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Reports

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Research Methodology and Study Design Working Group Report

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A B S T R A C T

The increasing numbers of hematopoietic cell transplantations (HCTs) performed each year, the changing demographics of HCT recipients, the introduction of new transplantation strategies, incremental improvement in survival, and the growing population of HCT survivors demand a comprehensive approach to examining the health and well-being of patients throughout life after HCT. This report summarizes strategies for the conduct of research on late effects after transplantation, including consideration of the study design and analytic approaches; methodologic challenges in handling complex phenotype data; an appreciation of the changing trends in the practice of transplantation; and the availability of biospecimens to support laboratory-based research. It is hoped that these concepts will promote continued research and facilitate the development of new approaches to address fundamental questions in transplantation outcomes.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is used with curative intent for malignant and nonmalignant conditions. In 2014, over 20,000 HCTs were performed in the United States, and the annual number of HCTs is increasing at the rate of ~5% per year (Center for International Blood and Marrow Transplant Registry [CIBMTR] estimates). Advances in transplantation strategies have yielded steady improvements in survival. Although 5-year survival rates now exceed 70% for patients who survive the first 2 years, HCT recipients are especially vulnerable to serious health problems, such as subsequent neoplasms, heart failure, and pulmonary toxicity, developing several years after transplantation. These complications are directly related to treatment (pre-HCT and HCT-related chemotherapy/radiation) and post-HCT chronic graft-versus-host disease (GVHD). Finally, the risk of these complications is likely modified by comorbidities [1-8].

The National Institutes of Health Blood and Marrow Transplantation Late Effects Initiative, comprised of pediatric and adult HCT health care providers, administrators, researchers, advocates and survivors across federal and non-federal groups and sponsored by the National Cancer Institute and National Heart, Lung and Blood Institute, aims to identify knowledge gaps, develop practice recommendations and formulate important research questions to improve transplant survivor monitoring and management (cite commentary). HCT survivors were defined as pediatric or adult, autologous or allogeneic HCT recipients who have survived for one year or longer after transplantation. The Research Methodology and Study Design (RMSD) Working Group, established as one of 6 working groups within this initiative, convened in September 2015 with the goal of providing recommendations for research methodology and study design in the field of HCT survivorship. The working group focused on identifying methodological challenges, describing historical transplantation

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Insert Box Recommendations

General recommendations for establishment of new cohorts or expansion/embellishment of existing cohorts to study late effects after hematopoietic cell transplantation

Comprehensive and complete follow-up of transplantation recipients

Capture of pre-HCT therapeutic exposures, conditioning regimens, post-HCT therapeutic and immunosuppressive therapy, extent and severity of chronic GVHD, sociodemographic data, PROs, and health care costs

Develop a biorepository of biospecimens before HCTs

Priority for data collection

High priority	*Examples of outcomes*	*Examples of exposures*
1. High incidence of morbidity, impairment, disability, premature mortality	1. Subsequent malignancies	**1. Pre-HCT exposures**
2. Excess risk compared with the general population	2. Cardiac toxicity	a. Radiation
3. Modifiable risk factors	3. Pulmonary dysfunction	b. Anthracyclines
	4. Osteonecrosis	c. Bleomycin
	5. Stroke	d. Nitrosoureas
	6. Pregnancy	e. Dexamethasone
	7. Menopause	**2. HCT-related exposures**
	8. Death (with cause)	a. TBI
		b. Busulfan
		c. Cyclophosphamide
		d. Etoposide
		e. Stem cell source
		f. Stem cell mobilization regimens
		3. Post-HCT exposures
		a. GVHD (acute and chronic)
		b. Calcineurin inhibitors
		c. Steroids
		d. Radiation
		e. Chemotherapy

Recommendations for data collection

Data collection should include the following data elements (at minimum)

a. **Demographic** characteristics (date of birth, sex, race/ethnicity, SES)
b. **Clinical** characteristics (primary diagnosis, date of diagnosis, date of transplantation, disease status at transplantation, comorbidities at HCT)
c. **Pre-HCT exposures** (radiation [field, dose], anthracyclines, alkylating agents, bleomycin, nitrosoureas, dexamethasone)
d. **HCT-related exposures** (conditioning regimens, stem cell source, stem cell mobilization)
e. **Post-HCT exposures** (GVHD, immunosuppressive therapy for GVHD prophylaxis and treatment, radiation, chemotherapy)
f. **Post-HCT outcomes** (subsequent malignancies [site, date of diagnosis], heart failure (date of diagnosis], pulmonary dysfunction [type, date of diagnosis], stroke [date of diagnosis], myocardial infarction [date of diagnosis], osteonecrosis [date of diagnosis], comorbidities, vital status (alive [date of last contact]/deceased [date of death, cause of death]
g. **Patient-Reported outcomes**: Strong consideration should be given to the inclusion of patient-centered outcomes (symptoms, functional status, financial toxicity, behavioral and lifestyle factors). They can be measured with PRO or with a performance-based measures (eg. 6-minute walk), or with sensor actigraphy.
h. **Investments should be made in solutions to reduce the data entry burden** (such as electronic data transfer and direct patient contact)

Priority for specimen collection

High priority	*Examples of outcomes*	*Examples of platforms (currently available)*
1. Germline DNA	Outcomes associated with therapeutic exposures	1. Genome-wide association studies
2. Total leukocyte or cell-specific RNA	1. Cardiac	2. Whole exome studies
3. Plasma/serum	2. Pulmonary	3. Whole genome sequencing
	3. Subsequent cancer	4. Methylome assay
	4. Stroke	5. Gene expression analysis
	5. Osteonecrosis	6. Metabolomics and proteomics

Recommendations for sample collection

1. Whole blood for DNA, RNA, plasma/serum/frozen cells to create lymphoblastoid cell lines
a. Before HCT
b. After HCT (at 1 year after HCT; annually thereafter, if resources available)
2. Fresh frozen tissue (paired normal and second cancer) for patients with subsequent malignancies

General recommendations for use of existing cohorts/resources

1. Use currently existing biospecimens—potentially pooling biospecimens from multiple sources/banks
2. Supplement existing registry/institutional databases to incorporate critical study-specific data elements

TBI indicates total body irradiation; SES, socioeconomic status

strategies, defining database and biospecimen requirements, and describing key study designs and analytical approaches in HCT survivorship studies. These findings were incorporated into draft recommendations for HCT survivorship study design and data and specimen collection and presented at a public meeting in June 2016, including over 150 participants with expertise across HCT survivorship. The findings were revised based on audience comments and are presented here (Insert Box).

METHODOLOGICAL CHALLENGES UNIQUE TO SURVIVORSHIP AFTER HCT

HCT survivors are uniquely vulnerable to long-term morbidity for the reasons detailed below.