MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Salt Lake City, UT
Monday, April 25, 2022, 12:15 – 1:45 pm MDT

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1. Introduction

The CIBMTR Late Effects and Quality of Life Working Committee (LEWC) meeting was called to order at 12:15pm MDT on Monday, April 25, 2022 by Dr. Rachel Phelan. She introduced the current working committee leadership and reviewed the CIBMTR COI policy. Dr. Betty Hamilton continued the introduction by outlining the processes of participating in the working committee, guidelines for voting, and rules of authorship. The two sources of HCT data (TED vs. CRF level) were introduced, mentioning that Late Effects data mostly comes from CRF level data. Dr. Hélène Schoemans gave a reminder that data sets from studies are publicly available for secondary analysis and encouraged attendees to visit the Collaborative Working Committee proposal session, taking place on Monday, April 25, 2022 at 2:00pm MDT.

2. **Presentations, published or submitted paper**

Dr. Hélène Schoemans gave an update on study presentations, and manuscripts that were published or submitted within the last year.

a. **LE18-02:** Neel S Bhatt, Ruta Brazauskas , Rachel B Salit, Karen Syrjala, Stephanie Bo-Subait, Heather Tecca, Sherif M Badawy, K Scott Baker, Amer Beitinjaneh, Nelli Bejanyan, Michael Byrne, Ajoy Dias, Nosha Farhadfar, César O Freytes, Siddhartha Ganguly, Shahrukh Hashmi, Robert J Hayashi, Sanghee Hong, Yoshihiro Inamoto, Kareem Jamani, Kimberly A Kasow, Raquel Schears, Tal Schechter-Finkelstein, Gary Schiller, Ami J Shah, Akshay Sharma, Trent Wang, Baldeep Wirk, Minoo Battiwalla, Hélène Schoemans, Betty Hamilton, David Buchbinder, Rachel Phelan, Bronwen Shaw. Return to work among young adult survivors of allogeneic hematopoietic cell transplantation in the united states. **Transplantation and Cellular Therapy. 2021 Aug 1; 27(8):679.e1-679.e8. doi:10.1016/j.jtct.2021.04.013.** ***Epub 2021 Apr 22. PMC8425287.***

b. **LE16-02b:** Late Effects after Allogeneic Hematopoietic Cell Transplantation Among Children and Adolescents with Non-Malignant Disorders: A Report from the Center for International Blood and

Marrow Transplant Research. ***Oral presentation, ASH 2021.***

c. **LE18-01:** Prakash S, Larisa B, Phelan R, Stella C, Brazauskas R, Buchbinder DK, Hamilton BK, Hélène S, Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies. ***Presented at 2022 Tandem Meetings in Salt Lake City.***

3. **Studies in progress**

Dr. Hélène Schoemans briefly listed all studies in progress.

a. **LE16-02b:** Late effects after AlloHCT for pediatric patients with non-malignant diseases (J Kahn/ P Satwani) ***Manuscript Preparation.***

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

c. **LE17-01a:** Late effects after hematopoietic stem cell transplantation for sickle cell disease. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) ***Manuscript Preparation.***

d. **LE17-01b:** Comparison of survival between transplanted and non-transplanted SCD patients. (E Stenger/R Phelan/S Shenoy/L Krishnamurti) ***Data File Preparation.***

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

f. **LE18-03:** Incorporating patient reported outcomes into individualized prognostication tools for survival and quality of life in transplant patients. (B 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) ***Analysis.***

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) ***Data File Preparation.***

i. **LE20-01:** Cardiometabolic risk after total body irradiation during childhood. (D Novetsky Friedman/E Chow) ***Data File Preparation.***

j. **LE20-02:** Association between PRO and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplantation. (M R. Taylor/J M. Knight/K. Scott Baker/S W. Cole) ***Analysis.***

k. **LE21-01:** Risk of subsequent neoplasms in patients with post-transplant cyclophosphamide use for graft-versus-host disease prophylaxis. (A Tomas/I Muhsen/L Yanez San Segundo/S K. Hashmi/ M-Angel Perales/A Kansagra) ***Data File Preparation.***

4. **Future/proposed studies**

a. **PROP 2110-27:** Bladder cancer incidence and mortality after hematopoietic stem cell transplantation (*Herr/Hahn*)

Dr. Megan Herr presented this proposal aiming to assess bladder cancer incidence and mortality rate after HCT and to identify risk factors for bladder cancer after HCT, including investigation of bladder cancer incidence as an effect of pre-HCT cyclophosphamide dosage. It was acknowledged that additional documentation would need to be requested for the study to proceed, since only 25% of 2nd GU cancers currently have path reports, and that study PIs would be willing to review this documentation.

After a comment from the audience, it was explained that bladder cancer was chosen as the event of interest based on clinical observations as PTCy exposures have increased over time. At least one audience member was concerned about accounting for smoking history in the analysis, which was addressed by stating that this information is captured on CRF forms (including pack-years). Some questions were posed about the data sources. One audience member asked how much pre-HCT data was available; this data includes number of cycles as well as start and stop dates. Another question was about the path reports and whether there was a concern about misclassification. Dr. Herr addressed this concern by stating that in previous experience reviewing melanoma path reports, there were few misclassification errors and would expect to see few errors in this project. The final question pertained to the relatively recent surge in PTCy use and whether this limited the scope of the study, although the presenter said that prior to PTCy use, many patients were still exposed above the chosen threshold for the study due to multiple lines of therapy. This proposal was not accepted due to resource constraints and low priority.

b. **PROP 2110-55:** Racial/ Ethnic Disparities in Long-Term Health Outcomes Among Survivors of Allogeneic Hematopoietic Cell Transplant Performed in Childhood. (*Neel S. Bhatt/Akshay Sharma*)

Dr. Neel Bhatt presented this proposal aiming to determine the effect of race/ethnicity on the incidence of non-malignant late effects among survivors of alloHCT performed during childhood and to investigate the differences in the risk of developing subsequent neoplasms by race/ ethnicity among survivors of alloHCT performed during childhood.

There was a suggestion to increase the age range of this study (i.e. include young adults) in order to capture more data, which was received by the presenter as a possible avenue of investigation as long as there is no overlap with other studies. This suggestion was given along with concerns of missingness in the data. Another concern involved the high representation of White/Caucasian patients and the possibility of detection bias due to the fact that the underrepresented patients may not be able to afford or seek care. One audience member suggested looking at HLA data for polymorphisms that may correlate with differences in outcomes, and the presenter acknowledged that this study could be a good first step that may eventually lead to that line of research. It was also acknowledged that disparities results from a wide range of factors, some of which are not mentioned in the initial proposal, such as poverty level. While zip codes and other SES variables were not collected for the entire duration of the study time period, there was a comment about potentially combining this study with the study involving poverty and late effects by Duncan and Jimenez-Kurlander (PROP 2110-240). This proposal was accepted, with a request to combine the study with PROP 2110-240.

c. **PROP 2110-74:** Cumulative Incidence and Risk Factors for Breast Cancer after Allogeneic Hematopoietic Cell Transplant. *(Kareem Jamani/K. Scott Baker)*

Dr. Kareem Jamani presented this proposal aiming to estimate the cumulative incidence of breast cancer after alloHCT; to elucidate risk factors for the occurrence of breast cancer after alloHCT, particularly the association between breast cancer and TBI (at varying dose and fractionation), age at alloHCT, and time post alloHCT; and to estimate the excess risk of breast cancer in alloHCT recipients as compared to the general population. It was mentioned that this study is important

because there already exists an effective screening modality for breast cancer, and the results of this study may lead to increased screening recommendations for low-dose TBI patients or younger patients.

There was a comment about whether the study will differentiate between pre-menopausal and post-menopausal breast cancer incidence, as exposure may have the most impact on pre-menopausal incidence. It is difficult to differentiate these patients except by an estimated age of menopause, although SIR analysis will account for age at diagnosis compared to the general population. There was a concern about the long length of time between HCT and the typical onset of breast cancer as a late effect, and the fact that this might lead to incomplete data as comprehensive reporting tapers off over time. In line with this comment, it was recommended that the time period for cohort selection was chosen with this lead time in mind. There were some questions about whether confounding factors are available in the data set or were considered for this study, such as hormonal status (i.e. ovarian insufficiency may be protective), anthracycline exposure (data available as exposed vs. not exposed without dosage levels), and predisposing factors for breast cancer (data not available). One audience member suggested including males in the study as they also have incidence of breast cancer, although rare. Mary Horowitz was concerned about the interval from diagnosis to breast cancer, doubt adding one-year survivors would help. Dr. Kareem explained that the interval could be long, maybe 5 years, he would look at it. This proposal was not accepted due to resource constraints and low priority.

d. **PROP 2110-240:** The Role of Poverty in Late Effects Following Hematopoietic Cell Transplantation. (*Christine Duncan/Lauren Jimenez-Kurlander*)

Dr. Lauren Jimenez-Kurlander virtually presented this proposal, via pre-recorded presentation, aiming to compare the cumulative incidence of late organ toxicity and mental health diagnoses in survivors of allogeneic HCT from areas of low and high-neighborhood poverty. Secondary aims include the determination of how patients and treatment-related factors influence the development of these effects, a report of the overall survival and transplant-related mortality of survivors of alloHCT coming from areas of low-versus-high neighborhood poverty, and a comparison of late organ toxicity and mental health late effects in alloHCT survivors with private insurance versus those with Medicaid/Medicare insurance coverage.

There was a question about where the data for mental health outcomes is sourced from; clinical diagnoses of depression, anxiety, and PTSD are collected on the forms, which provides some limited insight, although this does not capture sub-clinical levels of mental health distress. This may be a limitation in the study. A related inquiry concerned the existence of baseline mental health data; these diagnoses are not collected on the baseline forms, although HCT-CI data may be able to provide some limited information. One audience member suggested incorporating PROs data, which would be helpful in future studies, but there is not enough data for this yet. There was a concern about the feasibility of differential follow-up by socioeconomic status because the completeness index by zip code was not favorable- related to this concern, there was a suggestion that an analysis of late effects could simply be added on to the study by Kira Bona looking at neighborhood poverty. There was also a concern about the high missingness of insurance status for the study cohort because insurance status is only collected on CRF level forms, although this means insurance status could be analyzed on a subset of the population. Finally, there was a cautionary statement that this study would be descriptive at best and would be unable to uncover causation. This proposal was accepted as a combination with PROP 2110-55.

e. **PROP 2110-299:** Risk of secondary colorectal cancer development after allogeneic hematopoietic stem cell transplantation (HCT) (*Jed Calata/Larisa Broglie*)

Dr. Jed Calata virtually presented this proposal, via pre-recorded presentation, aiming to describe the incidence of colorectal cancer in HCT patients and compare to the general population, to characterize the location and type of colorectal cancer in HCT patients, and to identify risk factors for secondary colorectal cancers including the role of GVHD.

There was a comment that a study like this could be important for colon cancer screening guidelines, especially since a previous study that did not reveal increased risk of colon cancer after TBI exposure had only a small cohort of patients. There was a suggestion to increase the age range and include even younger patients, which was received by the presenter as a likely possibility for the final study, as the age range presented in the proposal was not a strict specification. There was some concern, however, that colon cancer incidence would be underreported in younger patients due to less frequent screening, which may be a limitation. There was also a concern that too few patients within the study population would have path reports submitted for secondary malignancy, and that this could also pose a limitation. This proposal was not accepted due to resource constraints and low priority.

Dropped proposed studies

a. **PROP 2110-05:** Fertility, Pregnancy, Post-Transplant Cyclophosphamide, Allogeneic hematopoietic cell transplant. ***Dropped due to feasibility.***

b. **PROP 2110-06:** Fracture and bony events in adult patients after allogeneic hematopoietic cell transplant with graft versus host disease prophylaxis using post-transplant cyclophosphamide as graft versus host prophylaxis. ***Dropped for overlap with an existing study.***

c. **PROP 2110-66:** Post-transplant Diabetes Mellitus in long term survivors of pediatric allogeneic hematopoietic cell transplantation: An Analysis of Trends and associated risk factors. ***Dropped due to feasibility.***

d. **PROP 2110-179:** Impact of Stem Cell Mobilization Regimen on Risk of Therapy-Related Myeloid Neoplasms (t-MN) and Non-Relapse Mortality. ***Dropped due to feasibility.***

e. **PROP 2110-186:** Impact of therapies for oral cGVHD oral therapies on the development of oral cancers. ***Dropped due to feasibility.***

f. **PROP 2110-196:** Impact of Granulocyte Colony-Stimulating Factor on Gonadal Function and Fertility Following Hematopoietic Cell Transplantation. ***Dropped due to feasibility.***

g. **PROP 2110-227:** Impact of graft-versus-host disease on late effects in pediatric and young adult patients undergoing hematopoietic cell transplantation for non-malignant hematologic conditions. ***Dropped for overlap with an existing study.***

h. **PROP 2110-288:** Depression and Anxiety During the COVID-19 Pandemic Following Pediatric and Young Adult Allogeneic HCT. ***Dropped due to feasibility.***

i. **PROP 2110-321:** Trends in Late Mortality for Middle Aged and Elderly Undergoing Allogeneic Hematopoietic Stem Cell transplant. ***Dropped for overlap with an existing study.***

5. **Other Business**

Dr. David Buchbinder introduced Dr. Rachel Cusatis to present an update on PROs data at CIBMTR and Dr. Seth Rotz to present on HCT Survivorship guidelines.

a. **Update on PROs data at CIBMTR**

Dr. Rachel Cusatis provided an overview of the Patient Reported Outcomes (PROs) program at CIBMTR. She then gave an update on the status of PROs data at CIBMTR, including enrollment trends and demographics. It was noted that future plans for PROs data includes expansion to new sites, with contact information for sites that may be interested in participating. Next steps also include translation of surveys to Spanish, surveys for pediatric patients, and making information available on new website. Questions were deferred to Dr. Cusatis' email in the interest of time.

b. **HCT Survivorship Guidelines**

Dr. Seth Rotz presented an update on recommended screening and preventative practices for long-term survivors of HCT. These survivorship guidelines are being updated 10 years after initially being established by multiple societies in collaboration, including CIBMTR. Objectives, methodology, and a timeline for the update were provided, as well as a list of team members associated with this update.

c. **EBMT/CIBMTR Late Effects Systematic Reviews**

An update on the EBMT/CIMBTR late effects systematic reviews, which now has a formal proposal process, was presented by Dr. Rachel Phelan. The 2019 focus of male-specifics late effects review has resulted in an adult-only publication in TCT and BMT, with a pediatric version close to completion. The second formal call for proposals occurred in late 2021, with 11 submitted proposals and a final selection of female-specific late effects, merging in two other related topics. A reminder was given to look for emails if interested in being involved.

6. **Closing Remarks**

Dr. Rachel Phelan concluded the session at 1:50pm MDT.

Working Committee Overview Plan for 2022-2023

Study Number and Title	Current Status	Chairs Priority
LE12-03: Solid organ transplantation and hematopoietic cell transplantation	Manuscript preparation	1
LE16-02b: Late effects after AlloHCT for pediatric patients with non-malignant diseases	Manuscript preparation	3
LE17-01a: Late effects after hematopoietic stem cell transplantation for sickle cell disease	Manuscript preparation	3
LE17-01b: Comparison of survival between transplanted and non-transplanted SCD patients	Data file preparation	3
LE18-01: Survival trends in two-year survivors of alloHCT	Analysis	2
LE19-01: Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients	Analysis	1
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.	Data file preparation	2
LE20-01: Cardiometabolic Risk after Total Body Irradiation during Childhood	Protocol development	1
LE20-02: Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant	Analysis	2
LE21-01: Risk of subsequent neoplasms (SN) after the use of post-transplant cyclophosphamide (PTCy) for Graft-versus-host disease (GvHD) prophylaxis	Data file preparation	3
EL22-01: The role of racial/ethnic disparities and poverty in long-term outcomes among survivors of allogeneic hematopoietic stem cell transplants	Protocol pending	3