



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

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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
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Assistant Scientific Director:	Rachel Phelan, MD, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-955-4153; E-mail: rphelan@mcw.edu
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Statistician:	Stephanie Bo-Subait, MPH, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0674; E-mail: sbosubait@mcw.edu

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, Agrawal 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, Agrawal 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,

Not for publication or presentation

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 CIBMTR 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.

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- 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.

Not for publication or presentation

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

Not for publication or presentation

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