasow K, Liesveld J, Rotz S, Badawy SM, Bhatt N, Yared J, Page K, Arellano M, Kent MW, Farhadfar N, Seo S, Hematti P, Freytes CM, Rovo A, Ganguly S, Nathan S, Burns L, Shaw BE, Muffly LS.* Late Effects After Ablative Allogeneic Stem Cell Transplantation for Adolescent and Young Adult Acute Myeloid Leukemia. ***Submitted.***

d. **LE17-01** Stenger E, Phelan R, Shaw BE, Battiwalla Minoo, Bo-Subait S, Brazauskas R, Buchbinder DK, Hamilton BK, Shenoy S, Krishnamurti L. Excellent Overall Survival and Low Incidence of Late Effects in Patients Undergoing Allogeneic Hematopoietic Cell Transplant for Sickle Cell Disease: A Report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Presented at 62nd ASH Annual Meeting and Exposition.***

e. **LE18-02** Bhatt NS, Brazauskas R, Bo-Subait S, Salit RB, Syrjala K, Tecca HR, Battiwalla M, Buchbinder DK, Hamilton BK, Phelan R, Shaw BE. Post-Transplant Work Status of Young Adult Survivors of Allogeneic Hematopoietic Cell Transplant: A Report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Presented at 62nd ASH Annual Meeting and Exposition.***

f. **LE12-03** Gupta M, Levine MH, Porter D, Bo-Subait S, Shaw BE, Brazauskas R, Phelan R, Battiwalla M, Buchbinder D, Hamilton B, Abt PL. Solid Organ Transplant (SOT) and Hematopoietic Cell Transplantation (HCT). **Poster Presentation at TCT 2020 in Orlando, Fl.**

4. Studies in progress (Attachment 3)

a. **LE99-01** Quality of life in late HCT survivors (J Wingard) **Manuscript Preparation**

b. **LE12-03** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) **Analysis**

c. **LE17-01** Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) **Analysis**

e. **LE18-01** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) **Protocol Development**

f. **LE18-02** Post-transplant Employment/ Student Status of Survivors of Young Adult (YA) Allogeneic Hematopoietic Cell Transplant (N Bhatt/R Salit/K Syrjala/BE Shaw) **Manuscript Preparation**

g. **LE19-01** Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) **Protocol Development**

h. **LE19-02** Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) **Protocol Development**

5. Future/proposed studies

a. **PROP 1911-23** Influence of Busulfan based vs melphalan based Chemo regimens On early and late cardiac toxicity post SCT (*Farhan*) (Attachment 4)

b. **PROP 1911-30** Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant (*Taylor/Knight/Baker/Cole*) (Attachment 5)

c. **PROP 1911-59** New Cancers after Autologous Hematopoietic Cell Transplantation for Systemic Light-Chain Amyloidosis *(Chakraborty/Majhail/Lentzsch)* (Attachment 6)

d. **PROP 1911-176** Cardiometabolic Risk after Total Body Irradiation during Childhood (*Friedman/ Chow*)(Attachment 7)

e. **PROP 1911-203** Pre-transplant body mass index and late effects among children, adolescent, and young adult (CAYA) childhood leukemia survivors following allogeneic hematopoietic cell transplantation (*Joffe/Broglie/Ladas/Kadan-Lottick/Satwani*) (Attachment 8)
f. **PROP 1912-07** Long-Term Survival and Late Deaths After Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) In The Modern Era *(Al-Mansour/Farhadfar/Socie/Wingard)* (Attachment 9)

Dropped proposed studies

a. **PROP 1911-27** Recurrence of primary solid cancers after allogeneic hematopoietic cell transplantation. *Dropped due to feasibility.*
b. **PROP 1911-103** Secondary malignancies after reduced intensity or non myeloablative stem cell transplantation in non-malignant disorders. *Dropped for overlap with an existing study.*
c. **PROP 1911-114** Incidence and Outcomes of Kaposi Sarcoma after Hematopoietic Stem Cell Transplantation: A CIBMTR study. *Dropped due to feasibility.*
d. **PROP 1911-188** Tumor Immunogenicity as a Predictor of Second Cancer Relapse after Allogeneic Hematopoietic Cell Transplantation in Patients with History of Solid Organ Cancer. *Dropped due to feasibility.*
e. **PROP 1911-195** Outcomes of long-term survivors of umbilical cord blood allogeneic HSCT. *Dropped for overlap with an existing study.*
f. **PROP 1911-223** Late treatment related mortality vs competing causes of death after all HCT for secondary AML and MDS in pediatric patients. *Dropped due to feasibility.*

6. Other Business

a. CIBMTR Late Effects and Quality of Life Working Committee and the EBMT Transplant Complications Working Party Review

7. Closing Remarks

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Houston, Texas
Wednesday, February 20, 2019, 2:45 – 4:45 pm

Co-Chair:	**Mary Flowers, MD, Fred Hutchinson Cancer Research Center, Seattle, WA; Telephone: 206-667-5191; E-mail: mflowers@fredhutch.org**
Co-Chair:	**Minoo Battiwalla, MD, MS, Sarah Cannon Research Institute, Nashville, TN; Phone: 301-742-7782; E-mail: minoo.battiwalla@hcahealthcare.com**
Co-Chair:	**David Buchbinder, MD, CHOC Children's Hospital, Orange, CA; Phone: 714-509-8744; E-mail: dbuchbinder@choc.org**
Scientific Director:	**Bronwen Shaw, MBChB, MRCP, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0700; E-mail: beshaw@mcw.edu**
Assistant Scientific Director:	**Rachel Phelan, MD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4153; E-mail: rphelan@mcw.edu**
Statistical Director:	**Ruta Brazauskas, PhD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-456-8687; E-mail: ruta@mcw.edu**
Statistician:	**Stephanie Bo-Subait, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0674; E-mail: sbosubait@mcw.edu**

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1. Introduction

The CIBMTR Late Effects and Quality of Life Working Committee (LEWC) meeting was called to order at 2:45pm on Wednesday, February 20, 2019, by Dr. David Buchbinder. He introduced the current working committee leadership and introduced the incoming chair, Dr. Betty Hamilton. The leadership thanked Dr. Mary Flowers, the outgoing chair, for her service to the LEWC over the past five years. The CIBMTR COI policy was reviewed and the processes of participating in the working committee, voting guidance, and rules of authorship were outlined.

a. Minutes and Overview Plan from February 2018 meeting (Attachment 1)
Minutes from February 2018 were approved by the LEWC.
b. Introduction of incoming Co-Chair: **Betty Hamilton, MD**; Cleveland Clinic Foundation; Email: hamiltb2@ccf.org; Telephone: 216-445-7580

2. Accrual summary (Attachment 2)

3. Presentations, published or submitted papers

a. **LE13-02** Herr MH, Curtis RE, Tucker MA, Tecca HR, Engels EA, Cahoon E, Battiwalla M, Buchbinder D, Flowers M, Brazauskas R, Shaw BE, Morton LM. Risk Factors for the Development of Cutaneous Melanoma after Allogeneic Hematopoietic Cell Transplantation. ***Presented at 60th ASH Annual Meeting and Exposition.***

b. **LE14-01** Radivoyevitch T, Dean RM, Shaw BE, Brazauskas R, Millard HR, Molenaar RJ, Battiwalla M, Savani BN, Flowers MED, Cooke KR, Hamilton BK, Kalaycio M, Maciejewski JP, Ahmed I, Akpek G, Bajel A, Buchbinder D, Cahn JY, D'Souza A, Daly A, DeFilipp Z, Ganguly S, Hamadani M, Hayashi

RJ, Hematti P, Inamoto Y, Khera N, Kindwall-Keller T, Landau H, Lazarus H, Majhail NS, Marks DI, Olsson RF,, Seo S, Steinberg A, William BM, Wirk B, Yared JA, Aljurf M, Abidi MH, Allewelt H, Beitinjaneh A, Cook R, Cornell RF, Fay JW, Hale G, Holter Chakrabarty J, Jodele S, Kasow KA, Mahindra A, Malone AK, Popat U, Rizzo JD, Schouten HC, Warwick AB, Wood WA, Sekeres MA, Litzow MR, Gale RP, Hashmi SK. Risk of acute myeloid leukemia and myelodysplastic syndromes after autologous transplant for lymphoma and plasma cell myeloma. ***Leukemia Research.***

c. **LE16-01** Norkin M, Shaw BE, Brazauskas R, Tecca HR, Leather HL, Gea-Banacloche J, Kamble R, DeFilipp Z, Jacobsohn DA, Ringden O, Inamoto Y, Kasow K, Buchbinder D, Shaw P, Hematti P, Schears R, Badawy SM, Lazarus HM, Bhatt N, Horn B, Chhabra S, Page K, Hamilton B, Hildebrandt GC, Yared JA, Agrawal V, Beitinjaneh A, Majhail NS, Kindwall-Keller T, Olsson RF, Schoemans H, Gale RP, Ganguly S, Ahmed I, Schouten HC, Liesveld J, Khera N, Steinberg A, Shah AJ, Solh M, Marks DI, Rybka W, Aljurf M, Dietz AC, Gergis U, George B, Seo S, Flowers MED, Battiwalla M, Savani BN, Riches ML, Wingard JR. Characteristics of late fatal infections after allogeneic hematopoietic cell transplant. ***Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.***

d. **LE16-03** Bhatt NS, Brazauskas R, Tecca HR, Carreras J, Burns LJ, Phelan R, Salit RB, Syrjala KL, Talano JM, Shaw BE. Post-transplantation employment status of adult survivors of childhood allogeneic hematopoietic cell transplant: A report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Cancer.***

e. **LE17-02** Lee CJ, Kim S, Tecca HR, Bo-Subait SL, Brazauskas R, Battiwalla, M, Buchbinder D, Flowers MED, Phelan R, Shaw BE, Muffly LS. Impact of Myeloablative Total Body Irradiation Versus Chemotherapy on Late Effects and Survival Among Adolescent and Young Adult Survivors of Hematopoietic Cell Transplantation for Acute Leukemia: A Center for International Blood and Marrow Transplant Research (CIBMTR) Analysis. ***Presented at 60th ASH Annual Meeting and Exposition.***

f. **LE17-G1a** Inamoto Y, Valdés-Sanz N, Ogawa Y, Alves M, Berchicci L, Galvin J, Greinix H, Hale GA, Horn B, Kelly D, Liu H, Rowley S, Schoemans H, Shah A, Stanghellini MTL, Argrawal V, Ahmed I, Ali A, Bhatt N, Byrne M, Chhabra S, DeFilipp Z, Fahnehjelm K, Farhadfar N, Horn E, Lee C, Nathan S, Penack O, Prasad P, Rotz S, Rovó A, Yared J, Pavletic S, Basak GW, Battiwalla M, Duarte R, Savani BN, Flowers ME, Shaw BE, Petriček I. Ocular graft-versus-host disease after hematopoietic cell transplantation: Expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.**

   Inamoto Y, Valdés-Sanz N, Ogawa Y, Alves M, Berchicci L, Galvin J, Greinix H, Hale GA, Horn B, Kelly D, Liu H, Rowley S, Schoemans H, Shah A, Stanghellini MTL, Argrawal V, Ahmed I, Ali A, Bhatt N, Byrne M, Chhabra S, DeFilipp Z, Fahnehjelm K, Farhadfar N, Horn E, Lee C, Nathan S, Penack O, Prasad P, Rotz S, Rovó A, Yared J, Pavletic S, Basak GW, Battiwalla M, Duarte R, Savani BN, Flowers ME, Shaw BE, Petriček I. Ocular graft-versus-host disease after hematopoietic cell transplantation: Expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Bone Marrow Transplantation.**

g. **LE17-G1b** Inamoto Y, Petriček I, Burns L, Chhabra S, DeFilipp Z, Hematti P, Rovó A, Schears R, Shah A, Agrawal V, Ahmed A, Ahmed I, Ali A, Aljurf M, Alkhateeb H, Beitinjaneh A, Bhatt N, Buchbinder D, Byrne M, Callander N, Fahnehjelm K, Farhadfar N, Gale RP, Ganguly S, Hildebrandt GC, Horn E, Jakubowski A, Kamble RT, Law J, Lee C, Nathan S, Penack O, Pingali R, Prasad P, Pulanic D, Rotz S, Shreenivas A, Steinberg A, Tabbara K, Tichelli A, Wirk B, Yared J, Basak GW,

Battiwalla M, Duarte R, Savani BN, Flowers MED, Shaw BE, Valdés-Sanz N. Non-GVHD ocular complications after hematopoietic cell transplantation: expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.**

Inamoto Y, Petriček I, Burns L, Chhabra S, DeFilipp Z, Hematti P, Rovó A, Schears R, Shah A, Agrawal V, Ahmed A, Ahmed I, Ali A, Aljurf M, Alkhateeb H, Beitinjaneh A, Bhatt N, Buchbinder D, Byrne M, Callander N, Fahnehjelm K, Farhadfar N, Gale RP, Ganguly S, Hildebrandt GC, Horn E, Jakubowski A, Kamble RT, Law J, Lee C, Nathan S, Penack O, Pingali R, Prasad P, Pulanic D, Rotz S, Shreenivas A, Steinberg A, Tabbara K, Tichelli A, Wirk B, Yared J, Basak GW, Battiwalla M, Duarte R, Savani BN, Flowers MED, Shaw BE, Valdés-Sanz N. Non-GVHD ocular complications after hematopoietic cell transplantation: expert review from the Late Effects and Quality of Life Working Committee of the CIBMTR and Transplant Complications Working Party of the EBMT. **Bone Marrow Transplantation.**

4. Studies in progress (Attachment 3)

Dr. Mary Flowers briefly listed all studies in progress. She introduced Dr. Lindsay Morton to present an update on LE13-02 and Dr. Prakash Satwani to present on LE16-02.

a. **LE99-01** Quality of life in late HCT survivors (J Wingard) **Manuscript Preparation**

b. **LE12-03** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) **Data file Preparation**

c. **LE13-02** Risk factors for melanoma following allogeneic hematopoietic stem cell transplantation (M Herr/L Morton) **Manuscript Preparation**
Dr. Lindsay Morton presented this study, which aimed to identify risk factors associated with the development of cutaneous melanoma after allogeneic HCT. This was a nested case-control study identified 140 melanoma cases and 557 melanoma free controls which were matched on age at transplant, sex, primary disease, and survival time. Novel risk factors for identified after alloHCT were conditioning regimen, acute GVHD, and chronic GVHD.

e. **LE16-02** An investigation of new malignant neoplasms in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation for non-malignant diseases (JM Kahn/P Satwani) **Manuscript Preparation**
Dr. Prakash Satwani presented this study which aims to determine the risk of subsequent neoplasms in children undergoing allogeneic HCT for non-malignant disorders. The population included 6,028 patients under the age of 21. Individual malignancy rates in the US population were compared to the general US population with age and sex matched controls. Patients who are alive 2 years post-transplant have excellent long-term survival. Incidence of subsequent neoplasms post-transplant is low overall and is increased compared to the general population.

f. **LE17-01** Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) **Data file Preparation**

g. **LE17-02** Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia (C Lee/L Muffly) **Manuscript Preparation**

h. **LE18-01** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) **Protocol Development**

i. **LE18-02** Post-transplant Employment/ Student Status of Survivors of Young Adult (YA) Allogeneic Hematopoietic Cell Transplant (N Bhatt/R Salit/K Syrjala/BE Shaw) **Data file Preparation**

5. Future/proposed studies

a. **PROP 1811-73** Late mortality in acute leukemia patients undergoing allogeneic transplantation (*Hashmi/Bar/Lazarus*) (Attachment 4)

Dr. Shahrukh Hashmi presented this proposal aiming to compare long term mortality of adult alloHCT survivors with that of general population utilizing standard mortality ratios. Preliminary population selection identified 7,200 patients eligible for this study. Working committee members were concerned about whether the findings of this study would be applicable to all countries around the world and suggested analyzing by geographical region to address this. Members also felt concerned about the proposed population due to changes in trends of the ages of transplanted patients; the 70 year old transplanted today is very different from the 60 year old transplanted in 2000, this may be difficult to adjust for. It was also suggested that it would be important to see how socioeconomic status and poverty impact mortality.

b. **PROP 1811-128** Incidence and predictors of long term toxicities and late side effects in elderly patients (≥ 60 years) receiving high dose therapy and autologous hematopoietic cell transplantation (HDT-AHCT) for lymphoma *(Dahi/Giralt/Jakubowski)* (Attachment 5)

Dr. Ann Jakubowski presented this proposal aiming to identify and evaluate the incidence of long-term organ toxicities and late effects of autoHCT in older adults. Preliminary population selection identified 745 patients eligible for this study. Working committee members felt it would be important to consider separating patients with Hodgkin's Disease and NHL, especially when considering differences in those who received post-transplant therapies. A suggestion was made to consider adding a comparison population using the SEER database. The numbers are relatively low for a late effects study (with rare events).

c. **PROP 1811-142** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients *(Zinter/Duncan)* (Attachment 6)

Dr. Matt Zinter presented this proposal aiming to utilize the RT14-03 study population (a population linking CIBMTR data with the VPS data; already cleaned with results) to analyze long term morbidity and mortality of critically ill pediatric alloHCT patients and to compare against a matched CIBMTR cohort that did not require PICU admission. The non-PICU population will be identified by finding patients that were transplanted at the same centers as patients in the RT14-03 cohort, but do not exist in the VPS database. Of the 936 patients in the RT14-03 population, there are 255 that are CRF level and survived 1-year post transplant. This study is innovative and builds on work already done. The results may lead to better screening and monitoring practices for pediatric patients who survive an ICU admission.

d. **PROP 1811-146** Use of data from the CIBMTR dataset of subjects exposed to ionizing radiations to refine and extend estimates of risk of radiation-induced solid cancers currently based on data from the atomic bomb survivors in the Radiation Effects Research Foundation (RERF) dataset, persons with cancer receiving conventional radiation therapy in the US Surveillance and End Results (SEER) dataset and other radiation exposure datasets *(Gale/Zablotska/Hoffman/Hashmi)* (Attachment 7)

Dr. Robert Peter Gale presented this proposal aiming to refine risk estimates of risk of new solid cancers following exposure to ionizing radiations. This proposal is not to study CIBMTR patients per se, but to use the radiation exposures and compare to patients in other datasets (A-bomb,

SEER). Preliminary population selection identified 8748 patients eligible for this study (exposed to TBI). Working committee members felt concerned about the amount of missing data on radiation exposure prior to transplant, as well as data such as specifics of the radiation delivered. A member asked about whether the data collected by the CIBMTR offered the granularity needed to conduct the proposed study. Members also felt concerned about how to determine in the transplant population, which secondary neoplasms are purely attributed to TBI, as multiple confounding factors are present.

e. **PROP 1812-04** Risk of sarcoma after allogeneic hematopoietic stem cell transplantation *(Advani/Morton/Curtis/Schonfeld)* (Attachment 8)

Dr. Lindsay Morton presented this proposal aiming to examine the association between patient- and transplant- related factors, pre-HCT therapies, and conditioning regimens with the development of sarcoma after alloHCT. Preliminary population selection identified 57,298 patients eligible for this study, 102 of which reported sarcoma. Working committee members thought it would be interesting to look at the incidence of sarcoma after autoHCT, but this may be difficult to address because of completeness of data on pre-transplant therapy. A member suggested that since ages less than 18 are included in this population it would be necessary to look at primary indication for transplant and exclude patients that had a syndrome predisposing them to sarcoma.

f. **PROP 1812-10** Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies *(Veeraputhiran/Pingali/Mukherjee/Muffly)* (Attachment 9)

Dr. Muthu Veeraputhiran presented this proposal aiming to evaluate incidence of long term toxicities and late effects in elderly patients. Preliminary population selection identified 5144 patients eligible for this study. Working committee members expressed interest in this topic as current survivorship guidelines were not developed for older patients. It was also raised that patients >60 receiving allografts in recent years are very different to those receiving allografts a few decades ago and more data is urgently needed to adequately counsel patients. There is very little literature on this topic, and the large numbers available through CIBMTR make this an important proposal which is likely to have a large impact.

Dropped proposed studies

a. **PROP 1811-13** Late effects and malignancies among survivors of second hematopoietic cell transplantation for graft failure in non-malignant disorders. *Dropped due to feasibility.*
b. **PROP 1811-179** Late effects and second neoplasms in de novo pediatric acute myeloid leukemia patient treated with TBI vs non-TBI conditioning regimens in the modern era. *Dropped due to feasibility and overlap with an existing study.*

6. Other Business

a. CIBMTR Late Effects and Quality of Life Working Committee and the EBMT Transplant Complications Working Party call for review proposals

Dr. Rachel Phelan announced the newly standardized review/guidelines proposal process which is a combined effort through CIBMTR and EBMT. There have been several reviews/guidelines developed in recent years that have been published in conjunction with our committees. Examples of these reviews were named and these can be found on the CIMBTR website within the Late Effects and Quality of Life Working Committee page. The first call for late effects review proposals was in fall of 2018. Of the 12 proposals received (with great representation from both CIBMTR

and EBMT), there were a number of different topics proposed. The CIBMTR Late Effects and Quality of Life Working Committee and the EBMT Transplant Complications Working Party leadership chose the topic for review in 2019 based on the following: proposal quality, young investigator representation, novelty of the topic, and timeliness of the topic (has a recent review been published related to this topic?). A common theme of male-specific late effects was identified among 3 proposals and they scored highly on the noted criteria. Leadership from both CIBMTR and EBMT and the PI's of these 3 proposals will develop the review on male-specific late effects. Members of the working committee are encouraged to participate in the review process as part of the writing committee. We are planning to develop one review/guideline related to late effects yearly. The next call for proposals will be in the fall of 2019.

7. Closing Remarks

Oversight Assignments for Working Committee Leadership (March 2019)

Minoo Battiwalla	**LE12-03** Solid organ transplant after HCT
	LE17-01 Long-term follow up after HSCT for sickle cell disease
	LE16-02 New malignant neoplasms after AlloHCT for pediatric pts with non-malignant diseases
David Buchbinder	**LE17-02** Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia
	LE18-01 Survival trends amongst two-year survivors of alloHCT
	LE18-02 Return to work or school status in survivors of young adult AlloHCT
Betty Hamilton	**LE19-01** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients
	LE19-02 Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies
Bronwen Shaw	**LE99-01** Quality of life in late HCT survivors

Working Committee Overview Plan for 2019-2020

a. **LE99-01** Quality of life in late HCT survivors. This study is ongoing.

b. **LE12-03** Solid organ transplant after HCT. This study is in data file preparation and we plan to start manuscript prep by July 2019.

c. **LE16-02** New malignant neoplasms after AlloHCT for pediatric pts with non-malignant diseases. This study is in manuscript preparation and we plan to have it submitted by March 2019.

d. **LE17-01** Long-term follow up after HSCT for sickle cell disease. This study is in data file preparation and we plan to complete the analysis and start manuscript preparation by July 2019.

e. **LE17-02** Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia. This study is in manuscript preparation and we plan to submit this paper by June 2019.

f. **LE18-01** Survival trends amongst two-year survivors of alloHCT. This study is in protocol development. We aim to be in data file preparation by July 2019.

g. **LE18-02** Return to work or school status in survivors of young adult AlloHCT. This study is in data file preparation and we aim to have it submitted by July 2019.

h. **LE19-01** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients. Protocol is pending on this study and hours will begin July 2019

i. **LE19-02** Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies. Protocol is pending on this study and hours will begin July 2019.

Statistical hour allocation

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2019	Hours allocated 7/1/2019-6/30/2020	Total Hours allocated
LE12-03 Solid organ transplantation and hematopoietic cell transplantation	Data file preparation	Manuscript preparation – July 2019	200	200	150	50	200
LE16-02 An investigation of new malignant neoplasms in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation for non-malignant diseases	Manuscript preparation	Submission – March 2019	10	10	10	0	10
LE17-01 Long-term follow up after hematopoietic stem cell transplantation for sickle cell disease	Data file preparation	Manuscript preparation – July 2019	220	220	150	70	220
LE17-02 Comparison of Late Effects Among Allogeneic Hematopoietic Cell Transplantation Survivors Conditioned with High Dose Total Body Irradiation (TBI) versus Non-TBI Based Ablative Regimens in Adolescents and Young Adults (15-39yo) With Acute Leukemia	Manuscript preparation	Submission – June 2019	60	60	50	10	60
LE18-01 Survival trends amongst two-year survivors of alloHCT	Protocol development	Manuscript preparation – July 2020	310	240	60	180	240

LE19-01 Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients	Protocol pending	NA	330	NA	0	200	200
LE19-02 Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies.	Protocol pending	NA	330	NA	0	100	100

Accrual Summary for the Late Effects and Quality of Life Working Committee

Follow-up of **adult** patients (age≥18) after **allogeneic** transplant reported to CIBMTR, 1990-2019

Variable	TED	CRF
All patients	179861	62248
3 year survivors	54086	18253
5 year survivors	37125	12497
10 year survivors	14540	5295
15 year survivors	5574	1671
Acute Myelogenous Leukemia	65532	20669
3 year survivors	17646	5834
5 year survivors	11595	3922
10 year survivors	3963	1442
Acute Lymphoblastic Leukemia	24916	7690
3 year survivors	6543	2018
5 year survivors	4176	1317
10 year survivors	1372	543
Chronic Myelogenous Leukemia	24105	9039
3 year survivors	9793	3109
5 year survivors	7571	2432
10 year survivors	4078	1392
Myelodysplastic/Myeloproliferative Diseases	26292	11446
3 year survivors	6761	2926
5 year survivors	4235	1780
10 year survivors	1402	622
Multiple Myeloma/Plasma Cell Disorders	3214	1102
3 year survivors	1058	326
5 year survivors	731	216
10 year survivors	313	75
Lymphoma	16904	5377
3 year survivors	5730	1719
5 year survivors	4210	1252
10 year survivors	1739	607

Variable	TED	CRF
Other Malignant	9094	3118
3 year survivors	2865	962
5 year survivors	1957	644
10 year survivors	600	236
Severe Aplastic Anemia	7020	2795
3 year survivors	2823	1060
5 year survivors	2076	744
10 year survivors	890	305
Immune deficiencies	384	118
3 year survivors	114	35
5 year survivors	59	21
10 year survivors	3	2
Other Non-malignant	2225	894
3 year survivors	719	264
5 year survivors	492	169
10 year survivors	167	71

Follow-up of **pediatric** patients (age<18) after **allogeneic** transplant reported to CIBMTR, 1990-2019

Variable	TED	CRF
All patients	54699	22473
3 year survivors	22136	8989
5 year survivors	16411	6715
10 year survivors	7097	3218
15 year survivors	2544	955
Acute Myelogenous Leukemia	10123	3932
3 year survivors	3590	1403
5 year survivors	2661	1041
10 year survivors	1243	493
Acute Lymphoblastic Leukemia	14368	5612
3 year survivors	5210	1981
5 year survivors	3891	1473
10 year survivors	1740	722
Chronic Myelogenous Leukemia	2159	848
3 year survivors	984	393
5 year survivors	770	318
10 year survivors	379	171
Myelodysplastic/Myeloproliferative Diseases	3002	1273
3 year survivors	1241	540
5 year survivors	927	427
10 year survivors	416	230
Multiple Myeloma/Plasma Cell Disorders	14	2
3 year survivors	5	0
5 year survivors	4	0
10 year survivors	4	0
Lymphoma	1184	433
3 year survivors	411	141
5 year survivors	290	105
10 year survivors	119	44

Variable	TED	CRF
Other Malignant	1086	421
3 year survivors	393	167
5 year survivors	287	130
10 year survivors	116	54
Severe Aplastic Anemia	5266	2112
3 year survivors	2567	978
5 year survivors	1949	729
10 year survivors	818	307
Immune deficiencies	5261	2449
3 year survivors	2328	1158
5 year survivors	1706	904
10 year survivors	716	434
Other Non-malignant	12207	5391
3 year survivors	5397	2228
5 year survivors	3920	1588
10 year survivors	1546	763

Follow-up of **adult** patients (age≥18) after **autologous** transplant reported to CIBMTR, 1990-2019

Variable	TED	CRF
All patients	230652	35424
3 year survivors	99208	14735
5 year survivors	63515	9012
10 year survivors	20050	2881
15 year survivors	6976	621
Acute Myelogenous Leukemia	7162	1336
3 year survivors	2507	421
5 year survivors	1815	289
10 year survivors	890	113
Acute Lymphoblastic Leukemia	1140	208
3 year survivors	281	40
5 year survivors	187	24
10 year survivors	94	11
Chronic Myelogenous Leukemia	656	206
3 year survivors	285	96
5 year survivors	189	56
10 year survivors	86	22
Myelodysplastic/Myeloproliferative Diseases	255	48
3 year survivors	111	23
5 year survivors	74	12
10 year survivors	30	3
Multiple Myeloma/Plasma Cell Disorders	98768	14786
3 year survivors	44456	7120
5 year survivors	26323	4280
10 year survivors	5443	1275
Lymphoma	89739	11091
3 year survivors	38818	4608
5 year survivors	26454	3016
10 year survivors	9490	1086

Variable	TED	CRF
Other Malignant	31712	7614
3 year survivors	12403	2364
5 year survivors	8220	1282
10 year survivors	3902	344
Severe Aplastic Anemia	14	3
3 year survivors	3	1
5 year survivors	2	1
10 year survivors	0	0
Immune deficiencies	14	2
3 year survivors	1	1
5 year survivors	0	0
10 year survivors	0	0
Other Non-malignant	1090	129
3 year survivors	291	60
5 year survivors	209	51
10 year survivors	87	26

Follow-up of **pediatric** patients (age<18) after **autologous** transplant reported to CIBMTR, 1990-2019

Variable	TED	CRF
All patients	16177	2799
3 year survivors	6267	1045
5 year survivors	4239	674
10 year survivors	1639	306
15 year survivors	607	80
Acute Myelogenous Leukemia	984	248
3 year survivors	390	50
5 year survivors	303	29
10 year survivors	158	15
Acute Lymphoblastic Leukemia	389	123
3 year survivors	127	19
5 year survivors	87	7
10 year survivors	46	0
Chronic Myelogenous Leukemia	23	3
3 year survivors	12	1
5 year survivors	7	0
10 year survivors	4	0
Myelodysplastic/Myeloproliferative Diseases	22	4
3 year survivors	7	0
5 year survivors	5	0
10 year survivors	3	0
Multiple Myeloma/Plasma Cell Disorders	105	3
3 year survivors	17	2
5 year survivors	12	2
10 year survivors	3	0
Lymphoma	2839	353
3 year survivors	1202	156
5 year survivors	841	100
10 year survivors	297	33

Variable	TED	CRF
Other Malignant	11548	2001
3 year survivors	4427	792
5 year survivors	2930	521
10 year survivors	1105	255
Severe Aplastic Anemia	7	3
3 year survivors	4	2
5 year survivors	4	2
10 year survivors	1	0
Immune deficiencies	55	42
3 year survivors	20	16
5 year survivors	8	7
10 year survivors	0	0
Other Non-malignant	178	19
3 year survivors	53	7
5 year survivors	36	6
10 year survivors	19	3

Quality of life data on **adult** patients

Variable	Baseline	100 day	6 months	1 year	2 year	3 year	4 year	5 year	≥ 6 year
No. of patients	263	171	159	153	21	16	13	9	11
Age at transplant - no. (%)									
Median (min-max)	55 (19-75)	55 (19-74)	55 (19-75)	56 (19-75)	68 (59-74)	68 (62-74)	67 (64-74)	64 (55-70)	61 (55-75)
18-29	34 (13)	17 (10)	19 (12)	11 (7)	0	0	0	0	0
30-39	24 (9)	17 (10)	13 (8)	14 (9)	0	0	0	0	0
40-49	40 (15)	23 (13)	23 (14)	22 (14)	0	0	0	0	0
50-59	77 (29)	58 (34)	56 (35)	47 (31)	2 (10)	0	0	3 (33)	5 (45)
60-69	78 (30)	52 (30)	43 (27)	50 (33)	13 (62)	13 (81)	10 (77)	6 (67)	4 (36)
70+	10 (4)	4 (2)	5 (3)	9 (6)	6 (29)	3 (19)	3 (23)	0	2 (18)
Gender - no. (%)									
Male	153 (58)	97 (57)	94 (59)	84 (55)	17 (81)	11 (69)	8 (62)	6 (67)	6 (55)
Female	110 (42)	74 (43)	65 (41)	69 (45)	4 (19)	5 (31)	5 (38)	3 (33)	5 (45)
Race/Ethnicity - no. (%)									
Caucasian/White	237 (90)	163 (95)	151 (95)	143 (93)	20 (95)	14 (88)	12 (92)	9 (100)	10 (91)
Black	12 (5)	0	2 (1)	4 (3)	0	1 (6)	1 (8)	0	0
Hispanic	7 (3)	4 (2)	2 (1)	1 (1)	0	0	0	0	0
Asian/Hawaiian/Pacific Islander	5 (2)	2 (1)	2 (1)	2 (1)	1 (5)	0	0	0	1 (9)
Unknown/Declined	2 (1)	2 (1)	2 (1)	3 (2)	0	1 (6)	0	0	0
Indication for transplant - no. (%)									
Acute leukemia	129 (49)	85 (50)	74 (47)	62 (41)	0	0	0	0	0
CML	19 (7)	11 (6)	12 (8)	10 (7)	0	0	0	0	0
MDS/MPS	49 (19)	32 (19)	28 (18)	43 (28)	21 (100)	16 (100)	13 (100)	9 (100)	11 (100)
Other leukemia	20 (8)	15 (9)	14 (9)	10 (7)	0	0	0	0	0
NHL	22 (8)	13 (8)	15 (9)	14 (9)	0	0	0	0	0
HD	6 (2)	3 (2)	4 (3)	4 (3)	0	0	0	0	0

Variable	Baseline	100 day	6 months	1 year	2 year	3 year	4 year	5 year	≥ 6 year
MM/PCD	7 (3)	4 (2)	4 (3)	4 (3)	0	0	0	0	0
Nonmalignant diseases	11 (4)	8 (5)	8 (5)	6 (4)	0	0	0	0	0
Year of transplant - no. (%)									
2011	25 (10)	12 (7)	12 (8)	12 (8)	0	0	0	0	6 (55)
2012	185 (70)	121 (71)	113 (71)	94 (61)	0	0	0	0	3 (27)
2013	53 (20)	38 (22)	34 (21)	28 (18)	0	0	0	2 (22)	2 (18)
2014	0	0	0	0	0	0	4 (31)	7 (78)	0
2015	0	0	0	0	0	3 (19)	9 (69)	0	0
2016	0	0	0	0	9 (43)	12 (75)	0	0	0
2017	0	0	0	11 (7)	11 (52)	1 (6)	0	0	0
2018	0	0	0	8 (5)	1 (5)	0	0	0	0
Measures completed - no. (%)									
FACT-BMT and SF-36	256 (97)	168 (98)	155 (97)	129 (84)	0	0	0	0	0
FACT-BMT only	7 (3)	1 (<1)	0	2 (1)	0	0	0	0	0
SF-36 only	0	2 (1)	4 (3)	3 (2)	0	0	0	0	0
PROMIS[a]	0	0	0	19 (12)	21 (100)	16 (100)	13 (100)	9 (100)	11 (100)
Follow-up - median (min-max)	72 (0-97)	72 (5-97)	72 (7-97)	72 (6-97)	24 (12-39)	36 (23-48)	48 (35-52)	59 (50-75)	74 (49-103)

[a] PROMIS measures are all cross-sectional

Quality of life data on **pediatric** patients

Variable	Baseline	100 days	6 months	1 year
Number of patients	77	45	46	37
Median age at transplant (range), years	7 (2-18)	7 (2-17)	8 (2-17)	7 (2-17)
2-4	24 (31)	14 (31)	13 (28)	9 (24)
5-7	21 (27)	12 (27)	11 (24)	12 (32)
8-12	18 (23)	9 (20)	10 (22)	7 (19)
13-18	14 (18)	10 (22)	12 (26)	9 (24)
Gender				
Male	42 (55)	28 (62)	28 (61)	21 (57)
Female	35 (45)	17 (38)	18 (39)	16 (43)
Race/Ethnicity				
Caucasian/White	63 (82)	39 (87)	39 (85)	33 (89)
Black	6 (8)	3 (7)	3 (7)	2 (5)
Hispanic	5 (6)	1 (2)	3 (7)	1 (3)
Asian/Hawaiian/Pacific Islander	2 (3)	1 (2)	1 (2)	1 (3)
Unknown/Declined	1 (1)	1 (2)	0	0
Indication for transplant				
AML	11 (14)	7 (16)	7 (15)	4 (11)
ALL	17 (22)	10 (22)	10 (22)	10 (27)
CML	1 (1)	0	1 (2)	1 (3)
MDS/MPD	4 (5)	2 (4)	3 (7)	1 (3)
Severe aplastic anemia	6 (8)	3 (7)	3 (7)	3 (8)
Inherited abnorm. of erythrocytes	17 (22)	12 (27)	12 (26)	10 (27)
SCID & other immune disorders	10 (13)	4 (9)	4 (9)	3 (8)
Inherited disorders of metabolism	1 (1)	0	0	0
Histiocytic disorders	9 (12)	6 (13)	5 (11)	5 (14)
Autoimmune diseases	1 (1)	1 (2)	1 (2)	0
Year of transplant				
2011	9 (12)	4 (9)	6 (13)	5 (14)
2012	50 (65)	29 (64)	29 (63)	22 (59)
2013	18 (23)	12 (27)	11 (24)	10 (27)
PedsQL measures completed				
Proxy only patients (age<5)	24 (31)	14 (31)	13 (28)	9 (24)
PedsQL and proxy completed	49 (64)	31 (69)	33 (72)	26 (70)
Only PedsQL completed	3 (4)	0	0	1 (3)
Only proxy completed	1 (1)	0	0	1 (3)
Median follow-up (range), months	71 (3-95)	70 (6-93)	70 (6-95)	72 (39-95)

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	39798	12259	7464
Source of data			
CRF	22542 (57)	6191 (51)	4354 (58)
TED	17256 (43)	6068 (49)	3110 (42)
Number of centers	251	224	338
Disease at transplant			
AML	13566 (34)	4431 (36)	2418 (32)
ALL	5866 (15)	1674 (14)	1232 (17)
Other leukemia	1340 (3)	349 (3)	235 (3)
CML	3283 (8)	894 (7)	747 (10)
MDS	6574 (17)	2328 (19)	1031 (14)
Other acute leukemia	408 (1)	138 (1)	80 (1)
NHL	3703 (9)	1012 (8)	606 (8)
Hodgkins Lymphoma	823 (2)	179 (1)	128 (2)
Plasma Cell Disorders, MM	793 (2)	235 (2)	128 (2)
Other malignancies	55 (<1)	13 (<1)	17 (<1)
Breast cancer	7 (<1)	3 (<1)	1 (<1)
SAA	1267 (3)	358 (3)	304 (4)
Inherited abnormalities erythrocyte diff fxn	697 (2)	222 (2)	136 (2)
SCIDs	694 (2)	223 (2)	204 (3)
Inherited abnormalities of platelets	38 (<1)	11 (<1)	10 (<1)
Inherited disorders of metabolism	270 (1)	72 (1)	84 (1)
Histiocytic disorders	354 (1)	93 (1)	78 (1)
Autoimmune disorders	16 (<1)	9 (<1)	5 (<1)
Other	44 (<1)	15 (<1)	20 (<1)
AML Disease status at transplant			
CR1	6997 (52)	2391 (54)	1108 (46)
CR2	2700 (20)	841 (19)	499 (21)
CR3+	259 (2)	73 (2)	53 (2)
Advanced or active disease	3459 (26)	1085 (24)	707 (29)
Missing	147 (1)	41 (1)	47 (2)
ALL Disease status at transplant			
CR1	2842 (48)	871 (52)	516 (42)
CR2	1699 (29)	456 (27)	358 (29)
CR3+	482 (8)	127 (8)	118 (10)
Advanced or active disease	798 (14)	206 (12)	206 (17)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	45 (1)	14 (1)	33 (3)
MDS Disease status at transplant			
Early	1299 (20)	383 (17)	236 (23)
Advanced	4769 (73)	1811 (78)	644 (63)
Missing	465 (7)	121 (5)	140 (14)
NHL Disease status at transplant			
CR1	483 (13)	173 (17)	69 (11)
CR2	684 (19)	177 (18)	101 (17)
CR3+	316 (9)	86 (9)	51 (8)
PR	431 (12)	108 (11)	78 (13)
Advanced	1711 (47)	451 (45)	294 (49)
Missing	46 (1)	8 (1)	10 (2)
Recipient age at transplant			
0-9 years	3515 (9)	937 (8)	943 (13)
10-19 years	3639 (9)	969 (8)	867 (12)
20-29 years	4192 (11)	1199 (10)	907 (12)
30-39 years	4637 (12)	1282 (10)	950 (13)
40-49 years	6197 (16)	1806 (15)	1185 (16)
50-59 years	8253 (21)	2481 (20)	1335 (18)
60-69 years	7889 (20)	2914 (24)	1114 (15)
70+ years	1476 (4)	671 (5)	163 (2)
Median (Range)	47 (0-84)	50 (0-79)	41 (0-79)
Recipient race/ethnicity			
Caucasian, non-Hispanic	33122 (86)	10232 (86)	5529 (85)
African-American, non-Hispanic	1831 (5)	516 (4)	319 (5)
Asian, non-Hispanic	883 (2)	399 (3)	267 (4)
Pacific islander, non-Hispanic	53 (<1)	19 (<1)	16 (<1)
Native American, non-Hispanic	147 (<1)	54 (<1)	26 (<1)
Hispanic	2375 (6)	631 (5)	339 (5)
Other	44 (<1)	26 (<1)	21 (<1)
Unknown	1343 (N/A)	382 (N/A)	947 (N/A)
Recipient sex			
Male	23241 (58)	7205 (59)	4411 (59)
Female	16557 (42)	5054 (41)	3053 (41)
Karnofsky score			
10-80	13300 (33)	4420 (36)	2281 (31)
90-100	24957 (63)	7241 (59)	4624 (62)
Missing	1541 (4)	598 (5)	559 (7)
HLA-A B DRB1 groups - low resolution			
<=3/6	22 (<1)	32 (<1)	1 (<1)
4/6	216 (1)	83 (1)	35 (1)
5/6	5551 (14)	1458 (14)	1056 (15)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
6/6	33446 (85)	9188 (85)	5845 (84)
Unknown	563 (N/A)	1498 (N/A)	527 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	845 (2)	81 (1)	32 (1)
6/8	1667 (4)	115 (1)	125 (3)
7/8	7742 (20)	1454 (18)	1030 (22)
8/8	28076 (73)	6626 (80)	3395 (74)
Unknown	1468 (N/A)	3983 (N/A)	2882 (N/A)
HLA-DPB1 Match			
Double allele mismatch	9305 (30)	759 (24)	381 (28)
Single allele mismatch	16827 (54)	1585 (51)	711 (52)
Full allele matched	5008 (16)	779 (25)	273 (20)
Unknown	8658 (N/A)	9136 (N/A)	6099 (N/A)
High resolution release score			
No	11077 (28)	12118 (99)	7291 (98)
Yes	28721 (72)	141 (1)	173 (2)
KIR typing available			
No	26106 (66)	12174 (99)	7425 (99)
Yes	13692 (34)	85 (1)	39 (1)
Graft type			
Marrow	14829 (37)	4153 (34)	3357 (45)
PBSC	24923 (63)	7973 (65)	4081 (55)
BM+PBSC	11 (<1)	6 (<1)	2 (<1)
PBSC+UCB	19 (<1)	117 (1)	2 (<1)
Others	16 (<1)	10 (<1)	22 (<1)
Conditioning regimen			
Myeloablative	25417 (64)	7348 (60)	4974 (67)
RIC/Nonmyeloablative	14204 (36)	4868 (40)	2389 (32)
TBD	177 (<1)	43 (<1)	101 (1)
Donor age at donation			
To Be Determined/NA	235 (1)	1392 (11)	77 (1)
0-9 years	6 (<1)	29 (<1)	1 (<1)
10-19 years	1105 (3)	397 (3)	157 (2)
20-29 years	17569 (44)	5031 (41)	2819 (38)
30-39 years	11434 (29)	3099 (25)	2318 (31)
40-49 years	7230 (18)	1763 (14)	1581 (21)
50+ years	2219 (6)	548 (4)	511 (7)
Median (Range)	31 (0-69)	30 (0-109)	33 (7-67)
Donor/Recipient CMV serostatus			
+/+	9790 (25)	3362 (28)	1809 (25)
+/-	4731 (12)	1591 (13)	939 (13)
-/+	13067 (33)	3680 (31)	2305 (32)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
-/-	11653 (30)	3208 (27)	2043 (29)
CB - recipient +	1 (<1)	11 (<1)	0
CB - recipient -	1 (<1)	4 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Unknown	555 (N/A)	402 (N/A)	368 (N/A)
GvHD Prophylaxis			
Ex vivo T-cell depletion	1114 (3)	288 (2)	309 (4)
CD34 selection	723 (2)	313 (3)	127 (2)
Post-CY + other(s)	1071 (3)	643 (5)	171 (2)
Post-CY alone	72 (<1)	31 (<1)	19 (<1)
Tacrolimus + MMF +- others	4732 (12)	1276 (10)	619 (8)
Tacrolimus + MTX +- others (except MMF)	17262 (43)	5492 (45)	2083 (28)
Tacrolimus + others (except MTX, MMF)	2077 (5)	794 (6)	297 (4)
Tacrolimus alone	962 (2)	327 (3)	120 (2)
CSA + MMF +- others (except Tacrolimus)	2654 (7)	637 (5)	613 (8)
CSA + MTX +- others (except Tacrolimus, MMF)	6541 (16)	1701 (14)	2276 (30)
CSA + others (except Tacrolimus, MTX, MMF)	996 (3)	303 (2)	286 (4)
CSA alone	466 (1)	115 (1)	293 (4)
Other GVHD prophylaxis	702 (2)	218 (2)	123 (2)
Missing	426 (1)	121 (1)	128 (2)
Donor/Recipient sex match			
Male-Male	16408 (41)	4862 (40)	2936 (40)
Male-Female	10010 (25)	2981 (25)	1703 (23)
Female-Male	6681 (17)	2171 (18)	1421 (19)
Female-Female	6450 (16)	1941 (16)	1307 (18)
CB - recipient M	10 (<1)	68 (1)	0
CB - recipient F	12 (<1)	57 (<1)	2 (<1)
Unknown	227 (N/A)	179 (N/A)	95 (N/A)
Year of transplant			
1986-1990	349 (1)	45 (<1)	85 (1)
1991-1995	1795 (5)	448 (4)	619 (8)
1996-2000	3149 (8)	1111 (9)	902 (12)
2001-2005	5001 (13)	988 (8)	1437 (19)
2006-2010	9204 (23)	1853 (15)	1418 (19)
2011-2015	12925 (32)	3555 (29)	1805 (24)
2016-2019	7375 (19)	4259 (35)	1198 (16)
Follow-up among survivors, Months			
N Eval	17027	5940	3016
Median (Range)	60 (0-365)	36 (0-336)	49 (1-350)

Unrelated Cord Blood Transplant Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and cord blood only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006-recipient only), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	5444	1351	1276
Source of data			
CRF	4129 (76)	1025 (76)	858 (67)
TED	1315 (24)	326 (24)	418 (33)
Number of centers	146	132	195
Disease at transplant			
AML	2044 (38)	451 (33)	409 (32)
ALL	1121 (21)	287 (21)	289 (23)
Other leukemia	91 (2)	26 (2)	24 (2)
CML	117 (2)	33 (2)	31 (2)
MDS	520 (10)	143 (11)	106 (8)
Other acute leukemia	85 (2)	18 (1)	22 (2)
NHL	378 (7)	83 (6)	85 (7)
Hodgkins Lymphoma	92 (2)	25 (2)	22 (2)
Plasma Cell Disorders, MM	35 (1)	10 (1)	7 (1)
Other malignancies	10 (<1)	0	1 (<1)
SAA	89 (2)	31 (2)	24 (2)
Inherited abnormalities erythrocyte diff fxn	157 (3)	48 (4)	31 (2)
SCIDs	236 (4)	71 (5)	97 (8)
Inherited abnormalities of platelets	17 (<1)	4 (<1)	5 (<1)
Inherited disorders of metabolism	332 (6)	93 (7)	84 (7)
Histiocytic disorders	100 (2)	26 (2)	33 (3)
Autoimmune disorders	9 (<1)	0	1 (<1)
Other	11 (<1)	2 (<1)	5 (<1)
AML Disease status at transplant			
CR1	1048 (51)	242 (54)	199 (49)
CR2	569 (28)	114 (25)	116 (28)
CR3+	50 (2)	6 (1)	12 (3)
Advanced or active disease	370 (18)	86 (19)	80 (20)
Missing	7 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	507 (45)	122 (43)	130 (45)
CR2	421 (38)	108 (38)	103 (36)
CR3+	120 (11)	39 (14)	31 (11)
Advanced or active disease	72 (6)	18 (6)	25 (9)
Missing	1 (<1)	0	0

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
MDS Disease status at transplant			
Early	163 (31)	36 (26)	48 (46)
Advanced	323 (62)	99 (70)	46 (44)
Missing	33 (6)	6 (4)	11 (10)
NHL Disease status at transplant			
CR1	59 (16)	5 (6)	16 (19)
CR2	71 (19)	18 (22)	24 (29)
CR3+	42 (11)	10 (12)	9 (11)
PR	65 (17)	12 (14)	11 (13)
Advanced	138 (37)	37 (45)	23 (27)
Missing	0	1 (1)	1 (1)
Recipient age at transplant			
0-9 years	1635 (30)	499 (37)	474 (37)
10-19 years	705 (13)	145 (11)	175 (14)
20-29 years	515 (9)	96 (7)	104 (8)
30-39 years	526 (10)	119 (9)	123 (10)
40-49 years	578 (11)	132 (10)	116 (9)
50-59 years	763 (14)	163 (12)	150 (12)
60-69 years	629 (12)	170 (13)	125 (10)
70+ years	93 (2)	27 (2)	9 (1)
Median (Range)	27 (0-83)	23 (0-77)	19 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	3033 (59)	802 (62)	704 (62)
African-American, non-Hispanic	783 (15)	181 (14)	147 (13)
Asian, non-Hispanic	315 (6)	85 (7)	81 (7)
Pacific islander, non-Hispanic	27 (1)	3 (<1)	14 (1)
Native American, non-Hispanic	36 (1)	6 (<1)	13 (1)
Hispanic	981 (19)	208 (16)	174 (15)
Other	0	1 (<1)	1 (<1)
Unknown	269 (N/A)	65 (N/A)	142 (N/A)
Recipient sex			
Male	3007 (55)	783 (58)	736 (58)
Female	2437 (45)	568 (42)	540 (42)
Karnofsky score			
10-80	1408 (26)	332 (25)	311 (24)
90-100	3885 (71)	928 (69)	886 (69)
Missing	151 (3)	91 (7)	79 (6)
HLA-A B DRB1 groups - low resolution			
<=3/6	73 (1)	33 (3)	8 (1)
4/6	2139 (41)	433 (41)	444 (37)
5/6	2324 (45)	430 (41)	566 (48)
6/6	666 (13)	150 (14)	168 (14)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	242 (N/A)	305 (N/A)	90 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	2560 (56)	440 (57)	510 (54)
6/8	1104 (24)	172 (22)	237 (25)
7/8	621 (14)	101 (13)	134 (14)
8/8	304 (7)	53 (7)	70 (7)
Unknown	855 (N/A)	585 (N/A)	325 (N/A)
HLA-DPB1 Match			
Double allele mismatch	725 (40)	55 (41)	55 (37)
Single allele mismatch	924 (51)	67 (50)	76 (52)
Full allele matched	169 (9)	12 (9)	16 (11)
Unknown	3626 (N/A)	1217 (N/A)	1129 (N/A)
High resolution release score			
No	3954 (73)	1301 (96)	1262 (99)
Yes	1490 (27)	50 (4)	14 (1)
KIR typing available			
No	4194 (77)	1345 (>99)	1264 (99)
Yes	1250 (23)	6 (<1)	12 (1)
Graft type			
UCB	5135 (94)	1234 (91)	1213 (95)
BM+UCB	1 (<1)	0	0
PBSC+UCB	279 (5)	117 (9)	54 (4)
Others	29 (1)	0	9 (1)
Number of cord units			
1	4572 (84)	0	1066 (84)
2	870 (16)	0	210 (16)
3	2 (<1)	0	0
Unknown	0 (N/A)	1351 (N/A)	0 (N/A)
Conditioning regimen			
Myeloablative	3579 (66)	870 (64)	828 (65)
RIC/Nonmyeloablative	1855 (34)	476 (35)	444 (35)
TBD	10 (<1)	5 (<1)	4 (<1)
Donor age at donation			
To Be Determined/NA	173 (3)	86 (6)	72 (6)
0-9 years	4843 (89)	1055 (78)	1117 (88)
10-19 years	254 (5)	116 (9)	51 (4)
20-29 years	50 (1)	30 (2)	6 (<1)
30-39 years	50 (1)	29 (2)	13 (1)
40-49 years	33 (1)	16 (1)	5 (<1)
50+ years	41 (1)	19 (1)	12 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-72)
Donor/Recipient CMV serostatus			

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
+/+	1259 (23)	273 (20)	260 (20)
+/-	543 (10)	129 (10)	116 (9)
-/+	1011 (19)	249 (18)	238 (19)
-/-	681 (13)	165 (12)	173 (14)
CB - recipient +	1112 (20)	285 (21)	246 (19)
CB - recipient -	755 (14)	201 (15)	198 (16)
CB - recipient CMV unknown	83 (2)	49 (4)	45 (4)
GvHD Prophylaxis			
Ex vivo T-cell depletion	28 (1)	9 (1)	4 (<1)
CD34 selection	219 (4)	93 (7)	45 (4)
Post-CY + other(s)	7 (<1)	6 (<1)	2 (<1)
Tacrolimus + MMF +- others	1476 (27)	357 (26)	210 (16)
Tacrolimus + MTX +- others (except MMF)	202 (4)	53 (4)	57 (4)
Tacrolimus + others (except MTX, MMF)	213 (4)	55 (4)	48 (4)
Tacrolimus alone	135 (2)	43 (3)	23 (2)
CSA + MMF +- others (except Tacrolimus)	2549 (47)	557 (41)	636 (50)
CSA + MTX +- others (except Tacrolimus, MMF)	93 (2)	27 (2)	38 (3)
CSA + others (except Tacrolimus, MTX, MMF)	313 (6)	109 (8)	138 (11)
CSA alone	56 (1)	16 (1)	44 (3)
Other GVHD prophylaxis	127 (2)	16 (1)	19 (1)
Missing	26 (<1)	10 (1)	12 (1)
Donor/Recipient sex match			
CB - recipient M	3007 (55)	783 (58)	734 (58)
CB - recipient F	2437 (45)	568 (42)	540 (42)
CB - recipient sex unknown	0	0	2 (<1)
Year of transplant			
1996-2000	0	2 (<1)	4 (<1)
2001-2005	105 (2)	82 (6)	30 (2)
2006-2010	1757 (32)	406 (30)	438 (34)
2011-2015	2574 (47)	494 (37)	575 (45)
2016-2019	1008 (19)	367 (27)	229 (18)
Follow-up among survivors, Months			
N Eval	2649	729	653
Median (Range)	60 (1-168)	47 (3-192)	51 (1-217)

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and donor only samples, Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006), Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	7714	1121	483
Source of data			
CRF	2971 (39)	349 (31)	219 (45)
TED	4743 (61)	772 (69)	264 (55)
Number of centers	86	68	52
Disease at transplant			
AML	2519 (33)	367 (33)	140 (29)
ALL	1219 (16)	215 (19)	83 (17)
Other leukemia	170 (2)	30 (3)	18 (4)
CML	256 (3)	26 (2)	11 (2)
MDS	1294 (17)	182 (16)	85 (18)
Other acute leukemia	102 (1)	16 (1)	3 (1)
NHL	747 (10)	102 (9)	65 (13)
Hodgkins Lymphoma	161 (2)	24 (2)	18 (4)
Plasma Cell Disorders, MM	230 (3)	33 (3)	18 (4)
Other malignancies	21 (<1)	0	0
Breast cancer	1 (<1)	0	0
SAA	346 (4)	40 (4)	13 (3)
Inherited abnormalities erythrocyte diff fxn	413 (5)	51 (5)	18 (4)
SCIDs	160 (2)	28 (2)	7 (1)
Inherited abnormalities of platelets	9 (<1)	0	0
Inherited disorders of metabolism	12 (<1)	2 (<1)	1 (<1)
Histiocytic disorders	38 (<1)	5 (<1)	2 (<1)
Autoimmune disorders	7 (<1)	0	1 (<1)
Other	9 (<1)	0	0
AML Disease status at transplant			
CR1	1570 (62)	243 (66)	86 (61)
CR2	391 (16)	42 (11)	15 (11)
CR3+	28 (1)	6 (2)	1 (1)
Advanced or active disease	520 (21)	73 (20)	36 (26)
Missing	10 (<1)	3 (1)	2 (1)
ALL Disease status at transplant			
CR1	765 (63)	136 (63)	56 (67)
CR2	326 (27)	49 (23)	16 (19)
CR3+	62 (5)	9 (4)	6 (7)
Advanced or active disease	66 (5)	20 (9)	5 (6)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Missing	0	1 (<1)	0
MDS Disease status at transplant			
Early	203 (16)	21 (12)	16 (19)
Advanced	1051 (81)	151 (83)	67 (79)
Missing	40 (3)	10 (5)	2 (2)
NHL Disease status at transplant			
CR1	126 (17)	19 (19)	11 (17)
CR2	141 (19)	20 (20)	11 (17)
CR3+	84 (11)	9 (9)	2 (3)
PR	65 (9)	13 (13)	7 (11)
Advanced	324 (44)	40 (40)	34 (52)
Missing	2 (<1)	0	0
Recipient age at transplant			
0-9 years	754 (10)	91 (8)	27 (6)
10-19 years	866 (11)	90 (8)	39 (8)
20-29 years	632 (8)	123 (11)	41 (8)
30-39 years	589 (8)	98 (9)	43 (9)
40-49 years	1006 (13)	150 (13)	66 (14)
50-59 years	1785 (23)	253 (23)	115 (24)
60-69 years	1817 (24)	278 (25)	139 (29)
70+ years	265 (3)	38 (3)	13 (3)
Median (Range)	50 (0-78)	50 (0-76)	53 (0-77)
Recipient race/ethnicity			
Caucasian, non-Hispanic	4973 (67)	622 (59)	323 (70)
African-American, non-Hispanic	906 (12)	118 (11)	45 (10)
Asian, non-Hispanic	342 (5)	90 (9)	20 (4)
Pacific islander, non-Hispanic	26 (<1)	3 (<1)	1 (<1)
Native American, non-Hispanic	29 (<1)	2 (<1)	1 (<1)
Hispanic	1119 (15)	214 (20)	71 (15)
Unknown	319 (N/A)	72 (N/A)	22 (N/A)
Recipient sex			
Male	4528 (59)	665 (59)	285 (59)
Female	3186 (41)	456 (41)	198 (41)
Karnofsky score			
10-80	2680 (35)	462 (41)	194 (40)
90-100	4846 (63)	628 (56)	266 (55)
Missing	188 (2)	31 (3)	23 (5)
Graft type			
Marrow	2221 (29)	259 (23)	137 (28)
PBSC	5443 (71)	841 (75)	336 (70)
BM+PBSC	6 (<1)	4 (<1)	0
BM+UCB	26 (<1)	7 (1)	1 (<1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
PBSC+UCB	0	0	8 (2)
Others	18 (<1)	10 (1)	0
Conditioning regimen			
Myeloablative	4418 (57)	649 (58)	257 (53)
RIC/Nonmyeloablative	3256 (42)	464 (41)	220 (46)
TBD	40 (1)	8 (1)	6 (1)
Donor age at donation			
To Be Determined/NA	18 (<1)	4 (<1)	3 (1)
0-9 years	535 (7)	60 (5)	21 (4)
10-19 years	770 (10)	95 (8)	38 (8)
20-29 years	980 (13)	151 (13)	60 (12)
30-39 years	1004 (13)	178 (16)	79 (16)
40-49 years	1247 (16)	185 (17)	69 (14)
50+ years	3160 (41)	448 (40)	213 (44)
Median (Range)	45 (0-81)	44 (0-79)	46 (0-76)
Donor/Recipient CMV serostatus			
+/+	3114 (41)	509 (46)	201 (43)
+/-	872 (11)	87 (8)	48 (10)
-/+	1890 (25)	264 (24)	110 (24)
-/-	1719 (23)	239 (22)	104 (22)
Unknown	119 (N/A)	22 (N/A)	20 (N/A)
GvHD Prophylaxis			
Ex vivo T-cell depletion	93 (1)	28 (2)	8 (2)
CD34 selection	123 (2)	32 (3)	9 (2)
Post-CY + other(s)	1568 (20)	215 (19)	107 (22)
Post-CY alone	34 (<1)	8 (1)	3 (1)
Tacrolimus + MMF +- others	793 (10)	70 (6)	27 (6)
Tacrolimus + MTX +- others (except MMF)	3165 (41)	392 (35)	217 (45)
Tacrolimus + others (except MTX, MMF)	619 (8)	224 (20)	49 (10)
Tacrolimus alone	64 (1)	6 (1)	2 (<1)
CSA + MMF +- others (except Tacrolimus)	206 (3)	27 (2)	7 (1)
CSA + MTX +- others (except Tacrolimus, MMF)	623 (8)	76 (7)	31 (6)
CSA + others (except Tacrolimus, MTX, MMF)	80 (1)	9 (1)	2 (<1)
CSA alone	68 (1)	9 (1)	1 (<1)
Other GVHD prophylaxis	118 (2)	12 (1)	8 (2)
Missing	160 (2)	13 (1)	12 (2)
Donor/Recipient sex match			
Male-Male	2525 (33)	399 (36)	159 (33)
Male-Female	1662 (22)	219 (20)	97 (20)
Female-Male	1978 (26)	253 (23)	120 (25)
Female-Female	1516 (20)	233 (21)	97 (20)
CB - recipient M	20 (<1)	12 (1)	6 (1)

Variable	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
CB - recipient F	8 (<1)	4 (<1)	4 (1)
Unknown	5 (N/A)	1 (N/A)	0 (N/A)
Year of transplant			
2006-2010	570 (7)	66 (6)	49 (10)
2011-2015	3617 (47)	469 (42)	194 (40)
2016-2019	3527 (46)	586 (52)	240 (50)
Follow-up among survivors, Months			
N Eval	4876	688	306
Median (Range)	33 (1-131)	24 (2-124)	26 (2-124)

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Late Effects and Quality of Life Working Committee Members

FROM: Bronwen Shaw, MBChB, MRCP, PhD, Scientific Director for the Late Effects and Quality of Life Working Committee; Rachel Phelan, MD, Assistant Scientific Director for the Late Effects and Quality of Life Working Committee

RE: Studies in Progress Summary

LE99-01: Quality of life in late HCT survivors (J Wingard) This is an ongoing project examining quality of life and social relationships of hematopoietic transplant survivors. Several manuscripts have already been produced. One final manuscript including a methodological analysis is in preparation.

LE12-03: Solid organ transplant after HCT (M Gupta/PL Abt/M Levine) This study aims to report outcomes of solid organ transplantation in HCT recipients and compare survival. The data derives from both CIBMTR and OPTN (UNOS) databases. After presentation at the stats meeting a decision was made to update the data with contemporary cases. New data was requested from UNOS in 2017. The study is in analysis and will be in manuscript prep by July 2020. TCT Poster Presentation during Session I on Wednesday, February 19th from 6:30pm to 8:00pm. Update to be given at meeting.

LE13-02: Risk factors for melanoma following allogeneic hematopoietic stem cell transplantation (M Herr/L Morton) This study will identify risk factors of developing melanoma and assess the clinical burden of melanoma in patients who received allogeneic HCT. The analysis was completed externally at the NCI. This study was published in Journal of the American Academy of Dermatology.
Herr MM, Curtis RE, Tucker MA, Tecca HR, Engels EA, Cahoon EK, Battiwalla M, Buchbinder D, Flowers ME, Brazauskas R, Shaw BE, Morton LM. Risk factors for the development of cutaneous melanoma after allogeneic hematopoietic cell transplantation. Journal of the American Academy of Dermatology. doi:10.1016/j.jaad.2019.10.034. Epub 2019 Oct 22.

LE16-02: An investigation of new malignant neoplasms in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation for non-malignant diseases (JM Kahn/P Satwani) This study is analyzing new cancers and late effects in children, adolescents, and young adults undergoing allogeneic hematopoietic cell transplantation for non-malignant diseases. The manuscript has been submitted.

LE17-01: Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) This study aims to describe incidence of late effects after HCT for sickle cell disease (SCD) and compare survival to a non-HCT cohort of SCD patients. The data for the transplant cohort has been prepared, and work will begin soon on matching the non-transplant cohort to the transplant cohort. This study was presented at ASH in 2019 and will be in manuscript preparation in July 2020. Update to be given at meeting.

LE17-02: Comparison of late effects among alloHCT survivors conditioned with high dose TBI versus non-TBI based ablative regimens in AYA with acute leukemia (S Lee/L Muffly) This study compared

subsequent malignancies and late effects after HCT in patients that received a TBI-containing regimen versus a non-TBI regimen. This study has been submitted.

LE18-01: Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) This study aims to evaluate trends in late mortality rates in children and young adults with hematologic malignancies. The study is in protocol development and will be in analysis by July 2020. Update to be given at meeting.

LE18-02: Post-transplant Employment/ Student Status of Survivors of Young Adult (YA) Allogeneic Hematopoietic Cell Transplant (N Bhatt/R Salit/K Syrjala/BE Shaw) This study aims to describe the return to school or work status of the survivors of hematopoietic cell transplant performed in young adult age group (18-39). This study was presented at ASH in 2019. The study is in manuscript preparation and will be submitted by July 2020. Update to be given at meeting.

LE19-01: Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) This study aims to analyze the risk for developing critical illness, model long-term survival and analyze long-term morbidity in critically ill patients within the pediatric alloHCT population by utilizing both CIBMT and VPS (Virtual Pediatric Systems) data. The study will build on a previous CIBMTR study cohort (RT14-03) but has a different set of aims. This study is currently in protocol development and will be in analysis by July 2020.

LE19-02: Incidence and predictors of long term toxicities and late side effects in elderly patients (>=50 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) This study will evaluate the incidence of late effects within the elderly population and evaluate the associated between age and cGVHD with the development of late effects. This study is in protocol development and will be in data file preparation by July 2020.

Proposal: 1911-23

Title:
Influence of Busulfan based vs melphalan based Chemo regimens on early and late cardiac toxicity post SCT

Farhan Shatha, MD, Sfarhan1@hfhs.org, Henry Ford Health system

Hypothesis:
Melphalan based Chemo therapy more cardiotoxic than busulfan based

Specific aims:
- rates of arrhythmias post SCT Mel vs bu based regimens early and late
- rates of heart failure post SCT Mel vs bu based regimens early and late

Scientific justification:
Making decisions regarding chemo regimen before stem cell transplant including taking disease risk and Pt risks into consideration but also toxicity. Cardiovascular disease and cardiovascular complications are one of the most common complications associated with HSCT. These complications can occur both acutely within the first 100 days as well as long-term, many years after the initial transplantation period. Prior studies report that 9–27 % of persons receiving HSCT develop arrhythmias, while other more recently published single institutions have reported incidences as low as 1 %.. The most common arrhythmias include atrial fibrillation, atrial flutter, and supraventricular tachycardia. Most studies were small but no large data about comparing the two major based regimens used

Patient eligibility population:
Patients with AML ALL MDS MPN lymphoid malignancies
Matched related and Matched and mismatched unrelated donors
Year of HSCT >=2008
HSCT with Bu based and Mel based regimens without RT or Cy

Data requirements:
This study will use the following forms:
Acute Myelogenous Leukemia, ALL and MDS/MPN and lymphoid malignancies Pre-HSCT Data
Acute Myelogenous Leukemia, ALL and MDS/MPN and lymphoid malignancies Post-HSCT Data
Pre-Transplant Essential Data
Post-transplant Essential data
List of Variables needed: Age of patient at diagnosis, gender of patient and donor, date of diagnosis, date of HSCT, Donor type, comorbidities before sct, conditioning regimen, GVHD prophylaxis, date of death, date of last follow up, post sct cardiac events and dates as in the pot sct form

Sample requirements:
None

Study design:
Data will be collected and analyzed. We will retrospectively reviewed patients who had-HSCT since year 2005 to treat Hematological malignancies and decided into 2 groups Bu based vs Mel based.

Objectives are to explore
Demographics, disease-related and transplant-related variables mentioned above will be collected and compared

Non-CIBMTR data source:
None

References:
1. Blaes et al Cardiovascular Complications of Hematopoietic Stem Cell Transplantation

First alloHCT (including prior autoHCT) for all malignancies except solid tumors between 2008-2018[a]

Characteristic	N (%)
No. of patients	26935
Age - no. (%)	
Median (min-max)	53.02 (0.05-87.77)
<18	3296 (12.2)
18-29	2504 (9.3)
30-39	2386 (8.9)
40-49	3672 (13.6)
50-59	6258 (23.2)
60-69	7278 (27)
70-79	1531 (5.7)
>=80	10 (0)
Sex - no. (%)	
Male	15838 (58.8)
Female	11097 (41.2)
Race - no. (%)	
Caucasian	21391 (79.4)
African-American	2184 (8.1)
Asian	1613 (6)
Pacific islander	146 (0.5)
Native American	163 (0.6)
Other	1 (0)
More than one race	253 (0.9)
Missing	1184 (4.4)
Performance score - no. (%)	
90-100%	16646 (61.8)
< 90%	9798 (36.4)
Missing	491 (1.8)
HCT-CI - no. (%)	
0	8494 (31.5)
1	3669 (13.6)
2	3407 (12.6)
3+	10656 (39.6)
TBD, review needed for history of malignancies	16 (0.1)
TBD, inconsistencies between parent and sub-questions	4 (0)
NA, f2400 (pre-TED) not completed	373 (1.4)
Missing	316 (1.2)
Country - no. (%)	
United States	23975 (89)
International (not EU)	2297 (8.5)
European Union	663 (2.5)
Disease - no. (%)	

Characteristic	N (%)
AML	10120 (37.6)
ALL	3998 (14.8)
Other leukemia	855 (3.2)
CML	855 (3.2)
MDS	7574 (28.1)
Other acute leukemia	309 (1.1)
NHL	2131 (7.9)
HD	553 (2.1)
PCD/MM	540 (2)
Conditioning regimen intensity - no. (%)	
MAC	14249 (52.9)
RIC	7979 (29.6)
NMA	3464 (12.9)
TBD	609 (2.3)
Missing	634 (2.4)
Conditioning regimen - no. (%)	
TBI/Cy	2827 (10.5)
TBI/Cy/Flu	3971 (14.7)
TBI/Cy/Flu/TT	222 (0.8)
TBI/Cy/TT	354 (1.3)
TBI/Cy/VP	232 (0.9)
TBI/VP	419 (1.6)
TBI/Mel	505 (1.9)
TBI/Flu	1909 (7.1)
TBI/other(s)	219 (0.8)
Bu/Cy/Mel	113 (0.4)
Bu/Cy	3403 (12.6)
Bu/Mel	307 (1.1)
Flu/Bu/TT	210 (0.8)
Flu/Bu	6563 (24.4)
Flu/Mel/TT	258 (1)
Flu/Mel	3389 (12.6)
FCR	164 (0.6)
Cy/Flu	238 (0.9)
Cy alone	11 (0)
CBV	24 (0.1)
BEAM	151 (0.6)
BEAM like	6 (0)
Mel alone	75 (0.3)
Mel/other(s)	82 (0.3)
Treosulfan	225 (0.8)
TLI	183 (0.7)

Characteristic	N (%)
Other(s)	311 (1.2)
None	37 (0.1)
Missing	527 (2)
Graft type - no. (%)	
Bone marrow	4237 (15.7)
Peripheral blood	17939 (66.6)
Cord blood	4702 (17.5)
Other	57 (0.2)
Donor - no. (%)	
HLA-identical sibling (may include non-monozygotic twin)	6409 (23.8)
Syngeneic (monozygotic twin)	236 (0.9)
Other relative	2 (0)
Unrelated donor	16417 (61)
HLA-matched other relative	347 (1.3)
HLA-mismatched relative	3317 (12.3)
HLA-mis. matched unrelated	1 (0)
Missing	206 (0.8)
Year of transplant - no. (%)	
2008	3018 (11.2)
2009	2726 (10.1)
2010	1855 (6.9)
2011	1309 (4.9)
2012	1350 (5)
2013	2533 (9.4)
2014	3170 (11.8)
2015	2987 (11.1)
2016	2863 (10.6)
2017	2696 (10)
2018	2428 (9)
Follow-up - median (min-max)	48.45 (0.03-132.86)
Congestive heart failure [b] - no. (%)	
No	25739 (95.6)
Yes - Pediatric	57 (0.2)
Yes - Adult	752 (2.8)
Missing	387 (1.4)

[a] Selections based on donor and conditioning regimen have not yet been applied

[b] Between 2008-2016 CHF is defined using EF <40%, and beginning 2017 EF is not included in definition for CHF.

Proposal: 1911-30

Title:
Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant

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Research hypothesis:
Expression of the conserved transcriptional response to adversity (CTRA) gene profile will be associated with patient-reported outcomes (PROs) and clinical outcomes among allogeneic hematopoietic cell transplant (HCT) recipients.

Specific aims:
- Describe associations between PROs (as measured by the SF-36, FACT-BMT, and PedsQL) and CTRA gene expression among pediatric and adult allogeneic HCT recipients
- Explore the relationship between the same PROs, CTRA gene expression, and meaningful clinical outcomes including relapse free survival (RFS, primary outcome) time to neutrophil engraftment, acute and chronic graft-versus-host disease (a/cGVHD), and overall survival (OS)

Scientific impact:
This study will investigate the role of a specific pre-transplant molecular profile in the association between PROs (composite and psychosocial/mental component summary subscales) and clinical outcomes. This mechanistic understanding of the interrelated PRO and medical outcomes will help identify patients at risk for poor outcomes and facilitate the development and dissemination of targeted interventions in the HCT population.

Scientific justification:
Patient-reported outcomes (PROs) have been shown to *independently* predict general cancer outcomes, including incidence, recurrence, and mortality.[1] This association between PROs and biomedical outcomes is apparent following hematopoietic cell transplant (HCT) as well. Studies of autologous HCT recipients have demonstrated greater optimism and lower anxiety was associated with accelerated neutrophil engraftment following transplant.[2] Additionally, pre-transplant depression has been associated with lower overall survival and higher risk of acute GVHD among allogeneic HCT recipients.[3] A recent analysis of CIBMTR data confirmed a significant relationship between baseline PRO data and survival following allogeneic HCT. After adjusting for patient-, disease-, and transplant-related risk factors, patients in the highest quartile for PRO scores had a 20% increase in 1-year survival compared to the lowest PRO quartile.[4] It is clear that psychosocial and environmental factors influence cancer biology, and may be particularly salient in the HCT population.[5] However, there is a gap in our understanding of how these biobehavioral relationships emerge.
It has been previously demonstrated through translational and clinical research that a subset of psychological risk factors plays a role in the development and progression of cancer. The stress response, through neuroimmune and endocrine pathways, causes downstream alterations in molecular signaling

profiles that result in dysregulated immune and nervous system function.[6] One such profile, called the Conserved Transcriptional Response to Adversity (CTRA), includes 53 genes involved in general inflammation, Type I interferon activity, and antibody production. Previous studies have shown that circulating immune cells show a systematic shift in basal CTRA expression profiles during extended periods of stress, threat, or uncertainty consistent with the physiology of stress-associated illness.[7] Recently, Knight et al demonstrated that HCT recipients of lower socioeconomic status (higher stress) display significantly increased expression of the CTRA gene profile, **which was associated with increased risk of relapse and decreased disease free survival (DFS)**.[8,9] Modification of the CTRA profile can be accomplished through behavioral[11] or pharmacologic intervention. For example, ß-adrenergic antagonism can reduce CTRA gene expression and related transcriptome dynamics among HCT recipients.[10] Transcriptome profiles such as the CTRA are directly relevant to HCT outcomes because immune cell-mediated inflammation and antimicrobial responses contribute to a significant proportion of short- and long-term transplant related morbidity and mortality.

Psychosocial and environmental factors directly influence cancer biology and may be particularly important in the HCT population. Nevertheless, we are just beginning to understand the complex network of clinically relevant biobehavioral pathways, and there is a critical need to build this data in the transplant population. In order to successfully identify patients at risk for poor outcomes and provide targeted intervention, we need to first characterize the underlying mechanisms responsible for the interrelated psychological and medical outcomes. This project will begin this work by:

- Exploring the relationship between CTRA gene expression profile and PROs
- Evaluating the relationship between CTRA gene expression and meaningful clinical outcomes

<u>The proposed study would be the first to leverage centralized, parallel PRO and biospecimen data in a large cohort of allogeneic HCT recipients.</u> This will provide robust foundational data and feasibility information that will facilitate ongoing work in biobehavioral transplant research.

Patient eligibility population:

Patients >2 years old undergoing allogeneic HCT (malignant or nonmalignant) who completed at least baseline PRO measures prior to transplant with available pre-transplant banked biospecimens (whole blood, peripheral blood mononuclear cells (PBMCs), or dried blood spot samples). Eligible patients will be identified from cohort published by Shaw, et al.[4]

Data requirements:

No supplemental data collection is required for this study. Samples from NMDP Biorepository will be needed. External funding is being pursued for biospecimen analysis.

Sample requirements:

This study requires that each participant have a pre-transplant biospecimen available for analysis. Our team of investigators has worked together previously on similar analyses in CIBMTR projects, and have demonstrated the ability to proficiently and effectively carry out the proposed testing methodology.

Dr. Cole has extensive experience with the proposed testing methodology of assessing gene expression profiles in the above biospecimens. Gene expression profiling and related bioinformatics analyses will be conducted by the UCLA Social Genomics Core (Directed by Dr. Steve Cole, co-PI). This Core will conduct global gene expression profiling using RNA sequencing. In these studies, the quantitative level of expression (i.e., mRNA concentration within the cell sample) for each of the ~22,000 genes in the human genome will be evaluated, and genome-wide bioinformatics analyses will be applied to identify the potential functional implications and upstream gene regulatory influences on the observed PRO-related

differences in gene expression. Total RNA will be extracted from samples, subjected to quality assurance assays to test suitable mass (by spectroscopy) and integrity (by Agilent Bioanalyzer RNA Integrity Score) for analysis, converted to cDNA (Lexogen QuantSeq 3' FWD), and sequenced on an Illumina HiSeq 4000 instrument in the UCLA Neuroscience Genomics Core Laboratory using standard protocols. Analyses target >10 million reads/sample, which will be mapped to the reference human transcriptome and quantified as gene transcripts per million mapped reads using the STAR aligner. Transcript-per-million values will be log2 transformed (and potentially subject to an additional reference gene normalization if needed to achieve consistency) for analysis by standard linear statistical models relating gene expression levels to PROs while controlling for relevant covariates (age, sex, race/ethnicity, BMI, smoking history, heavy alcohol consumption history and relevant disease measures). Genes showing maximum likelihood point estimates of > 1.5-fold differential expression over the range of a target PRO will be forwarded to bioinformatics analyses involving Gene Ontology functional annotations and TELiS promoter-based bioinformatics analyses of transcription factor activity. In addition to targeting transcription factors identified a priori as relevant to the CTRA hypothesis, we will also conduct ancillary exploratory/discovery analyses to identify novel transcription factor associations (while controlling for multiple testing using standard False Discovery Rate corrections for potentially correlated hypotheses).

Study design:

There are a total of n=199 HCT recipients with baseline PRO measures and available biospecimens. This sample size is comparable to other similar prior studies looking at similar altered gene expression profiles in HCT (n=78 and n=261)[8,9] and larger than most studies evaluating similar relationships in other populations.[12-14] Using higher-order bioinformatics analyses, relatively small sample sizes can yield hundreds of differentially expressed genes that generate statistically significant results when evaluating gene expression as a function of psychosocial factors, as we are currently proposing.[15-17] Additional technical and strategies will be used to optimize study power (gene set analysis, targeted cell sampling). Thus, we anticipate the current sample size to be large enough to provide appropriate power to detect the associations we are evaluating. Final study power to be calculated in consultation with statistical genomics expert upon initial proposal acceptance and formal CIBMTR statistical consultation. Descriptive analyses of patient-, disease-, and transplant-related factors will be prepared. The tables will list median and range for continuous variables and percent of total for categorical variables. Association between PROs (as measured by SF-36, FACT-BMT, and PedsQL scores – both composite and relevant psychosocial wellbeing subscales) and CTRA gene expression will be tested using the Kruskal-Wallis test for continuous variable forms, the Chi-square test for categorical forms, and the Spearman rank correlation. The differences of 3-year RFS (primary outcome), time to neutrophil engraftment, prevalence of acute and chronic GVHD, and 1 and 3-year OS between patients of different CTRA gene expression levels and PRO scores will be compared using multivariate Cox proportional hazards model. The variables to be considered in the univariate (and multivariate when possible) models are listed in the supplemental document. A stepwise model selection approach will be used to identify all significant risk factors. Factors which are significant at a 5% level will be kept in the final model. The potential interactions between main effect and all significant risk factors will be tested. Results will be presented as hazard ratios with 95% confidence intervals. The functional form of the relationship between quantitative CTRA gene expression levels and outcome will be explored using splines and by examining Martingale residual plots, and if appropriate an optimal cut point will be identified. Interactions between CTRA expression and other covariates will be examined. The probabilities of 3-year RFS and 1 and 3-year OS based on CTRA will be described using the Kaplan-Meier method, and the probabilities of neutrophil engraftment and aGVHD and cGVHD will be assessed with the cumulative-incidence function method.

Non-CIBMTR data source:
No external data source is required.

Study Variables

Patient-related:

- Age at HCT: continuous
- Gender: Male vs Female
- Race: Caucasian vs African-American vs Other
- Body mass index (BMI): Underweight(<18.5 kg/m2) vs Normal(18.5-25 kg/m2) vs Overweight(25-30 kg/m2) vs Obese(≥30 kg/m2)
- Karnofsky/Lansky Performance Status (KPS, LPS) at the time of transplant: <90 vs. >90
- SF-36 composite score: continuous
    - Mental Component Score (MCS): continuous
- FACT-BMT composite score: continuous
    - Social/family Wellbeing (SWB): continuous
    - Emotional Wellbeing (EWB): continuous
    - BMT Domain: continuous
- PedsQL score: continuous
    - Emotional Functioning Scale: continuous
    - Social Functioning Scale: continuous

Disease-related:

- Indication for transplant: hematologic malignancy/MDS vs nonmalignant
- Previous autologous or allogeneic transplant: Yes vs No
- Number of transplants: continuous
- Time from diagnosis to transplant: days

Transplant-related:

- Graft type: BM vs. PBSC vs. cord blood
- Donor age
- Donor-recipient sex match: M-M vs. M-F vs. F-M vs. F-F
- Donor BMI: Underweight(<18.5 kg/m^2) vs Normal(18.5-25 kg/m^2) vs Overweight(25-30 kg/m^2) vs Obese(≥30 kg/m^2)
- CMV status of donor and recipient: +/+ vs. +/- vs. -/+ vs. -/-
- ABO incompatibility: Yes vs No
- Conditioning regimen: Busulfan-based vs. TBI-based vs. other
- GVHD prophylaxis: Tac + MMF ± others vs Tac + MTX ± others (no MMF) vs Tac + others (no MTX, MMF) vs Tac alone vs CSA + MMF ± others (no Tac) vs CSA + MTX ± others (no Tac, MMF) vs CSA + others (no Tac, MTX, MMF) vs CSA alone vs Other GVHD prophylaxis
- Year of transplant
- Median CD34 cell dose, x 10^6/kg
- Recipient zip code
- Donor zip code

Conflicts of interest:
None

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Table 1. Samples available for patients with quality of life data

Characteristic	Sample available for recipient and donor N (%)	Sample available for recipient only N (%)	Sample available for donor only N (%)	No samples N (%)
Number of patients	164	35	16	132
TED or CRF track				
TED	123 (75)	31 (89)	12 (75)	111 (84)
CRF	41 (25)	4 (11)	4 (25)	21 (16)
Recipient age				
< 10 yrs	32 (20)	7 (20)	3 (19)	14 (11)
10-19 yrs	20 (12)	5 (14)	1 (6)	6 (5)
20-29 yrs	11 (7)	5 (14)	0	13 (10)
30-39 yrs	13 (8)	0	2 (13)	9 (7)
40-49 yrs	13 (8)	5 (14)	3 (19)	19 (14)
50-59 yrs	30 (18)	5 (14)	3 (19)	39 (30)
>= 60 yrs	45 (27)	8 (23)	4 (25)	32 (24)
Recipient sex				
Male	96 (59)	18 (51)	10 (63)	75 (57)
Female	68 (41)	17 (49)	6 (38)	57 (43)
Race				
Caucasian	146 (89)	28 (80)	13 (81)	128 (97)
African-American	10 (6)	4 (11)	3 (19)	2 (2)
Asian	5 (3)	2 (6)	0	2 (2)
Unknown	3 (2)	1 (3)	0	0
Karnofsky/Lansky performance score				
90-100%	112 (68)	22 (63)	12 (75)	85 (64)
< 90%	52 (32)	13 (37)	4 (25)	47 (36)
Primary disease				
AML-acute myelogenous leukemia	47 (29)	11 (31)	4 (25)	49 (37)
ALL-acute lymphoblastic leukemia	18 (11)	4 (11)	3 (19)	21 (16)
Other leukemia	9 (5)	0	0	11 (8)
CML-chronic myelogenous leukemia	12 (7)	2 (6)	1 (6)	5 (4)
MDS-myelodysplastic-myeloproliferative disorder	23 (14)	6 (17)	2 (13)	22 (17)
Other acute leukemia	2 (1)	1 (3)	0	2 (2)
NHL-non-Hodgkin lymphoma	14 (9)	0	3 (19)	5 (4)
HD-Hodgkin lymphoma	4 (2)	0	0	2 (2)
MYE-plasma cell disorder, multiple myeloma	2 (1)	2 (6)	1 (6)	2 (2)
SAA-severe aplastic anemia	6 (4)	2 (6)	1 (6)	3 (2)
Inherited abnormality of erythrocyte differentiation or function	17 (10)	0	0	2 (2)
SCID & other immune system disorders	6 (4)	1 (3)	1 (6)	6 (5)
Inherited disorder of metabolism	1 (<1)	0	0	0
Histiocytic disorders	2 (1)	6 (17)	0	2 (2)

Characteristic	Sample available for recipient and donor N (%)	Sample available for recipient only N (%)	Sample available for donor only N (%)	No samples N (%)
Autoimmune diseases	1 (<1)	0	0	0
Graft type				
Bone marrow	46 (28)	14 (40)	3 (19)	25 (19)
Peripheral blood	93 (57)	18 (51)	6 (38)	101 (77)
Umbilical cord blood	25 (15)	3 (9)	7 (44)	6 (5)
Donor type				
HLA-identical sibling	8 (5)	1 (3)	0	103 (78)
Other related	4 (2)	0	0	4 (3)
Well-matched unrelated (8/8)	106 (65)	17 (49)	7 (44)	13 (10)
Partially-matched unrelated (7/8)	20 (12)	5 (14)	2 (13)	3 (2)
Unrelated, match unknown	1 (<1)	9 (26)	0	2 (2)
Cord blood	25 (15)	3 (9)	7 (44)	6 (5)
Missing	0	0	0	1 (<1)
Year of transplant				
2011	17 (10)	3 (9)	2 (13)	12 (9)
2012	108 (66)	23 (66)	13 (81)	96 (73)
2013	39 (24)	9 (26)	1 (6)	24 (18)
Recipient whole blood available				
No	1 (<1)	1 (3)	16	132
Yes	163 (99)	34 (97)	0	0
Recipient filter paper available				
No	0	1 (3)	16	132
Yes	164	34 (97)	0	0
Median follow-up (range), months	65 (11-79)	64 (16-74)	72 (56-82)	30 (6-40)

Proposal: 1911-59

Title:
New Cancers after Autologous Hematopoietic Cell Transplantation for Systemic Light-Chain Amyloidosis

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Hypothesis:
We hypothesize that patients undergoing autologous hematopoietic cell transplantation [AHCT] for systemic light-chain amyloidosis [AL] are at a higher risk of subsequent cancers compared to demographically matched healthy controls.

Specific aims:
In patients transplanted for systemic AL amyloidosis in the US between 1995 and 2017, we aim:
- To determine the incidence of new cancers [including hematologic and solid neoplasms] after AHCT for AL amyloidosis
- To identify patient-related, disease-related, and treatment-related risk factors for subsequent cancers after AHCT
- To compare the incidence rate of subsequent cancers in AL amyloidosis survivors with demographically matched healthy controls and patients with multiple myeloma [MM]

Scientific impact:
Outcomes after AHCT for systemic AL amyloidosis has improved over time, with 100-day mortality decreasing from 20% in 1995-2000 to 5% in 2007-2012[1]. This has translated into improved 5-year overall survival [OS], from 55% to 77% in respective time-periods[1]. Furthermore, a large single institution study has shown that approximately a third of patients transplanted between 1996 and 2003 were alive at the 15-year mark[2]. With improvement in plasma-cell and fibril-directed therapies along with optimal patient selection for transplant, early mortality will continue to decrease, potentially leading to a growing population of long-term AL amyloid survivors. One of the essential elements of survivorship care in this population is to characterize the risk of secondary cancers from cytotoxic chemotherapy [high dose melphalan] used for conditioning prior to AHCT. With improvement in non-cytotoxic plasma-cell directed therapies [e.g. monoclonal antibodies], identifying the risk of second cancers will be critical for informed decision making regarding front-line therapy for AL amyloidosis in future.

<u>The results of this study will potentially:</u>
- Characterize the incidence and nature of second cancers after AHCT for AL amyloidosis
- Identify risk-factors and timeline for development of second cancers, which can inform future guidelines on survivorship care in this population

Scientific justification:
Epidemiologic data show an approximately three-fold increase in the prevalence of AL amyloidosis survivors between 2007 and 2015[3] due to increasing OS in this population. Furthermore, patients undergoing AHCT had a sharp decrease in early mortality after 2010, with the 2-year OS estimate being 94% among patients transplanted between 2010 and 2014[4]. With post-transplant relapse rate in AL amyloidosis being significantly lower compared to that in MM, a large proportion of patients enjoy

prolonged treatment-free remission after AHCT. Hence, there is an unmet need for optimal survivorship care in this population and identify late effects which can lead to morbidity and mortality. In patients with MM who undergo AHCT, there is an increased risk of subsequent acute myeloid leukemia and melanoma compared to demographically matched healthy controls, with the independent risk-factors being obesity, male sex, and older age[5]. However, little is known regarding the risk of second cancers after AHCT for AL amyloidosis. In a Mayo Clinic study, second cancers were the cause of late death in 8% of transplanted patients at a median follow-up of 17 years[2]. Another study from the Boston University group showed metastatic malignancy and therapy-related myeloid neoplasms to be the cause of late death in 15% and 10% of transplanted patients respectively who had died after achieving a complete response without any evidence of subsequent hematologic relapse[6].
Unlike MM, a large proportion of patients with AL amyloidosis receive AHCT without any planned pre- or post-transplant therapy. In a study by the Center for International Blood and Marrow Transplant Research [CIBMTR], the proportion of patients who did not receive any pre-transplant therapy was 85% in 2001-2006 and 67% in 2007-2012 cohorts[1]. Furthermore, post-transplant maintenance with immunomodulatory drugs is not a standard of care in AL amyloidosis. Also, the biology underlying development of therapy-related secondary neoplasms may be different in AL amyloidosis. For example, treatment with lenalidomide in AL amyloidosis is not associated with an increase in incidence of secondary cancers unlike that in MM[7]. Hence, it could be easier to isolate the impact of AHCT on development of second cancers in AL amyloidosis due to a lower probability of contamination by other exposures. With the advent of effective non-stem cell toxic agents, including proteasome inhibitors and monoclonal antibodies, information on the risk of second cancers with AHCT is valuable for patients and clinicians for risk-benefit analysis. Since second cancers are rare events with a long latency from the exposure of interest, analysis of a large prospectively maintained database like CIBMTR is ideal to answer this question.

Patient eligibility population:

- Patients undergoing AHCT between January 1st, 1995 and December 31st, 2017 in the US [This timeline was chosen since the latency between diagnosis and development of second cancers is around 3-5 years in the MM literature, necessitating adequate follow-up for accurate risk assessment]

Data requirements:

Data will be extracted from the following forms: AL amyloidosis pre-HCT data form, Recipient baseline data form, HCT infusion form, and AL amyloidosis post-HCT data form. The following patient-related, myeloma-related, and transplant-related variables will be collected for multivariable logistic regression analysis to identify predictors of second cancers after AHCT for AL amyloidosis.

Patient-related variables:
Age/Sex
Race/Ethnicity
Pre-transplant Karnofsky Performance Score
HCT comorbidity score
Body mass index
History of smoking before transplantation

Amyloidosis-related variables:
Year of diagnosis
Stage at diagnosis

Number of organs involved
Light chain isotype

Transplant and treatment-related variables:
Treatment before AHCT
Disease status at AHCT
Date of AHCT
Conditioning chemotherapy for AHCT

Post-transplant variables:
Best disease status after AHCT
Planned maintenance therapy [and type] after AHCT
Second malignancy [Type and date of diagnosis]
Date of last follow-up
Date of death and cause of death

Sample requirements:
None

Study design:
The person-years at risk for AHCT recipients will be calculated from the date of transplant until death, latest follow-up, or development of a second cancer, whichever comes first. For calculation of standardized incidence ratio [SIR; Observed/Expected], age-, sex-, and race-specific cancer incidence rates for all cancers and individual cancers of interest will be calculated from the Surveillance, Epidemiology, and End Results [SEER] database. Cox regression model will be used to identify risk factors for all second cancers and therapy-related myeloid neoplasms separately. Furthermore, a case-control study will be performed by matching cases to controls [for sex, age, race, and year of transplantation] to compute odds ratio for development of second cancers for risk-factors of interest.

The **specific endpoints of interest** are as follows:
- Incidence of second cancers as well as that of hematologic malignancies and solid neoplasms separately after AHCT for AL amyloidosis
- SIR for all cancers and therapy-related myeloid neoplasms for AL amyloidosis survivors
- Risk factors for development of second cancers

Data source:
We will primarily use data from CIBMTR for our study. Furthermore, we plan to compare the incidence of secondary malignancies with cancer incidence statistics from the SEER program, [accessed at https://surveillance.cancer.gov/statistics/types/incidence.html]. SEER is a population-based tumor registry developed by the National Cancer Institute that captures time of diagnosis, tumor details, and socio-demographic characteristics for adult individuals with cancer in the US. The CIBMTR has previously conducted studies within the Plasma Cell Disorders Working Committee using the SEER database to study transplant utilization in newly diagnosed myeloma patients and SIR for second malignancies in patients with MM[5,8].

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Table 1. First autoHCT for amyloidosis in the United States between 1995-2017[a]

Characteristic	N (%)
No. of patients	1064
Age - no. (%)	
Median (min-max)	59.56 (23.54-78.29)
18-29	3 (0.3)
30-39	25 (2.3)
40-49	115 (10.8)
50-59	341 (32)
60-69	388 (36.5)
70-79	87 (8.2)
Missing	105 (9.9)
Sex - no. (%)	
Male	632 (59.4)
Female	432 (40.6)
Race - no. (%)	
Caucasian	884 (83.1)
African-American	131 (12.3)
Asian	18 (1.7)
Pacific islander	1 (0.1)
Native American	6 (0.6)
Other	3 (0.3)
More than one race	3 (0.3)
Missing	18 (1.7)
Performance score - no. (%)	
90-100%	491 (46.1)
< 90%	550 (51.7)
Missing	23 (2.2)
HCT-CI - no. (%)	
0	179 (16.8)
1	81 (7.6)
2	123 (11.6)
3+	411 (38.6)
NA, f2400 (pre-TED) not completed	270 (25.4)
Conditioning regimen intensity - no. (%)	
MAC	26 (2.4)
RIC	5 (0.5)
TBD	11 (1)
Missing	1022 (96.1)
Conditioning regimen - no. (%)	
TBI/Mel	3 (0.3)
TBI/other(s)	7 (0.7)
Bu/Mel	1 (0.1)

Characteristic	N (%)
BEAM	5 (0.5)
Mel alone	1020 (95.9)
Mel/other(s)	10 (0.9)
Missing	18 (1.7)
Year of transplant - no. (%)	
1995	3 (0.3)
1996	1 (0.1)
1997	14 (1.3)
1998	14 (1.3)
1999	24 (2.3)
2000	15 (1.4)
2001	18 (1.7)
2002	13 (1.2)
2003	11 (1)
2004	31 (2.9)
2005	49 (4.6)
2006	58 (5.5)
2007	23 (2.2)
2008	81 (7.6)
2009	56 (5.3)
2010	3 (0.3)
2011	4 (0.4)
2012	3 (0.3)
2013	23 (2.2)
2014	155 (14.6)
2015	147 (13.8)
2016	170 (16)
2017	148 (13.9)
Follow-up - median (min-max)	47.89 (0.07-240.36)
New malignancy in merge - no. (%)	89 (8.4)

[a] Still need to apply CAP model (consent prior for cases prior to 2003)

Proposal: 1911-176

Title:
Cardiometabolic Risk after Total Body Irradiation during Childhood

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Hypothesis:
The primary research hypothesis to be tested is that childhood cancer survivors treated with total body irradiation (TBI) will manifest significant cardiovascular disease (CVD) comorbidities (diabetes, hypertension, dyslipidemia), which will increase with duration of time since therapy. We also hypothesize that survivors treated at younger ages will have an increased risk of diabetes, hypertension, and dyslipidemia. We expect TBI-associated growth hormone deficiency to be associated with this risk. We do not expect survivors treated with TBI to have a higher prevalence of obesity based on body mass index (BMI) alone.

Specific aims:
- Using existing data from the Childhood Cancer Survivor Study (CCSS), determine the relative risk of developing diabetes mellitus, hypertension, and dyslipidemia in childhood cancer survivors treated with TBI between 1970-1999 (n=571), when compared to: (a) survivors treated with chemotherapy and/or surgery alone (n=5,434) and (b) the sibling comparison group (n=5,059).
- Identify additional treatment, primary disease, demographic characteristics, and specific chronic conditions that modify diabetes, hypertension, dyslipidemia, and obesity risk in survivors treated with TBI.
- Assess whether lifestyle factors (physical activity, smoking, alcohol use) modify risk of diabetes, hypertension, dyslipidemia, and obesity risk in survivors exposed to TBI.

Scientific impact:
We expect this study to provide novel data about sociodemographic and lifestyle contributors to cardiometabolic risk after TBI exposure in aging childhood cancer survivors. Data from this work will clarify which survivors are at highest risk for CVD comorbidities, including diabetes, dyslipidemia, hypertension and/or obesity, based on age at treatment, attained age, sex, race/ethnicity, socioeconomic status, and lifestyle factors. These findings will inform risk prediction models to enable identification of those who should be targeted for future intervention studies. Possibilities for interventions in this cohort include targeted measures to increase physical activity, modify diet, implement smoking cessations strategies, or a combination thereof, and will largely depend on what we learn from this analysis. CIBMTR data will be needed to complement existing CCSS data and fill gaps regarding potential transplant-specific contributors to risk, such as type of transplant, graft source, and graft versus host disease (GVHD) data.

Scientific justification:
Marked advances in hematopoietic stem cell transplantation (HSCT) have resulted in improved survival rates with 70–80% of those surviving two-years expected to become long-term survivors. Enthusiasm over these dramatic improvements, however, must be curbed by the fact that survivors face a lifelong risk of multiple treatment-related morbidities. Cardiovascular disease (CVD) is the most common cause of non-cancer mortality in HSCT recipients. Those preconditioned with total body irradiation (TBI) are at

particularly pronounced risk for the development of difficult-to-control CVD comorbidities, including insulin resistance/diabetes, hypertension, dyslipidemia, and metabolic syndrome.

While much is known about the high burden of CVD comorbidities in TBI-exposed HSCT survivors, epidemiologic questions remain regarding how population-level sociodemographic and lifestyle factors impact risk. In this study, we will utilize linked Childhood Cancer Survivor Study (CCSS) and Center for International Blood and Marrow Transplant Research (CIBMTR) data to enrich our understanding of the relative contributions of clinical factors to cardiometabolic risk among an aging cohort of TBI-exposed HSCT survivors.

- **Epidemiology of hematopoietic stem cell transplantation (HSCT) survivorship:**
  HSCT has emerged as an important curative treatment for children with high-risk hematologic malignancies and solid tumors. By 2030, it is estimated that there will be 502,000 HSCT survivors in the United States of whom 64,000 will have been transplanted prior to age 18[1, 2]. As more children survive HSCT, however, it has become increasingly clear that survivors face a lifelong risk of multiple treatment-related adverse sequelae and reduced life expectancy compared to the general population[3-5].
- **Cardiovascular disease (CVD) and metabolic dysfunction after HSCT:**
  CVD is an important contributor to treatment-related morbidity, mortality, and reduced life expectancy in this cohort[6-11]; when compared to the general population, HSCT survivors have a four-fold risk of cardiovascular disease[3, 6, 7], which includes heart failure, myocardial infarction, and stroke. Survivors of HSCT are also known to be at increased risk for cardiovascular disease-related comorbidities, including diabetes, dyslipidemia, hypertension, and the metabolic syndrome[12-15], a clustering of cardiovascular risk factors associated with cardiovascular disease and all-cause mortality[16, 17].
- **The association between total body irradiation (TBI) and cardiometabolic dysfunction**
  TBI has been an important component of the preparative regimen for high-risk patients undergoing HSCT, but it is also associated with a wide range of late toxicities[18, 19]. With respect to cardiometabolic disease, prior work within the original cohort of CCSS demonstrated that TBI is a key independent risk factor for diabetes[20]; the cardiovascular risk factor cluster[21], a surrogate for metabolic syndrome; and risk of underweight in females[22]. Other cohort studies, which have either included individuals transplanted during adulthood or been limited by single-institutional design, similarly demonstrated an association between TBI, cardiovascular risk factors, and cardiometabolic disease[19, 23-25]. For those exposed to TBI during childhood, however, updated data are lacking on how the prevalence of cardiometabolic comorbidities changes as this population ages, when compared to conventionally treated survivors and healthy controls.

Patient eligibility population:
Eligible patients include five-year survivors of any childhood cancer treated with TBI and enrolled in CCSS. Patients will have been diagnosed 1970-1999 at age < 21 years at one of the North American participating CCSS centers.

Data requirements:
For this study, we would like to abstract transplant-specific variables in the CIBMTR database for five-year survivors of any childhood cancer treated with TBI who are also enrolled in the CCSS. These include patients diagnosed at age < 21 years between 1970-1999 at one of 31 North American participating CCSS centers.
Requested variables from the existing CIBMTR data collection forms include: confirmation of transplant status (yes/no), type of transplant, graft source, presence of acute GVHD, and grade, if applicable;

presence of chronic GHVHD, and grade, if applicable on patients enrolled in CCSS. The study will not require collection of additional data. The outcomes variables on CVD morbidities will be abstracted from the CCSS database.

Sample requirements:
No samples needed.

Study design (scientific plan):
For this analysis of CVD comorbidities after TBI exposure, summary statistics and graphical methods will be used to explore the data and understand the distributions of the variables, any trends over time, and the correlations between the different variables. Prevalence of the primary outcomes of interest (weight status, diabetes, dyslipidemia, hypertension) will be estimated and compared between groups using a regression framework.
In separate models for each outcome of interest (diabetes, dyslipidemia, hypertension, and weight status), the outcomes will be used as dependent variables and modeled as functions of independent variables using Poisson models with robust standard errors. Independent variables will include (1) treatment-related risk factors: anthracycline exposure, alkylating agent exposure (CED score), and corticosteroid exposure; (2) transplant-specific factors: type of transplant, graft source, GVHD prophylaxis regimen, acute and/or chronic GVHD; (3) sociodemographic risk factors: household income, insurance status, education level, employment status, physical activity, smoking status, alcohol use; (4) possible effect modifiers: age at survey completion (attained age), race/ethnicity, sex; and (5) an indicator of group membership, where the groups are: childhood cancer survivors treated with TBI; childhood cancer survivors treated with conventional chemotherapy (but not radiation); and siblings. The univariable associations between each treatment-related or sociodemographic factor and the different outcomes will be evaluated in separate models that include the group membership indicator and are adjusted for the possible effect modifiers. A multivariable model will then be developed. When deciding which variables to include in the multivariable model, we will carefully consider the correlations and overlap in information captured by different variables. We will also test interactions between variables, such as between sex and race/ethnicity, and may consider building diagnosis-specific models.
Model diagnostics will be used to evaluate the model assumptions of all the models described above, including the overall goodness of fit of the models and whether the functional forms of the different variables in the model are appropriate. Different functional forms for the covariates (e.g. using a logarithmic transformation or a squared term) may be used if the linear term does not appear to be the best fit. For a sensitivity analysis, we may also compare the results of these models to log-binomial models.
Of note, this project has been funded by the American Cancer Society; MSK statistician, Chaya Moskowitz, PhD, is committed to the statistical analysis of this project. Dr. Moskowitz has extensive experience working with the CCSS dataset and has previously led R01-funded CCSS analyses and worked closely with the CCSS statistical center, led by Dr. Wendy Leisenring.

Data source:
We plan to link the CIBMTR Research Database with the CCSS database, which is a robust database of exposure and outcomes data among 5-year childhood cancer survivors in North America but is limited with regard to transplant-specific information. The CCSS database does not include details on graft source, type of transplant, and GVHD data. Linkage with the CIBMTR database would thus fill a critical gap in the childhood cancer survivorship arena by adding well-validated, transplant-specific data for this analysis of CVD morbidities after TBI exposure during childhood.

The linkage would be performed using name, date of birth, age, gender, and treating institution. The precise methodology for the linkage of the databases is under discussion; a conference call was held on November 14, 2019, between CIBMTR and CCSS leadership to discuss the linkage methodology in detail. Given CIBMTR's existing relationship with the National Marrow Donor Program (NMDP), the possibility of NMDP serving as an honest broker for the linkage was discussed. A data use agreement and/or IRB approval will be obtained once the linkage methodology is finalized.

Beyond the current proposal, a CIBMTR-CCSS linkage would provide an outstanding resource for future investigators interested in exploring transplant-specific outcomes among childhood cancer survivors. It will also furnish investigators with the possibility of supplementing limited CIBMTR patient-reported outcomes and medical outcomes data with rich CCSS outcomes data. This linkage will provide researchers an enhanced resource for future inquiries into transplant-specific long-term outcomes among childhood cancer survivors.

Conflicts of interest:

None.

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Proposal: 1911-203

Title:
Pre-transplant body mass index and late effects among children, adolescent, and young adult (CAYA) childhood leukemia survivors following allogeneic hematopoietic cell transplantation.

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Research hypothesis:
- Children, adolescent, and young adult (CAYA) survivors of leukemia survivors with overweight or obese body mass index (BMI) at the time of allogeneic hematopoietic cell transplantation (alloHCT) will have an increased risk of avascular necrosis, cataracts, cardiac difficulties, hypertension, renal insufficiency, and stroke compared to those with normal BMI.
- CAYA survivors of leukemia with overweight or obese BMI at the time of alloHCT will have an increased risk of second malignant neoplasms (SMNs) compared to those with normal BMI.
- Leukemia CAYA survivors who underwent alloHCT and have an overweight or obese BMI at the time of alloHCT will have an increased risk of all-cause late mortality at two-years or more following alloHCT, compared to survivors who are of normal weight.

Specific aims:
Primary aim:
- To determine the cumulative incidence of late effect in CAYA patients who are obese, overweight, normal weight or underweight at the time of alloHCT.
- To determine the cumulative incidence of second malignant neoplasms in CAYA patients who are obese, overweight, normal weight or underweight at the time of alloHCT.

Secondary aims:
- To determine the incidence of late mortality among overweight or obese CAYA leukemia survivors who have undergone alloHCT as compared to those with normal weight.
- To compare long-term survival and development of SMNs among overweight or obese CAYA leukemia survivors and sex and age-matched controls from the general population.

Scientific justification:
The last four decades have seen a sharp increase in obesity rates across the United States. A recent National Health and Nutrition Examination Survey reported that nearly 40% of adults over the age of 20 (about 93.3 million people) fall into the obese category (1). In 2013-2016, the prevalence of obesity among those 2 - 19 years of age was 17.8%, while the prevalence of severe obesity was 5.8% (2). These trends in BMI are particularly notable among adolescents, with 14.8% of high school students reported to be obese and 15.6% overweight. In the general adult population, obesity is known risk factor for a myriad of chronic health conditions, including type II diabetes, cardiovascular disease, hypertension, dyslipidemia, stroke, osteoarthritis, and even cancer (3-5). Moreover, obesity is considered an independent prognostic factor for non-relapse mortality in adults undergoing alloHCT. It is hypothesized that the hyperadiposity linked with obesity likely results in chronic subclinical inflammation (6-8), which has been associated with tumor development and progression (6-9). Several obesity-associated cancers, such as those of the breast and visceral organs, arise either within or adjacent to adipose depots, further suggesting that altered adipose biology can promotes cancer growth.

Current understanding of the relationship between obesity and SMNs among childhood cancer survivors is limited. A case–control study utilizing the California Cancer Registry demonstrated a significantly higher incidence of SMNs among obese cancer patients (adjusted OR, 4.44 (1.37–14.34)) (10). Due to their disease and treatment-related exposures, it is well-known that alloHCT recipients are at increased risk for developing SMNs. Having an overweight or obese BMI during or after transplant may further predispose to the development of SMNs in this population.
In a recent CIBMTR analysis based on BMI of 3687 pediatric patients, it was reported that overweight children experienced a decreased incidence of relapse, trend towards higher transplant related mortality (TRM), and no significant difference in relapse-free survival or overall survival compared with other BMI groups (11). However, this study did not account for critical factors such as patient-related comorbidities, late mortality, and SMNs. The proposed study will utilize data from the CIBMTR database to address these critical gaps in the literature. Results from this study will inform intervention studies aimed at reducing the burden, and associated morbidity and mortality, of SMNs among future patients.

Scientific impact:
If we demonstrate that overweight and obese patients have a higher incidence of late effects, SMNs and late mortality, this study may provide impetus to create new guidelines for screening, prevention and management of late effects for this subpopulation of patients. This would promote future, prospective intervention studies, and ultimately improves survival and quality of life in this group.

Study population:
Inclusion criteria:
- Patients alive and with no evidence of disease at 2 years post-alloHCT
- Age 0-39 years at time of alloHCT
- Transplant date occurred between 1990-2010
- Transplant type – first alloHCT
- HCT Indication – ALL and AML
- Stem cell source – bone marrow, peripheral blood, umbilical cord blood.
- Received myeloablative conditioning

Exclusion criteria:
- Patients who experienced relapse, received a second transplantation, died, or were lost to follow-up within 2 years after HCT
- Patients at centers whose team follow-up completeness index was < 80% at 5 years
- Patients who suffered primary graft failure
- Patients who received non-myeloablative or reduced intensity conditioning

Outcomes of interest:
Primary outcomes:
- Cardiovascular disease: Congestive heart failure (EF<40%); Myocardial infarction; Arrhythmias
- Endocrinopathies: Diabetes/hyperglycemia; Gonadal dysfunction / infertility requiring hormone replacement; Growth hormone deficiency / growth disturbance; Hypothyroidism
- Renal disease: Renal failure severe enough to warrant dialysis
- Neurologic complications: Stroke/seizure
- Second malignant neoplasms

Secondary outcome:
- Mortality rate among survivors at 5 and 10 years post alloHCT

Variables to be described:

Patient related:

- Age at initial diagnosis
- Malignancy type (confirmed by pathology reports)
- Age at transplant (0-3y v 4-10y v 11-20y v 21-39y)
- BMI
- Ethnicity (Caucasian v African American v other)
- Gender (male v female)
- Recipient CMV status (positive v negative v missing)
- Donor-Recipient CMV match (pos-pos v pos-neg v neg-pos v neg-neg v missing)
- Indication for transplant (ALL, AML)
- Disease Status at time of Transplant (CR1, CR2, ≥CR3)
- Performance Status (90-100 v <90)
- Year of transplant (1990-1997, 1998-2005 v 2006-2014)
- Interval from alloHCT to SMN diagnosis (months)

Transplant related:

- TBI (yes v no)
- GVHD prophylaxis (ex-vivo T-cell depletion, CNI+MMF, CNI+MTX, CNI alone, other)
- In vivo T-cell depletion (ATG/Campath v none)
- TBI >800cGy (yes v no)
- Donor (Matched Related v Matched Unrelated v Mismatched Related v Mismatched Unrelated v Cord)
- Conditioning regimen (Bu + Cy, Bu +Flu, TBI + Cy, TBI + other)
- Conditioning intensity
- Graft Source (BM v PB v cord)

Post-transplant variables:

- aGVHD (yes v no)
- cGVHD (yes v no)
- avascular necrosis (yes v no)
- cataracts
- Cardiovascular disease: Congestive heart failure (EF<40%); Myocardial infarction; Arrhythmias
- Endocrinopathies: Diabetes/hyperglycemia; Gonadal dysfunction / infertility requiring hormone replacement; Growth hormone deficiency / growth disturbance; Hypothyroidism Performance status
- post-HCT (90-100 v 60-80 v <60)
- Change in BMT from pre-HCT (if available)

BMI Categories at the time of transplant

	BMI percentile (2-18 years)	BMI (>18 years)
Underweight	< 5th	< 18.5
Normal	5th to 85th	18.5 to <25
Overweight	86th to 95th	25.0 to <30
Obese	>95th	> 30.0

Study design:

Patients fitting the inclusion criteria will be collected from the CIBMTR database and included in this analysis. The cohort will be categorized based on the pre-transplant weight as underweight, normal weight, overweight, and obese; each weight category will be analyzed separately. The weight categories will defined based on CDC

guidelines and percentiles, as noted above. Descriptive statistics using frequencies for categorical variables and median/range for continuous variables will be used to describe patient and transplant characteristics.
The cumulative incidence of secondary malignancies will be assessed in each weight category and compared. The cumulative incidence of late effects (avascular necrosis, cardiac disease, renal failure, stroke) will be assessed in each weight category and compared. Survival probabilities at 5 and 10 years after alloHCT will estimated using Kaplan-Meier estimates, stratified by pre-transplant weight category, and compared using log-rank testing. Cause of death will be described. Cox regression analysis will be used to assess whether obesity pre-transplant increases the risk of mortality, after adjusting for other significant transplant factors.
Standardized morality ratios will report the ratio of observed overall survival in the study population relative to expected overall survival in age and sex-matched controls from the general population obtained from population life tables obtained from standardized actuarial tables in the National Vital Statistics Reports. The survival distribution of the standard population will be calculated based on the cumulative death rate for each subject.
Risk factors associated with mortality in obese patients will be assessed using a stepwise Cox regression analysis. Variables with $p<0.05$ will be adjusted for in the final regression model. Variables that will be assessed include: age, year of transplant, ethnicity, disease, donor match, conditioning regimen, acute and chronic GVHD,

Conflict of interest:
None

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Table 1. Patients < 40 who survived 2 years post-transplant following 1st allo (including prior auto) for AML or ALL with myeloablative[a] conditioning between 1990-2010 and reported height and weight prior to transplant[b]

Characteristic	N (%)
No. of patients	7315
Age - no. (%)	
Median (min-max)	18.5 (0.27-40)
<18	3562 (48.7)
18-29	2156 (29.5)
30-39	1428 (19.5)
Missing	169 (2.3)
Sex - no. (%)	
Male	4260 (58.2)
Female	3055 (41.8)
Race - no. (%)	
Caucasian	5936 (81.1)
African-American	247 (3.4)
Asian	642 (8.8)
Pacific islander	14 (0.2)
Native American	20 (0.3)
Other	323 (4.4)
More than one race	55 (0.8)
Missing	78 (1.1)
BMI prior to HCT - no. (%)	
Underweight	396 (5.4)
Normal	4064 (55.6)
Overweight	1470 (20.1)
Obese	1085 (14.8)
NA (age <2)	300 (4.1)
Performance score - no. (%)	
90-100%	5826 (79.6)
< 90%	1284 (17.6)
Missing	205 (2.8)
HCT-CI - no. (%)	
0	728 (10)
1	118 (1.6)
2	86 (1.2)
3+	162 (2.2)
NA, f2400 (pre-TED) not completed	6151 (84.1)
Missing	70 (1)
Country - no. (%)	
United States	3685 (50.4)
International (not EU)	1851 (25.3)
European Union	1779 (24.3)

Disease - no. (%)	
AML	3884 (53.1)
ALL	3431 (46.9)
Graft type - no. (%)	
Bone marrow	4818 (65.9)
Peripheral blood	1593 (21.8)
Cord blood	900 (12.3)
Other	1 (0)
Missing	3 (0)
Year of transplant - no. (%)	
1990	427 (5.8)
1991	398 (5.4)
1992	433 (5.9)
1993	435 (5.9)
1994	424 (5.8)
1995	508 (6.9)
1996	484 (6.6)
1997	439 (6)
1998	87 (1.2)
1999	69 (0.9)
2000	157 (2.1)
2001	272 (3.7)
2002	301 (4.1)
2003	319 (4.4)
2004	352 (4.8)
2005	371 (5.1)
2006	383 (5.2)
2007	371 (5.1)
2008	418 (5.7)
2009	356 (4.9)
2010	311 (4.3)
Follow-up - median (min-max)	119.51 (24.01-349.93)

[a] Prescribed conditioning intensity

[b] Still need to exclude patients who experienced relapse, or received a second transplantation within 2 years after HCT, patients at centers from centers with <80% completeness at 5 years, and patients who suffered primary graft failure

Proposal: 1912-07

Title:
Long-Term Survival and Late Deaths After Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) In The Modern Era

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Research hypothesis:
- Although life expectancy in 2-year allo-HCT survivors is lower than expected at 5 years, it gradually improves and eventually returns to that of the age, sex, and nationality-matched population at 10 or more years.
- There are several groups of allo-HCT survivors who have higher rates of late mortality and different causes of death:
    - Those with higher HCT-CI scores before HCT (due to higher rates of deaths from the co-morbidities),
    - Patients over the age of 59 (due to "accelerated aging" from the HCT
    - Patients who experience early GVHD and CMV infection (from residual late immune impairment).
- When adjusted for confounding variables, patients transplanted using reduced intensity and nonmyeloablative conditioning regimens (RIC/NMA) and those receiving cord blood grafts will have lower rates of late mortality (due to less genotoxic damage from less intensive chemotherapy and more robust late immunity, respectively).

Specific outcomes:
Primary objective:
- To determine overall mortality of allo-HCT survivors who were free of disease relapse at 2 years post allo-HCT.

Secondary objectives:
- To evaluate patient, disease, and transplant factors and/or causes associated with late mortality in 2-year survivors of allo-HCT.
- To compare survival/mortality rates with that of age/sex matched controls from the general population
- To compare changes in causes of death in various intervals after HCT
- To determine if late fatalities have declined in more recently transplanted patients
- To compare relative late fatality rates and causes of death in subgroups of patients; including older age (>59yo), higher hematopoietic cell transplant comorbidity index (HCT CI) vs. lower HCT-CI scores, different graft types and donor match, disease categories, conditioning regimen intensity, those with or without early GVHD and CMV infection.

Scientific impact:
Determining the effects of changes in allo-HCT practices on long-term survival and late mortality of HCT recipients will serve as a platform for early interventions to prevent, identify and treat late allo-HCT complications, which in turn will potentially optimize overall transplant outcomes.

Scientific justification:

Allo-HCT is often the only curative option for patients with a variety of hematologic conditions. Over the past 2 decades, allo-HCT practices have tremendously changed and survival after allo-HCT has significantly improved, hence inquiry into whether or not survival rates and causes of late mortality in long-term allo-HCT survivors have changed is warranted (1,2). The introduction of RIC/NMA regimens made it more feasible for older patients to undergo allo-HCT with promising outcomes (3). Furthermore, alternative donor sources including haploidentical, mismatched unrelated and cord blood have also expanded the numbers of patients undergoing allo-HCT for various disease indications and of all age groups. Furthermore, advances in HCT practices and supportive care strategies have led to increasing numbers of long-term HCT survivors worldwide. Currently, there is > 100 thousand HCT survivors in the United States alone, and this number is projected to increase to 500 thousand by 2030 with 25% over the age of 60 years at time of HCT (4). According to recent CIBMTR data, in 2016, 30% of allo-HCT recipients were older than 60 years with an increasing trend of transplant done over the age of 70 (5).

Early allo-HCT mortality (within the first 2 years) is mostly attributed to disease relapse, acute or chronic graft-versus-host disease (GVHD), infections or organ toxicity. Death beyond 2 years is infrequent, and though less common, treatment-related mortality, disease relapse and late infection still account for a substantial proportion of late mortality (6-10). In 1999 and again in 2011, The Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) has conducted two studies at ten-year intervals to determine the long-term survival of 2-year allo-HCT survivors and relative mortality compared to the general population (1-2). In the 2011 CIBMTR analysis, Wingard et al. reviewed outcomes of 3,788 patients who survived >/= 2 years post allo-HCT with a median follow up of 9 years. The probability of being alive 10 years after allo-HCT was reported to be 85% with the major risk factors of non-relapse late death being older age at transplant and chronic GVHD (cGVHD). When compared with age, gender, and nationality-matched general population, late death remained higher than expected for most diseases (1). Interestingly, results of the preceding 1999 CIBMTR analysis showed similar trends at 5 years (2). Each of these analyses provided new insights due to larger numbers of patients with longer survival and changes in transplant practices. We anticipate a third analysis after an additional ten years of data collection will similarly produce important findings.

While the 2 previous analyses represent the largest cohorts ever studied to examine long- term survival and causes of late mortality of allo-HCT, it should be noted that they only included patients receiving HCT using myeloablative HCT conditioning regimens *AND* mostly fully-matched donor sources. HCT practices have significantly changed over the past decade and currently HCTs frequently use alternative donor sources like cord blood, haploidentical and mismatched unrelated donor options as well as the increasingly used RIC/NMA regimens, particularly for older or less fit HCT eligible patients. With aforementioned changes in HCT practices and the increasing number of HCT survivors, it is worthwhile conducting the analysis again to determine the effects of changes in transplant practices to provide new insights into long-term survival and late mortality after allo-HCT in the current era.

Patient eligibility population:

This study will include all survivors of first allo-HCT who received transplant at age 40 or greater for any disease indication and of all ages who were alive and disease free >/= 2 years post HCT with follow up data reported to CIBMTR from January 1980 to Dec 2015. This will include allo- HCT recipients from any donor source (including matched related, haploidentical, mismatched unrelated and cord blood transplant) and of any regimen intensity (including myeloablative and RIC/NMA regimens). Patients with a history of a prior autologous HCT are eligible for inclusion

Outcomes:

Primary endpoint:

- To determine the overall mortality of allo-HCT survivors who were free of disease relapse at 2 years post allo-HCT

Secondary endpoint:

- To evaluate patient, disease, and transplant factors and/or causes associated with late mortality in 2-year survivors of allo-HCT.
- To compare survival/mortality rates with that of age/sex matched controls from the general population
- To compare changes in causes of death in various intervals after HCT
- To determine if late fatalities have declined in more recently transplanted patients
- To compare relative late fatality rates and causes of death in subgroups of patients; including older age (>59yo), higher HCT CI vs. lower HCT CI scores, different graft types and donor match, disease categories, / regimen intensity, those with or without early GVHD and CMV infection.

Variables to be collected/analyzed:

The following variables will be analyzed to determine their influence on the primary and secondary endpoints described above:

Patient-related:

- Sex (male vs. female)
- Age
- Ethnicity/race (Caucasian vs. Hispanic/Latino vs. African American vs. Asian/Pacific Island vs. others)
- Karnofsky score
- Hematopoietic comorbidity index (HCT-CI)
- Disease indication for allo-HCT
- Disease risk index (DRI) at time of allo-HCT
- Disease status at allo-HCT (remission vs. active disease)
- Follow up (in months)
- Duration of follow up (<3 years, 3-5 years, 5-10 years, 10-15 years, >15 years)
- CMV seropositivity

Transplant-related:

- Year of allo-HCT
- Intensity of conditioning regimen (myeloablative vs. RIC/NMA)
- Use of total body irradiation (TBI)
- Geographic area of HCT center (USA, Canada, Europe, Asia, Australia/New Zealand, Mideast/Africa, Central/South America)
- Time interval from diagnosis to HCT
- Donor type (MRD, MUD, MM unrelated or related, haploidentical, cord)
- Graft type (bone marrow vs. peripheral blood vs. cord blood)
- GVHD prophylaxis

- Use of T-cell depletion (none, ATG, ex vivo, other)
- Grade II-IV aGVHD
- cGVHD
- CMV infection

Study design:
This is a retrospective study to investigate causes of survival rates in long-term allo-HCT survivors, and further evaluate causes of delayed mortality and compare that to age- and sex-matched controls from the general population, taking into account the newer HCT practices like the increasing trend of transplant in elderly, alternative donor options and reduced intensity regimens. Eligible patients include 2-year survivors of first allo-HCT of all age groups who received a transplant for any disease indication, with any conditioning regimen and with any donor source. Data of all patients who underwent an allo-HCT in the period from January 1980 till Dec 2015 and meet the above criteria will be reviewed, and those who have follow up information regarding both survival and disease control are eligible for inclusion in the statistical analysis. To avoid the bias of selective reporting, patients who underwent a transplant in centers whose team follow-up completeness index, defined as the ratio of total observed person-time to the potential person-time follow up, was less than 80% at 5 years will be excluded (1,11).
The primary endpoint is the probability of 10-year survival of 2-year allo-HCT survivors who have remained in remission from their primary disease. To account for the differences in disease biology, the likelihood of relapse, pre-HCT treatment and conditioning regimens, different disease categories will be analyzed separately. Furthermore, two separate analyses will be conducted to identify any specific trends related to intensity of conditioning regimen (RIC/NMA vs. myeloablative), and to type of donor (matched-related, matched unrelated, haploidentical, mismatched unrelated and cord blood). The probability of disease-free survival and overall survival will be estimated using Kaplan-Meier method. Estimates of relative mortality will be investigated while accounting for age, gender and nationality differences among patients. Potential factors associated with death will be analyzed using Cox regression models. These will include age at HCT (> or < 59), sex, Karnofsky performance status, HCT-CI score (> or < than median for all patients), disease risk index, time from diagnosis to HCT, donor type, stem cell source, conditioning regimen intensity, use of TBI (and dose), GVHD prophylaxis regimen, acute and/or chronic GVHD, CMV infection within the first 2 years of allo-HCT, year of HCT and geographic area of transplant center. All potential risk factors will be checked with time-dependent covariates to ensure that assumptions of proportionality are met.

Data source:
All study variables needed for this analysis are to be extracted solely from CIBMTR Research Database.

Conflict of interest:
Primary investigators of this study disclose no conflict of interest.

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Two year survivors following first alloHCT (including prior autoHCT) at age 40 or greater between 1980-2015[a]

Characteristic	N (%)
No. of patients	39271
Age - no. (%)	
Median (min-max)	52.31 (40-83.54)
40-49	15967 (40.7)
50-59	14563 (37.1)
60-69	7947 (20.2)
70-79	790 (2)
>=80	4 (0)
Sex - no. (%)	
Male	22645 (57.7)
Female	16603 (42.3)
Missing	23 (0.1)
Race - no. (%)	
Caucasian	31157 (79.3)
African-American	1351 (3.4)
Asian	1694 (4.3)
Pacific islander	74 (0.2)
Native American	73 (0.2)
Other	601 (1.5)
More than one race	58 (0.1)
Missing	4263 (10.9)
Performance score - no. (%)	
80-100	27119 (69.1)
< 80	2282 (5.8)
Missing	9870 (25.1)
Country - no. (%)	
United States	27251 (69.4)
International (not EU)	6029 (15.4)
European Union	5991 (15.3)
Disease - no. (%)	
AML	12858 (32.7)
ALL	2823 (7.2)
Other leukemia	2379 (6.1)
CML	5215 (13.3)
MDS	6314 (16.1)
Other acute leukemia	265 (0.7)
NHL	5883 (15)
HD	381 (1)
PCD/MM	2351 (6)
SAA	655 (1.7)

Characteristic	**N (%)**
Inherited abnormalities of erythrocyte differentiation or function	62 (0.2)
SCID & other immune system disorders	11 (0)
Inherited abnormalities of platelets	1 (0)
Inherited disorders of metabolism	7 (0)
Histiocytic disorders	16 (0)
Autoimmune diseases	7 (0)
Other, specify	25 (0.1)
Missing	18 (0)
Graft type - no. (%)	
Bone marrow	10362 (26.4)
Peripheral blood	27350 (69.6)
Cord blood	1090 (2.8)
Other	47 (0.1)
Missing	422 (1.1)
Year of transplant - no. (%)	
1980-1985	131 (0.3)
1986-1991	1201 (3.1)
1992-1997	4058 (10.3)
1998-2003	7457 (19)
2004-2009	10363 (26.4)
2010-2015	16061 (40.9)
Follow-up - median (min-max)	84.87 (24.01-462.93)

[a] Still need to exclude malignant disease relapse within 2 years (approximately 30%)