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IRB Proposal

Comparing Long Term Outcomes in Survivors of Allogeneic Hematopoietic Cell Transplantation for Nonmalignant Disease by the Intensity of Preparative Regimen

Abstract
Survivors of allogeneic hematopoietic cell transplantation (alloHCT) are at risk of developing late toxicities as a result of their previous treatment. The goal of this proposal is to prospectively compare the prevalence and severity of late complications in survivors of alloHCT for nonmalignant disease by the intensity of the preparative regimen. Our specific aims are to: (1) describe the prevalence of late complications based on severity in a cohort of child and adult survivors, who underwent alloHCT as children for nonmalignant disease at a single institution; (2) compare late morbidities in alloHCT survivors by the preparative regimen received: myeloablative (standard very high dose chemotherapy) vs. reduced-toxicity (high dose chemotherapy) vs. reduced-intensity (low dose chemotherapy) conditioning; and (3) identify other host and treatment factors associated with adverse health outcomes in alloHCT survivors. Each participant will partake in an individual comprehensive survivorship visit, which will include a series of objective screening tests to assess morbidities. The screening measures, which include written surveys, physical exam findings, blood and urine samples, and radiographic tests, are based on available consensus guidelines (developed by American Society of Bone marrow Transplantation and Children's Oncology Group) for long-term term follow-up care after alloHCT. The results of this study may help elucidate how less intense preparative regimens prior to alloHCT affect the long-term health of children.

1. Study Purpose and Rationale

Progress in hematopoietic cell transplantation (HCT) has resulted in a significant improvement in survival. Over 80% of children who survive the first two years after allogeneic HCT are now expected to become long-term survivors (Bhatia et al, 2007). However, survivors are at increased risk of developing a myriad of late complications. It has been reported that 66% of HCT survivors develop at least one chronic health condition and 18% develop severe or life-threatening conditions (Sun et al., 2010). Much of the morbidity of HCT is due to the intense pre-transplant conditioning. Conventional myeloablative conditioning exposes children to total body irradiation and high dose alkylating agents. More recently, selected children (especially those with non-malignant diseases) have been prepared for HCT with reduced-toxicity or reduced-intensity conditioning (Satwani et al., 2008; Satwani et al., 2013). There is evidence, especially in the adult literature, that the less intense regimens decrease acute toxicities (Ringden et al., 2013). To our knowledge, however, there is no research examining the differences in long-term toxicities for those who receive the less intense conditioning. As preparative regimens evolve, it is important to investigate how they may affect long-term outcomes.

The goal of this proposal is to compare the prevalence and severity of late complications in survivors of allogeneic HCT for nonmalignant disease by the intensity of the preparative regimen. Each participant will partake in an individual comprehensive survivorship visit, which will include a series of objective screening tests to assess morbidities. Only survivors who were transplanted for nonmalignant diseases will be included in the study to reduce the variability in pre-transplant exposures.

2. Study Design and Statistical Procedures

Subjects: This is a prospective study of survivors of HCT for nonmalignant disease, who received transplants at Morgan Stanley Children's Hospital of New York Presbyterian between 2001 and 2012. Other eligibility criteria include: (1) transplant prior to age 21, and (2) at least two years between transplant and time of study enrollment.

The indications for HCT in the cohort include sickle cell anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, immunodeficiencies, and other metabolic disorders.

Three different classes of preparative regimens were utilized, which included the following exposures:

1. Myeloablative conditioning: TBI-based or Busulfan with Melphalan or Cytoxan ± Thiotepa
2. Reduced-toxicity conditioning: Cytoxan or Busulfan in combination with Fludarabine or ATG.
3. Reduced-intensity conditioning: Fludarabine-based regimens in combination with an alkylating agent (Cytoxan, Melphalan or Busulfan).

The eligible participants were not exposed to other chemotherapeutic agents pre-transplant. Post-transplant exposures included Tacrolimus, Mycophenolate Mofetil and Corticosteroids.

We are aiming to recruit 100 participants for this study. Approximately 130 children meet the inclusion criteria, of which approximately 110 are surviving.

Variables: The following variables will be collected via the methods listed below

<u>Chart review</u>
Age at time of transplant
Underlying disease
Time elapsed since transplant
Donor (matched, related vs. unrelated)
History of acute or chronic GVHD
CMV risk status
CD34 selection
Exposure to r-ATG and/or alemtuzumab

Exposure to total body irradiation
Preparative regimen

Questionnaires
Current age
Gender
Race/ethnicity
Quality of life

Screening test outcomes
The outcomes will be graded based on severity (on the Common Terminology Criteria for Adverse Events - version 4.0). Examples of specific outcomes and the way in which they will be assessed are:

- Osteopenia/osteoporosis: DEXA scan, vitamin D levels
- Cataracts: ocular exam with measurement of visual acuity and funduscopic exam
- Chronic kidney disease: blood pressure, BUN/Creatinine, urinalysis, and urine micro-albumin
- Metabolic syndrome: body mass index, fasting glucose, lipid profile

Data Analysis: Subject characteristics, including age, gender, race/ethnicity, diagnosis and treatment parameters will be summarized and compared between participants and eligible nonparticipants using an exact chi-square test to evaluate the potential for response bias.

The categorical outcome variables (i.e. selected late effects, presence of at least one chronic health condition) will be summarized as percentages and the continuous outcome variables (i.e. number of late complications) will be summarized as mean ± standard deviation. The comparisons between groups will be done by t-tests and ANOVAs for continuous variables and by chi-square tests for categorical variables. P values of <0.05 will be considered significant. The analyses will be carried out with SAS 9.2. The following risk factors for selected late effects will be analyzed with both univariate and multivariate regression modeling: age, gender, diagnosis, donor type (matched sibling vs. matched unrelated), CMV risk status, conditioning regimen (reduced-intensity vs. reduced-toxicity vs. myeloablative), total body irradiation, r-ATG, alemtuzumab, CD34 selection, and acute or chronic GVHD.

The anticipated sample size of this pilot study will have the power to detect differences in broader outcomes (i.e. incidence of at least one chronic medical condition, but not incidence of cataracts). Future larger studies will be needed to detect differences in some of the more specific, less frequent outcomes.

3. Study Procedures

Transplant survivors continue to be seen in the Hematology/Oncology/Stem Cell Transplant clinic for monitoring of late effects. Guidelines exist that recommend screening based on treatment exposure.

Each participant will come to the Hematology/Oncology/Stem Cell Transplant clinic for an individual follow-up visit. At the start of the visit, the participant will complete a demographic survey and quality of life questionnaire. Then, the patient will meet with a physician for a complete history and physical examination. After, the patient will have a blood and urine samples taken. Each patient will also be scheduled for the following:

1. Bone density (DEXA) scan
2. Electrocardiogram (ECG) and echocardiogram
3. Chest x-ray and pulmonary function tests

All tests are considered standard of care for follow up of transplant survivors.

4. Study Drugs or Devices

None

5. Study Instruments (attached)

PedsQL (Pediatric Quality of Life Inventory): Validated for children 2-18 years old, translated into multiple language
EuroQOL EQ-5D Health States: Youth version, validated for children 7-12 years old. Regular version, validated for adults and children over 12 years old. Translated into multiple languages

6. Study Subjects

(see "study description and statistical procedures")

7. Recruitment

Eligible patients will be contacted by phone to schedule their follow-up visit. If they are unable to be contacted by phone, they will be contacted by mail. In the event that an email address is available and patients have designated that they would like to be contacted by email, they will be sent an encypted email message.

8. Informed Consent Process

One of the study investigators will obtain informed consent from participants. For participants under 18 years old, the primary caregiver will consent, the patients themselves will provide assent. Participants 18 years and old will consent for themselves.

9. Confidentiality of Study Data

Data will be stored on a private computer and files will be encrypted and password protected. Raw data will be coded. Only the study investigators will have access to the link between the data and the identifier.

10. Privacy Protections
Patients name, age, gender and medical record number will not be published. All aggregate data will be de-identified.

11. Potential risks
Minor risks associated with routine blood draws including pain, bleeding or infection. The risk associated with the chest x-ray includes very low dose radiation exposure. None of the other imaging tests have radiation exposure.

12. Data and safety monitoring
NA

13. Potential benefits
There will be no additional benefits to the patients other than the information that is gathered as part of a routine office visit. The aggregate data collected will have benefits for future benefits by assessing whether different preparative regimens are associated with different long-term toxicities.

14. Alternatives
Patients may choose not to be in this study. If that is the case, they will receive the same office visit and screening tests.

15. Research at external sites
Columbia is the only research site