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National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: Consensus Recommendations for Research Methodology and Study Design

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Abstract

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.

Keywords

National Institutes of Health; consensus; Late effects; Hematopoietic cell; transplantation

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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]. In this report, we provide general recommendations for establishment of new cohorts or expansion/embellishment of existing cohorts to study late effects after HCT (Insert Box). We also provide priorities for data and biospecimen collection.

METHODOLOGICAL CHALLENGES UNIQUE TO SURVIVORSHIP AFTER HCT

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

Therapeutic Exposures

As shown in Figure 1, HCT recipients are exposed to chemotherapy and radiation before HCT (for management of primary cancer), at HCT (for the transplantation procedure), and after HCT (for management of GVHD and possibly relapse of primary cancer). Thus, unlike cancer patients treated in a nontransplantation setting with conventional doses of chemotherapy/ radiation, HCT survivors have typically received higher exposures to chemotherapy and radiation—both with respect to intensity as well as cumulative lifetime exposures. This cumulative exposure places them at a muchc higher risk of long-term morbidity [9]. In addition, the immunosuppressive therapy for management of GVHD increases risks for a variety of chronic health problems, such as chronic kidney disease, metabolic syndrome, osteonecrosis, and subsequent malignancies. Patients are frequently referred to dedicated HCT centers after treatment by physicians who do not provide this highly specialized type of treatment. This arrangement makes it difficult for HCT study teams to gather detailed information regarding therapeutic exposures that occurred before referral for HCT and after post-HCT relapse. For this reason, most previous studies have focused solely on therapeutic exposures at HCT (ignoring the prereferral exposures) when examining determinants of long-term morbidity. As a result, post-HCT complications have been attributed to HCT-related exposures alone, even though prereferral exposures have likely contributed to etiology.

Post-Transplantation Follow-Up

After transplantation, most patients are discharged from the transplantation center and referred back to their primary oncologists or primary care providers. This arrangement makes it difficult for study teams to ensure complete long-term follow-up. Very often, post-HCT complications have a long latency (Table 1). Incomplete follow-up at the transplantation center can bias estimated frequencies of late effects, depending on the reasons for loss to follow-up (discharged/lost to follow-up because they live far away from the center, loss of health insurance/job, or inability to afford follow-up care, or good health precluding perceived need to be followed by the transplantation center).

Technological solutions to address these problems of incomplete follow-up and data reporting burden are urgently needed. These should aim to reduce duplicate data entry and facilitate data transfer between databases. The electronic health record (EHR) is ideally positioned to facilitate patient-centered data collection, as data will theoretically continue to be collected through the EHR regardless of the patient's location years after transplantation. Transplantation professionals and clinical informaticians should engage with existing vendors to build transplantation-specific data collection modules that will standardize the timing and data variables that are important for late effects research. Such systems must be designed to use standardized terminology, such as those developed by the National Cancer Institutes (NCI) common data elements initiative (https://wiki.nci.nih.gov/display/caDSR/CTEP+Common+Data+Elements#CTEPCommonDataElements-OverviewoftheCDEProject). In an ideal state, data entered once within the EHR would be transferred directly to research organizations without requiring duplicate entry by data professionals, while remaining compliant with consent requirements and protections for privacy and confidentiality.

Assessment of Health Status and Health-Related Complications

Ideally, a comprehensive health assessment of HCT survivors (in a clinic setting) would optimize accurate characterization of long-term survivor health. Although some institutions follow American Society for Blood and Marrow Transplantation guidelines [10] and conduct a clinical assessment of their survivors (albeit for varying lengths of time), others are unable to do so for a variety of reasons (insurance, distance, resources, etc.). In fact, the resources needed for comprehensive clinical assessment in large, geographically dispersed cohorts are often prohibitive. As a more practical approach, large cohort studies (for example, Women's Health Initiative, Nurses' Health Study, and Childhood Cancer Survivor Study [CCSS]) have relied upon self report of health outcomes.

The CCSS and the Bone Marrow Transplant Survivor Study (BMTSS) include survey questions regarding diagnosis by a health care provider of physical health conditions (endocrinopathies, central nervous system compromise, cardiopulmonary dysfunction, gastrointestinal and hepatic sequelae, musculoskeletal complications, and subsequent neoplasms) with age at diagnosis. These studies have shown that HCT survivors can report major health complications with acceptable levels of accuracy [11]. In studies focusing on late effects, strong consideration should be given to the inclusion of patient-centered outcomes (symptoms, functional status, financial toxicity, behavioral and lifestyle factors).

These outcomes can be measured with patient-reported outcomes (PRO) or with a performance-based measure (eg, 6-minute walk) or sensor actigraphy. Although these methods allow assessment and capture of outcomes that are clinically overt (eg, fracture), they represent an underestimation of clinically asymptomatic disease (such as osteoporosis) and this limitation needs to be acknowledged when conducting these large studies.

Other modes of data collection can be very helpful to complement and augment clinician-reported outcomes and PRO. Comparatively few reports use performance-based measures. Additional methodologic work is needed to evaluate validity and responsiveness in HCT survivors. Explicit standards for the collection, analysis, and interpretation of patient-centered outcomes have been articulated by several professional groups and provide important guidance in the use of these endpoints.

The inclusion of health status assessments gathered using self-reported, performance-based measures or sensors can be optimized by procuring informed consent before HCT, covering the following elements: (1) consent to abstract relevant clinical information from the medical records at the transplantation center; (2) consent to contact other health care providers or facilities following the patient for relevant clinical information; (3) consent to contact patients in the future for new research initiatives; and (4) consent to bank biospecimens (in compliance with the latest National Institutes of Health guidelines for biospecimen research). Often, the patients are asked for the preferred option to contact and offered the ability to be contacted by mail, phone, email, or social media. Contact information of the patient and at least 1 other relative or friend should be obtained to minimize loss to follow-up. For patients younger than 18 years of age at HCT, reconsenting is required when they reach the age of majority.

Another approach is obtaining consent from the patient for direct contact through a centralized body (for example, CIBMTR), which could allow data to flow from the patient to their CIBMTR transplantation record and then back to the transplantation center. This model may be particularly of interest to smaller transplantation centers or those lacking the infrastructure to collect long-term data themselves. The EHR could be used as direct patient-contact portals for data exchange. For example, the EHR could be used to send reminders directly to patients to schedule specific follow-up tests at certain time points, and they could enable patients to report the results or other data (eg, clinical, medication or PROs) that could then be linked to their transplantation record. The collection of behavioral and lifestyle factors (eg, current use of tobacco, alcohol consumption, physical activity, diet quality, stress, and depression) can also leverage data elements that are being gathered increasingly as part of general health histories using electronic portals that link to the EHR. The EHR could also be used to communicate survivor-ship care plans directly to the patient and other providers. Such a centralized data collection model may also be possible outside of the EHR (in countries where the EHR is not yet prevalent, for example) using other free online data entry portals such as REDCap (https://redcap.vanderbilt.edu/) or patientslikeme (https://www.patientslikeme.com/).

TRENDS IN TRANSPLANTATION STRATEGIES DURING THE PAST FOUR DECADES

Numerous studies have shown associations between patient demographic, disease, and transplantation characteristics and the risk of specific long-term complications after HCT. These characteristics have changed over the past 4 decades; thus, an awareness of the specific nature of these changes is critical to understanding trends in long-term morbidity over time.

We used CIBMTR data to examine international trends in transplantation strategies over the past 4 decades. CIBMTR has been collecting HCT outcomes data worldwide for more than 40 years, resulting in a research database with information on more than 425,000 patients. Table 2 shows select data for registered recipients of first allogeneic or autologous transplantation for any disease during each of the 4 decades between 1980 and 2014 (first decade: 1980 to 1989; second decade: 1990 to 1999; third decade: 2000 to 2009; fourth decade: 2010 to 2014).

Patient Characteristics

The median age at HCT has increased steadily during the 4 decades for both autologous HCT (34 years to 58 years) and allogeneic HCT (24 years to 47 years) (Figure 2). Furthermore, the upper age at HCT has also increased for autologous HCT (66 years to 84 years) and allogeneic HCT (72 years to 84 years).

Disease and Transplantation Characteristics

Conditioning regimens for allogeneic HCT have changed significantly during the past 4 decades (Figure 2). In the earliest decades, pretransplantation conditioning was always given with myeloablative intent. Since the 1990s, the intensity of conditioning regimens has decreased. Reduced-intensity conditioning regimens were used for 26% of patients in the 2000s and for approximately 40% of transplantations since 2010. High-dose total body irradiation remains a part of the conditioning regimen in >50% of children treated for malignant diseases, but the use of total body irradiation in adults has decreased to <50% in both the myeloablative and reduced-intensity conditioning setting [12].

Myeloma has become the most common indication for autologous HCT in adults, accounting for >50% of all autologous transplantations since 2010, compared with 11% in the 1990s [9,13]. In the 1980s, nearly one-third of the pediatric autologous transplantations were performed for treatment of hematological malignancies such as acute leukemia [14]. Nearly all pediatric autologous transplantations are now performed for treatment of nonhematological malignancies.

Allogeneic HCT has been performed predominantly for acute leukemia in patients of all ages. In adults, chronic myeloid leukemia was the most frequent indication for al-logeneic HCT in the 1980s [15]. This indication now represents <5% of cases, whereas myelodysplastic syndromes are now the most common indications for allogeneic HCT. In

children, nonmalignant disease indications, such as severe aplastic anemia, have remained a focus for allogeneic HCT across all 4 decades.

Donor and Stem Cell Source—[16–20] HLA-identical siblings were the predominant source of stem cells in the early years of HCT, but grafts now come more frequently from unrelated than from related donors. HLA-haploidentical family donors were used with variable success before 2000. Since then, improvements with this approach have been dramatic. Successful HLA-haploidentical transplantation protocols have used innovative strategies to obtain large numbers of donor cells, together with in vitro or in vivo depletion of T cells or post-transplantation cyclophosphamide to decrease the risks of graft rejection and severe GVHD. The use of umbilical cord blood as a stem cell source was introduced in the 1980s. In the early 2000s, cord blood transplantation became widely accepted for both adults and children.

In the 1980s, aspirated marrow was used as the source of stem cells for nearly all allogeneic and autologous transplantation recipients. Transplantation of mobilized peripheral blood stem cells (PBSCs) was introduced in the 1990s. Mobilized PBSCs now represent the stem cell source of choice for autologous HCT for both adults and children. Likewise, mobilized PBSCs now represent the predominant stem cell source used for allogeneic HCT in adults (Figure 3). The use of marrow has predominated for pediatric HCT from the beginning to the present. Medications used for mobilization have changed over time as well. Granulocyte colony–stimulating factor has been used since the 1990s. Survival rates are comparable after HCT with granulocyte colony–stimulating factor–mobilized blood cells versus bone marrow, but the risk of chronic GVHD after allogeneic HCT is increased among those receiving mobilized blood cells [21]. Within the past 10 years, plerixafor has also been used to mobilize cells for autologous HCT. The long-term effects of using plerixafor for mobilization have not yet been assessed [22].

Characteristics of HCT Survivors

We used data from BMTSS to summarize the demographic and clinical characteristics of individuals who received HCT at 2 large transplantation centers (City of Hope and University of Minnesota) and survived 2 or more years (Table 3). These characteristics reflect the changes in transplantation strategies over the past 4 decades.

INFRASTRUCTURE TO UNDERSTAND THE MOLECULAR UNDERPINNINGS OF POST-TRANSPLANTATION MORBIDITY

Studies using biologic specimens represent a mainstay for understanding the pathogenesis of post-transplantation complications. The utility of such biospecimens for hypothesis-driven studies is greatly enhanced by the availability of well-annotated data summarizing the clinical history of study subjects. Although no existing biorepositories have been historically designed to collect biological specimens specifically for research related to post-HCT late complications, several currently available resources could possibly be utilized. Table 4 summarizes the strengths and limitations of these existing sources of biospecimens.

Several considerations should be applied for prospective collection of biospecimens to study late effects after HCT. First, the nature of biospecimens and the timing of collection should be driven by clearly stated questions that address specific hypotheses and the specific assays needed to address the questions. For example, a DNA sample collected from the patient before HCT can be used to investigate how variation in the patient's germline might affect the patient's ability to handle toxicity stemming from therapies received before HCT and those related to the conditioning regimen. On the other hand, post-HCT DNA can be used to understand how chimeric donor-derived cells affect the risks of late complications after HCT. Distinctions should be made for predictive hypotheses requiring samples from before HCT or early after HCT to predict future events versus pathogenic hypotheses or diagnostic evaluations requiring samples from the time of onset of the late effect. Hypothesis-driven sample collection permits the biorepository and the end user to develop the optimal technical protocols to ensure that the specimens will meet the specific needs of the research. This hypothesis-driven approach has several limitations: specimens will take time to accrue, previously collected specimens might not be optimal for new research questions, and specimens originally collected for other specific studies might be limited in their scope and utility to the original hypothesis.

Another consideration for the collection of biospecimens to study HCT late effects is the feasibility of prospective collection of specimens from every patient at serial prespecified time points before and after autologous or allogeneic HCT. This would serve as an ambitious and expensive undertaking, requiring significant coordination with the treating physician and patient, and would be limited by the attrition of those who die at the intermediate time points. However, this approach in a subset of patients could enable an understanding of the intermediate events (eg, subclinical cardiotoxicity) before development of the overt complication (eg, heart failure).

A third consideration pertains to the need for collaborative multidisciplinary efforts to conduct research in late effects after transplantation. Coordinated efforts across laboratories and research teams to capture data and retain the history of testing for each specimen will enrich and enhance the entire research effort. A centralized database with details regarding the specific assays performed on each specimen would prevent duplication of effort and could expedite discovery. The resource requirements to assemble and maintain such a database, as well as an effective data governance framework, are required to ensure the availability, usability, integrity, and security of data.

A fourth consideration is the availability of detailed clinical annotation for patients with and without late effects. The use of existing biorepositories is an efficient and practical methodological approach, but the clinical annotation may not exist or be sufficiently detailed, thus requiring additional data collection efforts. Development of a comprehensive infrastructure consisting of clinically annotated biospecimens and accompanying bioinformatic support to address a multitude of hypotheses in the future, while keeping pace with technological advances is a critical initiative necessary for the study of HCT late effects. It is here that PROs could play a role in efficiently and validly capturing specific aspects of the phenotype (eg, comorbid conditions, depression, social support, socioeconomic status, body composition, and health behaviors [tobacco use, alcohol

consumption, diet quality, sun exposure, and physical activity]) that are known to mediate or moderate the relationship between exposures and late complications of HCT. Consensus within the research community will be needed to determine the essential constructs required for this deep characterization, and to define a core measure set to capture these data. Resources will also be needed for electronic data capture and follow-up to ensure data completeness.

Lastly, the technical requirements and best practices for biorepositories will always be a moving target, as technological platforms become more sophisticated. Publicly available resources, such as the NCI Biospecimen Research Database [23], NCI Recommended Best Practices for Biospecimen Resources [24], and NCI Biospecimen Research Network [25], can provide peer-reviewed expert guidance on these considerations.

MAJOR STUDY DESIGNS AND ANALYTIC APPROACHES

In this section, we describe methodological approaches used to conduct HCT survivorship research. Fundamentally, the study designs and analytic approaches that are relevant to research on late effects after HCT are not different from those applicable to any other medical condition. The primary factors affecting the design and analytic approach are defined by the particular study question and the data that are available to address it. In Table 5 we provide a summary of the strengths and limitations of the various study designs. Finally, we provide an integrated schematic overview in Figure 4, describing some of the key steps and decision points involved in planning and designing a study focused on long-term complications after transplantation. These points are elaborated below.

1. What are the study parameters as defined by the study question?

For example, what is the population of interest—is it defined by type of transplantation, by disease, or by outcome? What is the endpoint of interest; when does it occur (ie, latency); how frequently does it occur; is it a single irreversible event (eg, renal failure, subsequent malignant neoplasm, stroke, osteonecrosis, cataracts, etc.) or is it reversible and recurrent (eg, infection)? Is it a clinical endpoint derived from specific diagnostic or laboratory studies, a clinician-reported outcome (eg, chronic GVHD grading), or a PRO? What are the risk factors or exposures that are of interest; when do they occur; and how frequently do they occur? Does the research question require longitudinal data, derived at different points in time, or does it require cross-sectional data, from a single point in time. Is it a time-varying variable (eg, tobacco use, or comorbid conditions) or is it a fixed variables (ie, age at HCT, transplantation type etc.)?

2. Does a relevant transplantation cohort exist, with the requisite data routinely collected, available and accessible?

This could be a single-institution cohort, a multi-institutional cohort, a registry cohort (eg, CIBMTR), or a clinical trial cohort. Table 6 summarizes the strengths and limitations of the different types of cohorts. A major limitation of many existing cohorts is a lack of data pertaining to non-GVHD late effects or lack of data pertaining to pre-HCT exposures and risk factors. Some institutional cohorts may have excellent follow-up covering particular late

effects of long-standing interest but no data on other late effects. Registries may collect data on some pre-HCT risk factors in the immediate pre-HCT period (eg, the HCT comorbidity index), but detailed summaries of prior exposures are typically not collected. Cohorts assembled from 1 or more clinical trials may provide some of the data lacking in other traditional cohorts, although the strengths and limitations will reflect the entity sponsoring the trial (single institution versus cooperative group) and the goals of the study with respect to late effects, which may be merely incidental to the main purpose or may, in fact, help to define the trial. For the most part, clinical trials are not geared to collect morbidities developing 10 or more years after HCT in a comprehensive fashion.

Although CIBMTR now captures data on every allogeneic transplantation performed in the United States, this practice was not previously the case. The collection of data items has changed over the years. For example, the HCT comorbidity index was added to the report forms in 2007. In addition, financial constraints allow for specific data related to late effects and their risk factors to be collected only in a minority of patients (those on the comprehensive research form track). The intermittent nature of the data is such that temporal associations of events cannot always be gauged, and detail of changes over time are lacking.

3. If existing cohorts are deficient as they stand, can they be adapted with reasonable effort to provide the requisite data?

For example, if pretransplantation characteristics of interest have not been systematically collected, could they be reliably acquired through retrospective chart review? Are banked samples available, even if they were originally collected for a different purpose? Could a special sub-study be implemented to ascertain the cross-sectional prevalence of the late effect of interest?

4. If an existing or modifiable cohort is available, are sufficient numbers of patients available in the population of interest to perform a study with reasonable power and precision?

The answer to this question will depend on many factors, including the study design and analytic methods, as well as the usual parameters of effect size, variability, type I and type II error rates, among other considerations. Table 7 provides estimates of sample size for a common scenario evaluating the impact of a risk factor on the incidence or prevalence of a late effect. The range of sample sizes required for standard specifications of power and type I error rates varies by more than an order of magnitude. Sample size is particularly sensitive to effect size (the difference in risk or prevalence) and it is important to consider effects that are both plausible and clinically relevant. Other important considerations for planning sample size include the number of factors under study—ie, is it a study of the association between a single risk factor and a single late effect, or an “omics” study of a large number of single nucleotide polymorphisms or other markers? In the latter case, one must consider issues of multiple comparisons, as well as an overall strategy for discovery and replication. Even in the former case, accounting for complex phenotypes or exposures in the presence of patient heterogeneity may require many more patients, if only to permit stratification and subset analysis. These issues emphasize the need for statistical expertise when planning the size and power for a study.

5. How can appropriate controls be selected?

Assessment of the magnitude of risk of an adverse event in any population necessitates inclusion of a reference population or a control group. Selection of an appropriate control group is dependent on the hypothesis which is being tested. The selected control population should be as similar as possible to the experimental group, so that the outcome difference between the two groups can be attributed to the exposure of interest. However, there are inherent problems in obtaining a valid concurrent control group for patients undergoing HCT. Ideally, a control group for HCT patients should consist of cancer patients identical in all respects (demographics, clinical characteristics) but randomized to conventional chemotherapy without HCT. However, such a situation occurs rarely in the setting of randomized clinical trials—where the limited sample size precludes assessment of rare late effects. A real-life control group consisting of patients who have cancer but are not undergoing HCT (ie, a cancer control group) will generally include patients with more favorable stages of disease, and with lower cumulative exposures to chemotherapy and radiation.

An alternative (or concurrent) approach would be to obtain a healthy control group matched for age at study participation and gender. Recruitment of a representative control population can be challenging. Typically, controls are selected from 1 of the following sources: general population, spouse, friend(s), or sibling(s) of the experimental group. Control populations can also be obtained from large nontransplantation registries such as Surveillance, Epidemiology and End Results (SEER) and the SEER linkage databases and payer databases, such as Anthem, GroupHealth, and Kaiser. These sources serves as a good resource for providing expected age and sex-specific rates. Table 8 summarizes the advantages and limitations associated with the use of each of these groups. Siblings provide the following: (1) the ability to make direct comparisons with survivors, (2) data on outcomes in general population that are not available from other sources (eg, vital statistics, NHIS, etc.), and (3) an additional comparison group to determine consistency of findings between data sources (ie, SEER, NHIS). Siblings in other survivor studies (such as CCSS and BMTSS) have proven to be an effective comparison group, associated with high participation rates, ease of access, and general uniformity of socioeconomic status and level of health awareness. We recognize that siblings may not be representative of an unaffected population for psychosocial distress and quality of life, and we do not recommend the use of siblings for these comparisons.

6. What is the specific study design and analytic approach?

Study design and analytic methods can affect the choice of study population and sample size. Table 9 briefly summarizes some typical analytic approaches for common types of research questions. The list is by no means comprehensive, nor does it mandate that a particular analytic method be used for a particular type of study. Choosing the study design and analysis plan should involve input from statistical and epidemiological collaborators.

A few issues are worth noting regarding analysis of late effects in general. By definition, these arise in the surviving members of the transplantation cohort, which in the present context requires survival for at least 1 year. The method of analysis has to be chosen so that

the quantities estimated are interpretable relative to the population of interest. For example, risk factors related to incidence of late effects in the transplantation cohort as a whole must take into account censoring and the competing risk of death. These are best handled by using time-to-event cohort methods. On the other hand, if the interest is in risk factors for late effects constrained to a population of survivors at a defined point in time, then case-control methods may be used. The risk estimates from cohort studies and case-control studies are not interpretable interchangeably, particularly when the risk factor is also related to survival.

As noted above, studies of incidence of late effects (or of outcomes subsequent to late effects) may need to account for the risk of competing endpoints. Death is an obligatory competing risk, since it precludes the development of any future endpoint. Recurrence of disease or disease progression, although not usually precluding subsequent late effects, could be treated as a competing risk (if interest in the late effect is focused on patients for whom disease control is not the primary medical issue) or as an exposure of interest, if additional treatment of disease relapse is hypothesized to cause of late effects. Similarly, other late effects themselves might be considered as competing risks. For example, chronic GVHD might be treated as a competing risk for studies of non–GVHD-related infection or lung disease.

More generally, late effects often do not occur in isolation. Patients frequently experience multiple late effects or multiple instances of the same late effect, and it may be of interest to explore the relationship among different late effects. Some late effects could become baseline covariates or time-dependent covariates for the primary effect of interest. Alternatively, the number of late effects, of a single type or of multiple types, may be modeled as a multistate counting process. Cox regression models can be flexibly generalized to handle many of these situations, as can Poisson regression models. These methods focus primarily on the underlying hazard rate for the late effect, but other methods are possible, such as competing risks regression that directly models the incidence of a late effect.

Missing data in late effects studies are as problematic as in any other setting. In some cases, they represent only a minor annoyance; in other cases, they can compromise the ability of the study to draw valid conclusions. The key considerations are the proportion of data that are missing and whether the data are missing at random or are informatively associated with the late effect itself or with covariates of interest. For example, in longitudinal studies of quality-of-life endpoints with repeated assessments, one should carefully consider whether a missing assessment is truly random or reflects some information about the endpoint of interest or other factors. Randomly missing data are far more easily accommodated, perhaps using complete case series (if the amount of missing data is small), linear mixed models, or GEE models. Options may be limited if the missing data is thought to be nonrandom. One can evaluate the endpoint under different patterns of missing data or perhaps employ sensitivity analysis to evaluate the impact of different assumptions about the missing data. A full accounting for nonrandom missing data can only be accomplished through joint modeling of the endpoints of interest and the mechanism producing the missing data. This may be difficult or impossible and will likely rest on untestable assumptions about the reasons for missing data.

The above considerations reinforce the message that studies of late effects of HCT may be potentially difficult to design and analyze. Collaboration with statisticians and epidemiologists with relevant experience and expertise is essential to ensure that such studies are as informative as possible.

CONCLUSIONS

The key to achieving success in this challenging and rapidly growing field is a multidisciplinary approach. Key stakeholders include HCT recipients, healthcare providers, outcomes researchers, registries, molecular epidemiologists, statisticians, clinical informaticians and bioinformaticians, health economists, and policy makers as well as funding agencies. Critical pieces for establishing a long-term infrastructure include a core set of clearly defined validated outcomes, a strategic collection of clinically annotated biospecimens, mechanisms to follow patients for the outcomes long-term, and an ability to capture key exposures. PROs should be a key component of measuring the burden of morbidity in HCT survivors. Findings from these studies should set the stage for identifying patients at highest risk and developing targeted interventions.

To ensure that we are able to perform appropriate studies in the future, we call for funding initiatives for logistical support to improve data capture (short- and long-term) and reduce redundancy, and to improve biospecimen collection and biobanking. An immediate need is for data transfer initiatives to leverage sharing between existing data and samples sources, including registries, clinical trials, biorepositories, and single-center efforts, to perform the outcome analyses now which will inform the questions to be studied in the future.

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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	Cardiac toxicity	**a.**	Radiation
		3	Pulmonary dysfunction	**b.**	Anthracyclines
2	Excess risk compared with the general population	**4**	Osteonecrosis	**c.**	Bleomycin
		5	Stroke	**d.**	Nitrosoureas
		6	Pregnancy	**e.**	Dexamethasone
		7	Menopause	**2**	**HCT-related exposures**
3	Modifiable risk factors	**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
		2	Pulmonary	**3**	Whole genome sequencing
		3	Subsequent cancer	**4**	Methylome assay
				5	Gene expression analysis
3	Plasma/ serum	**4**	Stroke	**6**	Metabolomics and proteomics
		5	Osteonecrosis		

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

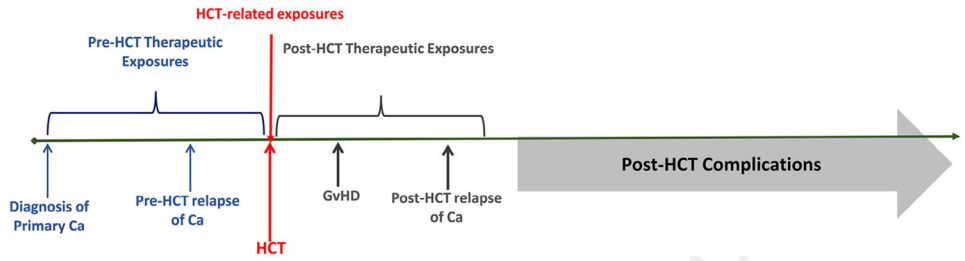

Figure 1.
Therapeutic exposures associated with risk of late complications developing after HCT.

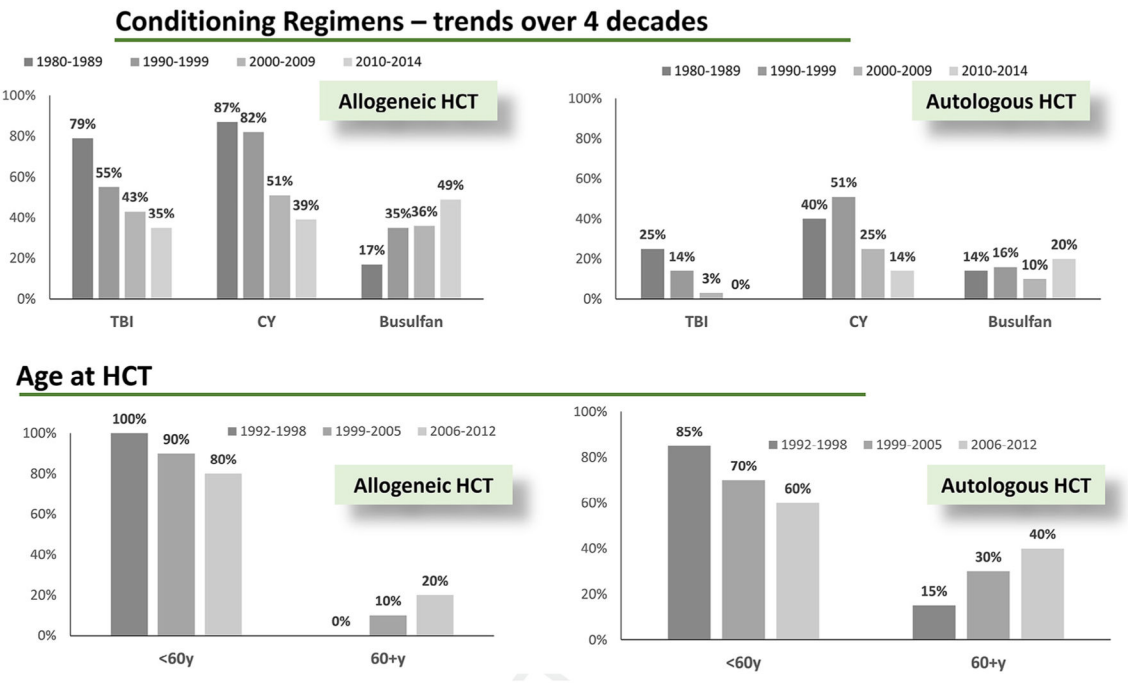

Figure 2.
International trends in conditioning regimens and age.

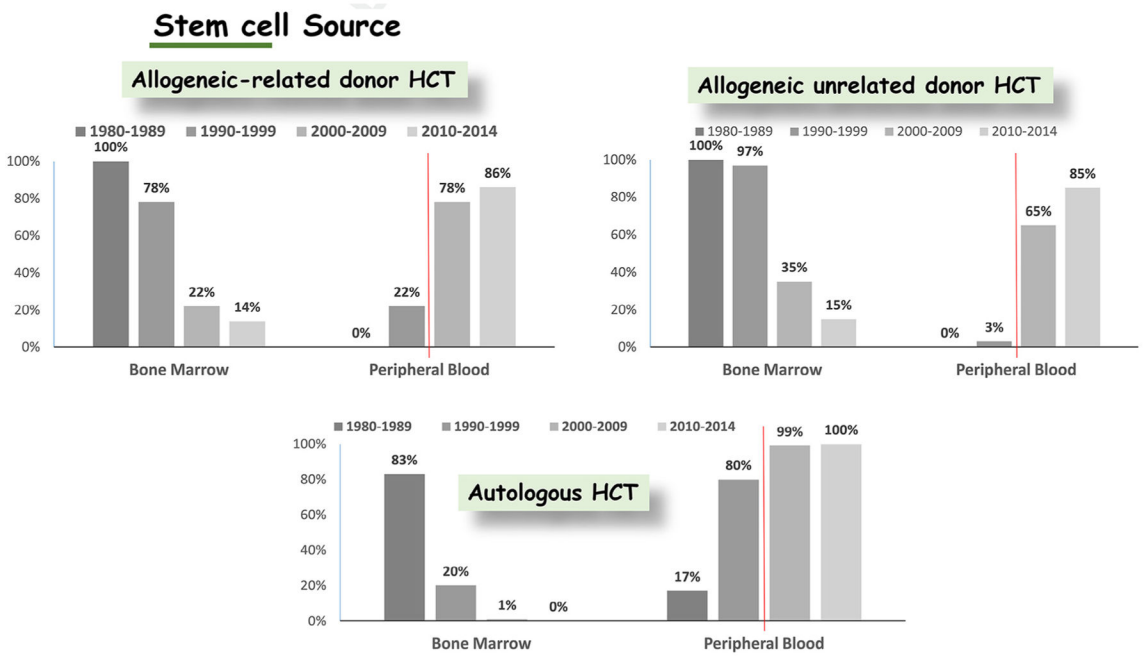

Figure 3.
International trends in stem cell source.

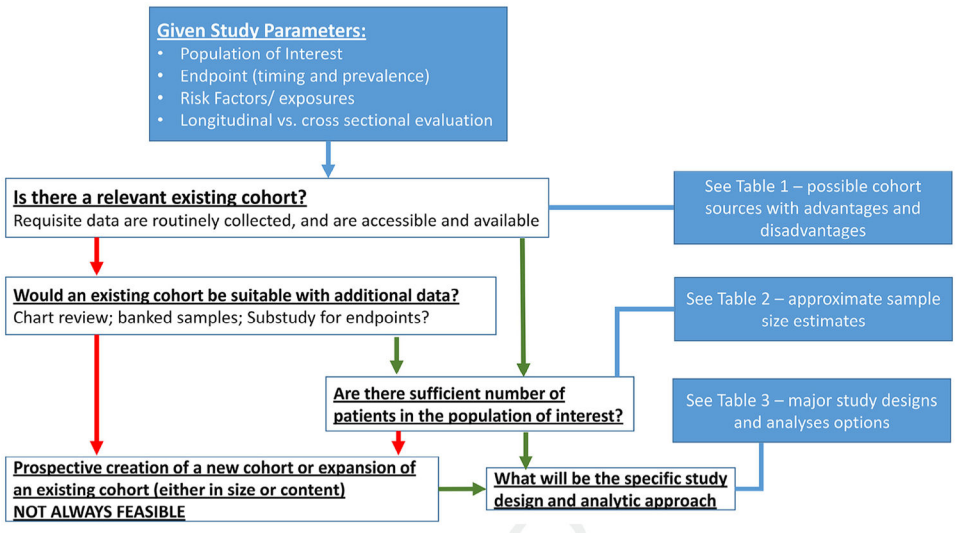

Figure 4.

Integrated schematic overview of design of a study focusing on long-term complications after HCT.

Table 1

Frequent Complications after HCT: Onset, Latency, and Course

Post-HCT Complication	Earliest Onset	Median Latency	Plateau?
Gonadal failure	<1 Yr	0–6 Mo	Yes
Infertility	<1 Yr	0–6 Mo	Yes
Cardiac dysfunction	<1 Yr	3–4 Yr	No
Coronary artery disease	3–4 Yr	10–15 Yr	No
Pulmonary dysfunction	<1 Yr	0–12 Mo	No
Therapy-related leukemia	<6 Mo	3–4 Yr	Yes - 15 Yr
Solid malignancies	2–3 Yr	10–15 Yr	No
Endocrine complications	<1 Yr	2–3 Yr	No

Table 2

International Trends in HCT Strategies during the Past Four Decades

	1980–1989	1990–1999	2000–2009	2010–2014
Autologous HCT				
No. of patients	1551	57423	71999	49697
Age at transplantation, median (range), yr	34 (<1–66)	45 (<1–79)	53 (<1–86)	58 (<1–84)
Allogeneic HCT				
No. of patients	14138	57829	80019	44223
Age at transplantation, median (range), yr	24 (<1–72)	31 (<1–79)	37 (<1–83)	47 (<1–84)
Primary diagnosis by stem cell source (age ≥18 at HCT)				
Autologous HCT				
No. of patients	1324	53250	66620	46846
Primary diagnosis				
AML	190 (14)	2873 (5)	2986 (4)	466 (<1)
ALL	46 (3)	546 (1)	309 (<1)	49 (<1)
NHL	366 (28)	14262 (27)	21534 (32)	13702 (29)
HL	333 (25)	5345 (10)	8370 (13)	4424 (9)
MM	29 (2)	5698 (11)	29137 (44)	26986 (58)
Other	360 (27%)	24526 (46%)	4284 (6%)	1219 (2.6%)
Stem cell source				
Bone marrow	1103 (83)	10432 (20)	919 (1)	107 (<1)
Peripheral blood	221 (17)	42816 (80)	65698 (99)	46681
Umbilical cord	0	2 (<1)	3 (<1)	58 (<1)
Allogeneic HLA identical sibling HCT				
No. of patients	7683	28364	30864	12850
Primary diagnosis				
AML	2326 (30)	7756 (27)	10319 (33)	5127 (40)
ALL	1332 (17)	3325 (12)	3846 (12)	2036 (16)
CML	2382 (31)	8262 (29)	3971 (13)	590 (5)
MDS	354 (5)	2238 (8)	3431 (11)	2136 (17)
NHL	262 (3)	2381 (8)	3893 (13)	1244 (10)
SAA	701 (9)	1489 (5)	1630 (5)	670 (5)
Other	326 (4%)	2913 (10%)	3774 (12%)	1047 (8%)
Stem cell source				
Bone marrow	7682 (99)	22143 (78)	6915 (22)	1737 (14)
Peripheral blood	1 (<1)	6221 (22)	23949 (78)	11113 (86)
Allogeneic other related HCT				
No. of patients	882	2844	3787	2617
Primary diagnosis				
AML	259 (29)	781 (27)	1362 (36)	1115 (43)
ALL	151 (17)	371 (13)	504 (13)	328 (13)
CML	277 (31)	839 (30)	325 (9)	113 (4)

	1980–1989	1990–1999	2000–2009	2010–2014
MDS	39 (4)	227 (8)	443 (12)	383 (15)
NHL	37 (4)	251 (9)	518 (14)	289 (11)
SAA	74 (8)	77 (3)	128 (3)	92 (4)
Other	45 (5)	298 (10)	507 (13)	297 (11)
Stem cell source				
Bone marrow	882 (100)	2082 (73)	796 (21)	842 (32)
Peripheral blood	0	762 (27)	2991 (79)	1775 (68)
Allogeneic unrelated HCT				
No. of patients	402	9162	22339	17582
Primary diagnosis				
AML	66 (16)	1998 (22)	8529 (38)	7653 (44)
ALL	38 (9)	1243 (14)	3320 (15)	2340 (13)
CML	244 (61)	4143 (45)	2515 (11)	705 (4)
MDS	20 (5)	852 (9)	3361 (15)	3433 (20)
NHL	1 (<1)	315 (3)	1965 (9)	1430 (8)
Stem cell source				
Bone marrow	402	8866 (97)	7780 (35)	2709 (15)
Peripheral blood	0	296 (3)	14559 (65)	14873 (85)
Cord blood (age ≥18 at HCT)				
No. of patients	N/A	233	2075	2282
Primary diagnosis				
AML		65 (28)	853 (41)	1117 (49)
ALL		42 (18)	398 (19)	434 (19)
CML		75 (32)	154 (7)	103 (5)
MDS		15 (6)	216 (10)	263 (12)
NHL		12 (5)	207 (10)	174 (8)
Primary diagnosis by stem cell source (age <18 at HCT)				
Autologous HCT				
No. of patients	227	4173	5379	2851
Primary diagnosis				
AML	56 (25)	589 (14)	224 (4)	29 (1)
ALL	25 (11)	280 (7)	51 (<1)	0
NHL	38 (17)	353 (8)	328 (6)	114 (4)
HL	21 (9)	386 (9)	648 (12)	342 (12)
Other malignancies	83 (37)	2450 (59)	4045 (75)	2316 (81)
Stem cell source				
Bone marrow	216 (95)	2057 (49)	482 (9)	76 (3)
Peripheral blood	11 (5)	2115 (51)	4887 (91)	2770 (97)
Umbilical cord	0	1 (<1)	10 (<1)	5 (<1)
Allogeneic HLA-identical sibling donor				
No. of patients	3653	8671	7877	2943
Primary diagnosis				

	1980–1989	1990–1999	2000–2009	2010–2014
AML	739 (20)	1708 (20)	1580 (20)	414 (14)
ALL	1207 (33)	2456 (28)	1880 (24)	621 (21)
SAA	570 (16)	1134 (13)	1142 (14)	405 (14)
Other	1137 (31%)	3373 (39%)	3275 (42%)	1503 (51%)
Stem cell source				
Bone marrow	3653	8105 (93)	5817 (74)	2469 (84)
Peripheral blood	0	566 (7)	2060 (26)	474 (16)
Allogeneic other related donor				
No. of patients	987	2110	1881	812
Primary diagnosis				
AML	133 (13)	340 (16)	349 (19)	126 (16)
ALL	262 (27)	603 (29)	451 (24)	144 (18)
Other				
Stem cell source				
Bone marrow	987	1718 (81)	921 (49)	499 (61)
Peripheral blood	0	392 (19)	960 (51)	313 (39)
Allogeneic unrelated donor				
No. of patients	187	4207	5685	3029
Primary diagnosis				
AML	17 (9)	650 (15)	1104 (19)	571 (19)
ALL	53 (28)	1561 (37)	1794 (32)	678 (22)
SAA	24 (13)	298 (7)	425 (7)	304 (10)
Other	93 (50)	1698 (40)	2362 (42)	1476 (49)
Stem cell source				
Bone marrow	187	4111 (98)	4128 (73)	2228 (74)
Peripheral blood	0	96 (2)	1557 (27)	801 (26)
Cord blood				
No. of patients	2	917	4288	2105
Primary diagnosis				
AML	0	174 (19)	845 (20)	406 (19)
ALL	0	274 (30)	1204 (28)	514 (24)
Other	2 (100)	469 (51)	2239 (52)	1185 (56)

AML indicates acute myeloid leukemia; ALL, acute lymphoid leukemia, NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; CML, chronic myeloid leukemia; MDS, myelodysplastic leukemia; SAA, severe aplastic anemia.

Table 3

Demographic and Clinical Characteristics of Two-Year Survivors Who Underwent Transplantation between 1974 and 2010 in the United States, Regardless of Current Vital Status

Table	BMTSS-2 n = 11,465
Type of HCT	
Related	3240 (28%)
Unrelated	1573 (14%)
Autologous	6652 (58%)
Age at HCT	
<18 Yr	**1161 (10%)**
18 to 45 Yr	**5116 (45%)**
46 to 60 Yr	**3469 (30%)**
>60 Yr	**1719 (15%)**
Race/ethnicity	
Whites	**9276 (81%)**
Hispanics	**1215 (11%)**
Blacks	**512 (5%)**
Asians	**462 (4%)**
Diagnosis	
AML/ALL	**4149 (36%)**
CML	**1272 (11%)**
NHL/HL	**4295 (38%)**
Other	**1749 (15%)**
Intensity of conditioning	
RIC	**1011 (9%)**
Stem cell source	
Marrow	**3498 (31%)**
PBSC	**7485 (65%)**
Cord	**482 (4%)**
Vital status	
Deceased	**3673 (32%)**
Length of follow-up	
>10 Yr	**4190 (37%)**

RIC indicates reduced-intensity conditioning.

Table 4

Current Sources of Biospecimens for Studies of Late Effects after HCT: Sample Types, Strengths and Weaknesses

Biorepository	Sample Types	Strengths	Weaknesses
CIBMTR	• Allogeneic BMT recipients and donors • Samples drawn pre-BMT only • Blood, marrow, PBMCs	• Represents a large proportion of allogeneic HCT recipients in the United States (unrelated, related and cord blood) • Consistent collection, shipment and storage methods (SOP driven)	• No samples from autologous HCT patients • No samples after HCT • No tissue, urine, feces, hair, or nail samples
BMT CTN 1202	• Allogeneic HCT recipients and donors • Pre-HCT and post-HCT blood samples • Randomized subset of recipient samples for RNA/gene expression studies	• Serial samples from allogeneic HCT patients (multiple time points) • Consistent collection, shipment and storage methods (clinical trial protocol driven)	• Small proportion of all US allogeneic HCT patients • No samples from autologous HCT patients • No samples later than 6 months after HCT • No tissue, urine, feces, hair, or nail samples
BMT CTN trials	• Homogeneous within trials • Heterogeneous if pooling data across multiple trials	• Pre- or post-HCT samples may be available • Tied to clinical trials of specific treatments	• Sample collection and storage is trial specific • Limited to patients treated on a clinical trial (not representative of all HCT patients)
CALGB/ACTION, SWOG, ECOG, COG, other cooperative group trials	• Homogeneous within trials • Heterogeneous if pooling data across multiple trials	• Pre- or post-HCT samples may be available • Tied to clinical trials of	• Sample collection and storage is trial specific • Limited to patients treated on a clinical trial

Biorepository	Sample Types	Strengths	Weaknesses
		specific treatments	(not representative of all BMT patients)
Individual transplantation centers	• Heterogeneous if pooling samples across multiple individual centers, ie, different centers have different protocols for sample collection • Homogeneous within a single center, or heterogeneous if protocols changed over time	• Autologous and allogeneic HCT patient samples • Remnant tissue from cancer diagnosis, GVHD or negative biopsies	• Unknown number of centers with biorepositories • Heterogeneous sample collection timepoints, specimen types, auto/allo HCT, before/after HCT, processing and storage methods within and across individual centers

BMT indicates; CIBMTR, ; BMT, ; CTN, ; CALGB/ACTION, ; SWOG ECOG, ; COG,

Table 5

Designs Used for Studies of Long-Term Morbidity after HCT: Definitions, Strengths and Limitations

Study Design	Definition	Strengths	Limitations
Cross-sectional	Examines relationship between exposure and outcome prevalence in a defined population at a single point in time	• Less time-consuming than case control or cohort studies • Inexpensive • Good, quick picture of prevalence of exposure and prevalence of outcome	• Difficult to determine temporal relationship between exposure and outcome (lacks time element) • May have excess prevalence from cases with low fatality
Case-control	Examines multiple exposures in relation to an outcome; subjects are defined as cases and controls, and exposure histories are compared	• Relatively inexpensive • Less time-consuming than cohort studies • Can evaluate effects of multiple exposures • Efficient for rare outcomes or outcomes with long latency periods • They are advantageous when studying dynamic populations in which follow-up is difficult.	• Subject to recall bias (based on subjects' memory and reports) • Subject to selection bias • Inefficient for rare exposures • Difficult to establish clear chronology of exposure and outcome • They generally do not allow calculation of incidence (absolute risk).
Prospective, longitudinal, cohort studies	• Examines multiple health effects of an exposure; subjects are defined according to their exposure levels and followed over time for outcome occurrence	• Multiple outcomes can be studied • Design study allows collection of all possible variables needed for study • Ability to assess outcomes in real time—as they develop or at predetermined time points—thus temporal relation can be established	• Ability to assess outcomes with long latency is limited • follow-up is usually limited to few years after study initiation • Ability to assess impact of practice across different eras is limited • Expensive (and takes a long time to complete)

Study Design	Definition	Strengths	Limitations
		• Investigator defines and applies outcome criteria a priori • Outcomes can be validated or objectively measured	• Need to manage/ monitor attrition • Participation bias • Changes can take place over time in both exposure and outcome assessment
Retrospective Cohort Studies	• Examines previously collected data from an existing cohort. Data may have been collected retrospectively after the fact or prospectively in real time for a different original purpose.	• Good for studying multiple outcomes • Allows assessment of outcomes with long latency • Allows assessment of impact of change in practice across different eras • Relatively inexpensive (outcome/ exposure have already occurred) • Relatively shorter time period required for study completion	• Large sample size needed to study rare outcomes • Dependent on availability/ quality of data collected in the past • Self-report of outcomes—subject to recall bias • Need to ensure comprehensive follow-up—subject to participation bias • Temporal relation often difficult to determine
Nested case-control studies	• A **nested case control study** is a variation of a **case-control study** where all incident **cases** in the cohort are compared to a random subset of participants who do not develop the disease of interest.	• Efficient—not all members of parent cohort require diagnostic testing • Flexible—allows testing of hypotheses not anticipated when the cohort was drawn (at t0) • Reduces selection bias—cases and controls sampled from same population • Reduces information bias—risk	• Reduces power (from parent cohort) because of reduced sample size

Study Design	Definition	Strengths	Limitations
			factor exposure can be assessed with investigator blind to case status

Table 6

Relative Strengths and Limitations in Studies of Late Effects after HCT, According to Cohort Type

Strength or Limitation	Single Institution	Multi-Institution Consortium	Registry (eg, CIBMTR)
Patient numbers	+	+++	+++++
Rare outcomes	+	++	+++++
Outcomes with long latency	+++	+++	+++
Control/matching	+++	+++	+++
Center bias	+++++	+++	+
Multiple risk factors	+++	+++	+++++
Long term follow up (intensive)	+++++	++++	+++
Pre-HCT exposures	+++++	++++	++
Consistency in data points over time	+++++	+++	++
Associated biospecimens	+++++	++++	++
Expense	++	++++	+++++

Table 7

Sample Size Estimates*

Incidence /Prevalence of Late Effect	Risk Difference	Proportion with Risk Factor				
		10%	20%	30%	40%	50%
.05	**.05**	1980	1070	780	650	600
.05	**.10**	560	300	210	170	—
.10	**.10**	920	500	370	310	280
.10	**.20**	250	140	100	80	—
.20	**.10**	1500	830	620	540	500
.20	**.20**	390	220	160	130	120
.30	**.10**	1900	1060	800	690	660
.30	**.20**	480	270	200	170	160

*Sample size required for 80% power at a 2-sided .05 level of significance to detect specified difference in risk

*These estimates represent the best case scenario where only a single late effect/risk factor is being assessed.

Table 8

Sources of Control Populations—Advantages and Limitations

	Healthy Controls				Cancer Controls	
Consideration	**General Population**	**Spouse**	**Friends**	**Siblings**	**Non-HCT Controls**	**HCT Controls**
Age and gender	Age, gender are frequency-matched to case pool	Age might be comparable; opposite gender	Age, gender frequency-matched to case pool	Age and gender frequency- match may or may not possible	Age, gender are frequency- matched to case pool	Age, gender are frequency matched to case pool
Availability	Random digit dialing; linkage with administrative databases, registries	Dependent on availability of a spouse	Dependent on availability of friend(s)	Dependent on availability of sibling(s)	Dependent on size of patient population	Dependent on size of patient population
Willingness	Participation rates very low; difficult to recruit/retain for serial tests; less motivated; participation bias; significant costs	Motivated to participate	Better than general control; highly motivated to participate.	If geographically distant, on- site testing could be challenging	Participation rates generally similar to those of HCT cases	Participation rates generally similar to the case population
Socio-economic status	May not be comparable to case	Similar	Similar	Similar	Similar	Similar
Genetic factors	Different	Different	Different	Similar profile	Different	Different
Overmatching?	No	Living environment; stress	Probably not	Genetic/early environmental	Probably not	Dependent on study question
Pool	Dependent on participation rate	One per case	Dependent on no. of friends	Dependent on family size	Dependent on patient pool at hospital	Dependent on patient pool at hospital

Table 9

Major Types of Designs and Analytic Approaches in Studies of Late Effects after HCT

Prospective and retrospective cohort study—Risk factors for incidence of late effects

- Discrete diagnosis of a condition at some time after transplantation
- Competing risks may be present that preclude the late effect (death due to other causes)
- Risk factors may be defined prior to transplantation (or other reference time)
- Risk factors may be defined after transplantation (or other reference time) as time-dependent covariates
- Time-to-event methods (generally Cox regression) are commonly used

Examples

Rizzo et al. Solid cancers after allogeneic hematopoietic cell transplantation—evaluated risk factors for solid cancers in a multi-institutional cohort of allogeneic HCT recipients [8].

Sun et al. Chronic health conditions after hematopoietic cell transplantation—examined the magnitude of risk of chronic health conditions in a cohort of 2 + year survivors of HCT.[26]

Cross-sectional study—Risk factors for prevalent late effects

- The late effect is present or absent in a cross-sectional sample of patients and may be further distinguished in terms of active or resolved disease
- Risk factors may be defined at any prior time
- Logistic regression methods are commonly used

Example

Bhatia et al. Bone mineral density in patients undergoing bone marrow transplantation for myeloid malignancies—bone mineral density measured at a single time point in patients who had undergone HCT to determine the prevalence of osteopenia/osteoporosis.[27]

Prospective longitudinal study—Risk factors for late effects

- The late effects are evaluated at various points in time, on a quantitative, ordinal, or binary scale
- Risk factors may be defined at baseline, or during the course of follow-up
- Linear mixed models or GEE models are commonly used

Examples

Syrjala et al. Prospective neurocognitive function over 5 years after allogeneic hematopoietic cell transplantation for cancer survivors compared with matched controls at 5 years. This study prospectively examined the trajectory and extent of long-term cognitive dysfunction, with a focus on 1 to 5 years after treatment.[28]

Wong et al. Long-term recovery after hematopoietic cell transplantation: predictors of quality of life concerns—This prospective longitudinal study examined the QOL after HCT and identified risk factors for poor QOL.[29]

Case-control sampling

- in large cohorts, if extra effort and expense are required to determine risk factors or endpoints, it may not be necessary to assess all patients
- usually, all patients with the late effect, and a random sample of controls, are selected
- most appropriate for cross-sectional sampling
- logistic regression methods are commonly used

Example

Chakraborty et al. Accelerated telomere shortening precedes development of therapy-related myelodysplasia or acute myelogenous leukemia after autologous transplantation for lymphoma. A prospective longitudinal study formed the sampling frame for a nested case-control study to compare changes in telomere length in serial blood samples from patients who developed t-MDS/AML with matched controls who did not develop this outcome.[30]

GEE indicates; QOL, quality of life; t-MDS.