Nicole Meyers, MD, PGY2
Mentor: Dr. Monica Bhatia
CRC Project Proposal, August 2020

Assessing Quality of Life and Neurocognitive Changes among Sickle Cell Disease Patients Following Allogeneic Hematopoietic Cell Transplantation

A. Study Purpose and Rationale

Currently, allogeneic hematopoietic cell transplantation (alloHCT) is the only known curative treatment for sickle cell disease (SCD). Advances in patient and donor selection coupled with reduced-toxicity preparative regimens, especially for those with nonmalignant disease, have led to significant improvements in survival. Matched sibling alloHCT for SCD has consistently demonstrated >90% overall survival (Gluckman, 2017; Tanhehco, 2019). With this progress, however, comes the need to carefully investigate not only the late effects of HCT on patients' physical health, but also the long-term impact on their emotional and psychosocial well-being. In fact, the research focus has in many ways shifted from morbidity and mortality to a more specific, patient-centered outcome: health-related quality of life (HRQoL).

The trajectories of HRQoL in children who undergo HCT for both malignant and nonmalignant disease are currently being elucidated. Current evidence points to a decline immediately post-transplant with an overall improvement at the 1-year mark. However, there have been minimal longitudinal studies evaluating HRQoL changes in the SCD pediatric transplant population specifically. Kelly et al. assessed 13 parent-child dyads (with different hemoglobinopathies) and demonstrated return to baseline levels of functioning at 3 months post-transplant. Our institution published data showing improvements in the physical and emotional domains of QoL at 1-year follow-up. The social domain did not show significant improvement at 1-year follow-up, likely secondary to continued isolation and absence from school. As this isolation period is standard of care, school function was not included in the 1-year analyses (Bhatia, 2015).

A number of gaps exist in the literature on HRQoL post-HCT, especially among the SCD population. There is a paucity of research documenting HRQoL follow-up beyond the 1-year time point. Specific functional areas such as neurocognition, albeit closely linked to the school and social domains of QoL, have also not been explored in depth. This is an area of particular interest as HCT survivors are at risk for neurocognitive impairment secondary to the neurotoxic agents used in the conditioning phase, as well as the prophylaxis/treatment of graft versus host disease (GVHD). Moreover, SCD patients at baseline often have significant cognitive deficits in a variety of domains (Shenoy, 2017). Prior studies have generally found stability of neurocognitive function post-transplant, including one study that focused on the 1 and 2-year follow-up time points (Kupst, 2002). However, this did not include SCD patients and cannot be extrapolated given the varied conditioning

regimens and nuances of HCT for the SCD population. Longer follow-up, which is currently lacking, may also be necessary to fully appreciate any true impact on neuropsychological function (Parsons, 2012). Cognitive function is a necessary area for future study as it has great implications for children's adherence to medical treatment and future educational attainment (Shenoy, 2017).

Notably, there are certain groups of children at greater risk for impaired HRQoL, including those of particular ethnic backgrounds, female gender and older age (Brice, 2011). Bhatia et al. found that among SCD patients, those with private insurance had lower self-reported HRQoL at 1 year-post transplant than those with public insurance. Other studies have focused on modifiable risk factors for impaired QoL, such as caregiver stress and social support, which help identify potential areas for intervention (Loiselle, 2016).

This study will focus specifically on the SCD population post-transplant and its purpose is multifold: 1) to elucidate the long-term trajectory of HRQoL beyond 1 year of follow-up, 2) to investigate a specific area of function closely linked to QoL: neurocognition, 3) to better understand existing disparities underlying changes in HRQoL.

B. Study Design and Statistical Analysis

Subjects:
This study's population will be pediatric (<21 y/o) SCD patients post-HCT who underwent transplant at Morgan Stanley Children's Hospital of New York (MSCHONY) between 2004 and 2020. Patients will be included regardless of preparative regimen used (myeloablative vs. reduced intensity).

For the QoL component of the study, we intend to include ~40 patients (15 of which already have HRQoL data collected pre-HCT and beyond 1 year post; remainder will be collected over the phone or in-person at upcoming visits). With these additional patients/families we reach (~25), we will collect post-HCT neurocognitive measures.

Variables/Measures:
Subject characteristics e.g. age, gender, race/ethnicity, insurance status and HCT-specific variables e.g. preparative regimen, donor source, and presence of GVHD will be collected through chart review. HRQoL and cognitive ability will be measured using validated tools: PedsQL 4.0 Generic Core Scale (Varni, 2013) and PROMIS, respectively. 3 different version of the PedsQL 4.0 Scale will be used: a self-report for children ages 5 to 18, self-report for young adults 18-25 (only up to 21 in our study), and a proxy report for parents/caregivers of children ages 2 to 18. The scale includes 23 items; 8 to assess physical functioning, 5 for social, 5 for psychological/emotional, and 5 for school. Composite scores will be calculated for each of these domains, as well as for overall HRQoL and a psychosocial health summary score. For the neurocognitive measures specifically, the PROMIS Parent

Proxy Item Bank v1.0 (cognitive function, short form 7a) and Neuro-QOL Item Bank v2.0 (pediatric cognitive function, short form 7a) will be administered.

Data Analysis:
Descriptive statistics and percentages will be calculated for all demographic and HCT-specific variables. The continuous variables, including the component/overall HRQoL scores both pre and post-HCT, as well as the cognitive scores, will be summarized using mean and standard deviation. Mixed-effect linear models (unadjusted + adjusted for significant covariates) will be used to assess changes in HRQoL from baseline to a time-point beyond 1 year in each of our subjects. Initial focus will be on the 2, 3, 4, 5 and 6-year post-HCT time points as these have the most existing HRQoL data. Pearson correlations will be calculated to compare parent (proxy) and patient scores across HRQoL domains and time points.

Post-HCT neurocognitive measures will be compared to population norms for chronically ill/healthy children using t-tests. We do not currently have existing data for pre-HCT neurocognition in our patient population. With a projected sample of 25 HCT survivors completing neurocognitive measures (power 0.80 and alpha 0.05), a difference of 0.81 between groups can be detected.

C. Study Procedure

HCT survivors are followed closely by the Hematology/Oncology/Stem Cell Transplant clinic at MSCHONY. Guidelines currently recommend the routine collection of HRQoL at these follow-up visits. We will encourage collection of HRQoL for all patients who are at one of the following post-HCT time points (2, 3, 4, 5, and 6-year). These patients/caregivers will also provide basic demographic data and complete the PROMIS cognitive measures. If not scheduled for a clinic visit in the next several months and eligible for one of these time points, this battery of scales will be administered over the phone. Interpreter services for both in-person and phone encounters will be used as needed.

D. Study Drugs

No study drugs, approved or investigational, will be used in this study.

E. Medical Devices

No medical devices will be used in this study.

F. Study Questionnaires

HRQoL: PedsQL 4.0 Generic Core Scale

Neurocognitive Measures: PROMIS Parent Proxy Item Bank v1.0 (cognitive function, short form 7a) and Neuro-QOL Item Bank v2.0 (pediatric cognitive function, short form 7a)

G. Study Subjects

Subjects will include SCD patients at MSCHONY who underwent transplant and are at the time points of interest (2, 3, 4, 5 and 6 years post-HCT).

H. Recruitment of Subjects

Subjects, meeting inclusion criteria for the study, will be consented in-person prior to their appointment. Again, if not scheduled for an upcoming appointment, they will be recruited and consented over the phone.

I. Confidentiality of Study Data

Study data will be stored on a password-protected computer and database, and only accessed by study investigators who have completed necessary training. Once at the data analysis phase, all subjects will be de-identified.

J. Potential Conflict of Interest

There are no potential conflicts of interest for any of the study investigators.

K. Location of the Study

Data will be collected over the phone or in-person at MSCHONY's hematology/oncology/stem cell transplant clinic.

L. Potential Risks

The only risk is the potential for loss of confidentiality, which will be minimized by the security measures outlined above.

M. Potential Benefits

There will be no individual benefits to subject participants. Insight gained from the study however will help us better understand how to support patients/families through the transplant process.

N. Alternative Therapies

There will be no therapies offered through this study.

O. Compensation to Subjects

There will be no compensation to study subjects.

P. Costs to Subjects

The only cost to study subjects will be their time; we approximate the measures collection to take approximately 25-30 mins.

Q. Minors as Research Subjects

The population of interest will include minors, but participation has minimal risk and will not affect the care they receive in any way.

R. Radiation or Radioactive Substances

There will be no radiation or radioactive substances used in the study.

S. References

Bhatia M, Kolva E, Cimini L, Jin Z, Satwani P, Savone M et al. Health-related quality of life after allogeneic hematopoietic stem cell transplantation for sickle cell disease. *Biology of Blood and Marrow Transplantation*. 2015;21(4):666-672.

Brice L, Weiss R, Wei Y, Satwani P, Bhatia M, George D, et al. Health-related quality of life (HRQoL): The impact of medical and demographic variables upon pediatric recipients of hematopoietic stem cell transplantation. *Pediatric Blood & Cancer*. 2011;57(7): 1179-1185.

Gluckman E, Cappelli B, Bernaudin F, Labopin M, Volt F, Carreras J et al. Sickle cell isease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood*. 2017;129(11):1548-1556.

Kelly MJ, Pennarola BW, Rodday AM, Parsons SK. Health-related quality of life (HRQL) in children with sickle cell disease and thalassemia following hematopoietic stem cell transplant (HSCT). *Pediatr Blood Cancer*. 2012;59(4):725-731.

Kupst MJ, Penati B, Debban B, Camitta B, Pietryga D, Marolis D et al. Cognitive and psychosocial functioning of pediatric hematopoietic stem cell transplant patients: a prospective longitudinal study. *Bone Marrow Transplant*. 2002;30(9):609-617.

Loiselle KA, Rausch JR, Bidwell S, Drake S, Davies SM, Pai ALH. Predictors of health-related quality of life over time among pediatric hematopoietic stem cell transplant recipients. *Pediatric Bood & Cancer*. 2016;63(10):1834-1839.

Parsons, SK, Phipps S, Sung L, Baker KS, Pulsipher MA, Ness KK. NCI, NHLBI/PBMTC first international conference on late effects after pediatric hematopoietic cell

transplantation: health-related quality of life, functional, and neurocognitive outcomes. *Biology of Blood and Marrow Transplantation*. 2012;18(2):162-171.

Shenoy S, Angelucci E, Arnold SD, Baker KS, Bhatia M, Bresters D, et al. Current results and future research priorities in late effects after hematopoietic stem cell transplantation for children with sickle cell disease and thalassemia: A consensus statement from the second pediatric blood and marrow transplant consortium international conference on late effects after pediatric hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation.* 2017;23(4): 552-561.

Tanhehco YC, Bhatia M. Hematopoietic stem cell transplantation and cellular therapy in sickle cell disease: where are we now? *Curr Opin Hematol.* 2019;26(6):448-452.

Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;3(6): 329-41.