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The Report from the Working Group on Research Methodology and Study Design

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Abstract

The increasing number of hematopoietic cell transplantations (HCTs) performed annually, the evolving demographics of HCT donors, the introduction of novel transplantation techniques, continuous improvements in survival rates, and the expanding population of HCT survivors underscore the need for a comprehensive examination of the health and well-being of individuals post-transplantation. This report provides an overview of strategies for conducting research on late effects after transplantation, including considerations for study design and analytical approaches, methodological challenges associated with handling complex phenotype data, awareness of changing trends in transplantation practices, and the importance of biospecimen repositories to support laboratory-based research. It is anticipated that these insights will facilitate ongoing research efforts and foster the development of innovative approaches to address fundamental questions in the field of transplantation.

Keywords: National Institutes of Health agreement; Late goods; Hematopoietic cell transplantation

Introduction

Hematopoietic cell transplantation (HCT) is utilized for therapeutic purposes in both malignant and non-malignant conditions. In 2014, the United States witnessed over 20,000 HCT procedures, with an annual increase estimated at 5%. Thanks to advancements in transplantation techniques, survival rates have steadily improved. However, HCT donors remain susceptible to serious health issues, including posterior tumors, heart failure, and pulmonary toxicity, which can manifest years after the transplantation process [1]. These complications stem directly from the treatment received before and during HCT, including chemotherapy and radiation, as well as post-transplant graft-versus-host disease (GVHD). Additionally, the risk of such complications may be influenced by underlying comorbidities. To address the gaps in knowledge and improve monitoring and management of transplant survivors, the National Institutes of Health Blood and Marrow Transplantation Late Effects Initiative was established. Comprising a diverse group of stakeholders from paediatric and adult HCT healthcare providers, researchers, advocates, and survivors, this initiative is supported by the National Cancer Institute and National Heart, Lung, and Blood Institute [2]. As part of this initiative, the Research Methodology and Study Design (RMSD) Working Group were formed in September 2015. The group's objective was to provide recommendations for research methodology and study design specifically focused on HCT survivorship. The working group tackled various challenges related to methodology, characterized contemporary transplantation strategies, delineated criteria for database and biospecimen sample inclusion, and outlined essential study designs and analytical approaches for HCT survivorship research [3]. The findings of the RMSD Working Group were synthesized into draft recommendations, which were presented at a public meeting in June 2016, attended by over 150 stakeholders representing diverse perspectives on HCT survivorship. Subsequent revisions were made based on feedback received from the participants, resulting in the finalized recommendations presented below.

Materials and methods

Therapeutic exposures

Individuals undergoing hematopoietic cell transplantation (HCT) are exposed to chemotherapy and radiation therapy before the procedure (for primary cancer treatment), during HCT (for the transplantation process), and after HCT (for graft-versus-host disease (GVHD) management and possibly for relapse of primary cancer) [4]. Therefore, unlike cancer patients treated in a non-transplantation setting with conventional doses of chemotherapy/radiation, HCT survivors typically experience intensified exposures to chemotherapy and radiation—both in terms of intensity and cumulative duration. This heightened exposure places them at a significantly increased risk of long-term morbidity. Additionally, the immunosuppressive therapy for GVHD management raises the risk for various chronic health issues, such as chronic kidney disease, metabolic disorders, osteonecrosis, and secondary malignancies [5]. Patients are often referred to specialized HCT centers for treatment by physicians who do not provide this highly specialized type of care. This arrangement makes it challenging for HCT research teams to gather detailed information regarding therapeutic exposures that occurred before referral for HCT and after post-HCT relapse. Consequently, most previous studies have focused solely on therapeutic exposures at the time of HCT (ignoring the pre-referral exposures) when examining determinants of long-term morbidity. As a result, post-HCT complications have been attributed to HCT-related exposures alone, even though pre-referral exposures have likely contributed to the etiology [6].

Post-transplantation follow-up

Following 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 research teams to ensure complete long-term follow-up. Often, post-HCT

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complications have a prolonged latency period. Inadequate follow-up at the transplantation center can underestimate the frequency of late effects, depending on the reasons for loss to follow-up (e.g., discharged/lost to follow-up due to geographic distance from the center, loss of health insurance/employment, or inability to access follow-up care, or good health leading to perceived lack of need for continued follow-up at the transplantation center) [7].

Disease and transplantation characteristics

Treatment protocols for allogeneic HCT have evolved significantly over the past four decades. In the early decades, pre-transplantation conditioning was always administered with myeloablative intent. Since the 1990s, the intensity of conditioning regimens has decreased. Reduced-intensity conditioning regimens were used for 26% of cases in the 2000s and for approximately 40% of transplantations since 2010. High-dose total body irradiation remains a component of the conditioning regimen in over 50% of children treated for malignant conditions, but its use in adults has decreased to less than 50% in both the myeloablative and reduced-intensity conditioning settings. Multiple myeloma has become the most common indication for autologous HCT in adults, accounting for over 50% of all autologous transplantations since 2010, compared with 11% in the 1990s. In the 1980s, nearly one-third of pediatric autologous transplantations were performed for the treatment of hematological malignancies such as acute leukemia [8]. Nowadays, almost all pediatric autologous transplantations are conducted for the treatment of non-hematological malignancies.

Discussion

Assessing the degree of risk of an adverse event in any population requires comparison with a reference population or a control group. The selection of an appropriate control group depends on the hypothesis being tested. The chosen control population should closely resemble the experimental group, allowing any differences between the two groups to be attributed to the exposure of interest. However, there are inherent challenges in establishing a valid concurrent control group for individuals undergoing hematopoietic cell transplantation (HCT). Ideally, a control group for HCT patients should consist of cancer patients identical in all respects (demographics, clinical characteristics) but randomized to receive conventional chemotherapy without HCT [9]. Unfortunately, such scenarios are rare in the context of randomized clinical trials, where limited sample sizes often prevent the assessment of rare late effects. A real-life control group comprising cancer patients who do not undergo HCT (i.e., a cancer control group) will typically include individuals with more favorable disease stages and lower cumulative exposures to chemotherapy and radiation.

Study design and analytical approaches can influence the selection of the study population and sample size. The table below succinctly outlines some common analytical approaches for various types of research questions. It is important to note that this list is not exhaustive, and the choice of study design and analysis plan should involve input from statistical and epidemiological experts [10].

Conclusion

Success in this rapidly evolving field requires a multidisciplinary approach involving various stakeholders. Key participants include hematopoietic cell transplantation (HCT) donors, healthcare providers, researchers, registries, molecular epidemiologists, statisticians, clinical informaticians, bioinformaticians, health economists, policymakers, and funding agencies. Establishing a robust long-term framework necessitates several critical components, including a standardized set of validated outcomes, a strategic collection of clinically annotated bio specimens, mechanisms for long-term follow-up of patients, and the ability to capture important exposures. Patient-reported outcomes (PROs) should play a pivotal role in assessing the morbidity burden in HCT survivors. The findings from these studies can inform risk stratification and guide the development of targeted interventions.

To ensure the ability to conduct relevant studies in the future, there is a need for funding initiatives to support logistical infrastructure enhancements aimed at improving data capture (both short- and long-term) and reducing redundancy. Additionally, there is a need to enhance biospecimen collection and biobanking efforts. An immediate priority is the establishment of data transfer initiatives to facilitate data and sample sharing among various sources, including registries, clinical trials, biorepositories, and single-center studies. This will enable comprehensive outcome analyses that can inform future research questions.

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Conflict of interest

None

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