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Clinical Research: Analysis

Establishment of Definitions and Review Process for Consistent Adjudication of Cause-specific Mortality after Allogeneic Unrelated-donor Hematopoietic Cell Transplantation

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A B S T R A C T

Clinical trials commonly use adjudication committees to refine endpoints, but observational research or genome-wide association studies rarely do. Our goals were to establish definitions of cause-specific death after unrelated-donor allogeneic hematopoietic cell transplantation (URD-HCT), to estimate discordance between reported and adjudicated cause-specific death, and to identify factors contributing to inconsistency in cause-specific death determination. A consensus panel adjudicated cause-specific death in 1484 patients who died within 1 year after HCT, derived from 3532 acute leukemia or myelodysplasia patients after URD-HCT from 2000 to 2011 reported by 151 US transplant centers to the Center for International Blood and Marrow Transplant Research. Deaths were classified as disease-related or transplant-related. The panel agreed with >99% of deaths reported by centers as disease-related and 80% reported as transplant-related. Year of transplant (cohort effect) and disease status significantly influenced agreement between the panel and centers. Sensitivity analysis of deaths < 100 days post-transplant yielded the lowest agreement between the panel and centers for myelodysplastic syndrome patients. Standard predefined criteria for adjudicating cause-specific death led to consistent application to similar clinical scenarios and clearer delineation of cause-specific death categories. Other studies of competing events such as cancer-specific versus treatment-related mortality would benefit from our results. Our detailed algorithm should result in more consistent reporting of cause-specific death by centers.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) offers the only curative therapy for some hematologic malignancy/disorder patients but has a 1-year post-HCT mortality rate exceeding 30% [1]. Allogeneic HCT can precipitate a multifactorial cascade of events, the sequence and severity of which differs between patients. Not all patients who die after HCT experience all potential post-HCT events. Moreover, surviving patients may experience a similar sequence of events as those who did not survive. Patients' clinical courses can significantly differ across and within cause-specific mortality. Additionally, comorbidities carry their own risks and are difficult to discern from HCT-specific causes of death.

As an example, a patient with moderate (not severe) graft-versus host disease (GVHD) treated with multiple systemic immunosuppressive agents develops an infection and

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dies. The initiating (primary) and contributory (secondary) causes are not easily delineated, leading to ambiguity of whether GVHD or infection should be reported as the primary cause-specific death. Patients with severe GVHD, requiring prolonged immunosuppression might die of severe GVHD without infection. Likewise, patients can die of infection in the absence of GVHD. Hence, GVHD and infection are not always concurrent causes of death. Discerning the initiating and contributing cause-specific deaths is critical in HCT patients who often have competing and correlated outcomes.

Endpoint assessment committees are often used to determine clinical trial endpoints [2,3] but are rarely used for observational research. The only published study investigating cause-specific death (GVHD, infection, disease, other) within the first year post-HCT used the primary cause of death reported by the transplant center [4]. Two additional studies examined cause-specific death in HCT patients who had survived beyond 2 and 5 years post-HCT [5,6]. The first study defined outcomes (death due to disease recurrence, GVHD, or infection) but did not review or adjudicate individual cases [5], whereas the second study used cause of death reported per the National Death Index in addition to review of medical data for individual cases [6]. These methods work for landmark analyses or observational studies that describe changes over time, but genetic studies investigating cause-specific deaths that are incorrectly or inconsistently assigned could result in biased estimation of the association between genetic variants and each cause [7].

In preparation for a genome-wide association study (GWAS) of cause-specific mortality after unrelated donor (URD) allogeneic HCT, we convened a consensus panel to review and adjudicate cause-specific deaths to reduce endpoint misclassification and subsequent over- or underestimation of genetic effects. Our ongoing GWAS, named DISCOVeRY-BMT (Determining the Influence of Susceptibility-COnveying Variants Related to 1-Year mortality after unrelated-donor Blood and Marrow Transplant) is designed to investigate donor and recipient genetic factors that contribute to 1-year cause-specific mortality after URD-HCT. We report our cause-specific death definitions, process for adjudication, and degree of concordance between the causes of death reported by individual transplant centers and the consensus panel.

METHODS

Research Ethics

All patients and donors provided written informed consent for their clinical data to be used for research purposes and were not compensated for their participation. This study was reviewed and approved by the Roswell Park Cancer Institute Institutional Review Board. All patient data were deidentified. Summary data are provided in this article with the exception of Supplemental Tables 4 and 5, which contain patient-specific data that have been altered slightly to further protect patient identity and confidentiality.

Study Population

Two independent cohorts were studied to determine the consistency of adjudication results. These cohorts were defined as a training and validation cohort for the main GWAS.

Cohort 1 included 2609 10/10 HLA-matched, first, T cell–replete URD-HCT recipients treated with myeloablative or reduced-intensity conditioning regimens from 2000 to 2008 for acute myeloid or lymphoblastic leukemia (AML, ALL) or myelodysplastic syndrome (MDS) who were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) and had banked biorepository samples from recipient and donor [8]. Of 2609 patients, 1116 (43%) died within 1-year after HCT.

Cohort 2 included 572 patients who had a URD-HCT between 2009 and 2011 who otherwise met the same criteria as Cohort 1, together with 351 patients who were 8/8 HLA-matched URD-HCT between 2000 and 2011 but otherwise met the same criteria as Cohort 1. Of 923 patients in Cohort 2, 368 (40%) died within 1 year after HCT.

Patient data and recipient–donor blood samples were contributed by 151 transplant centers. Procedures for the completion and review of CIBMTR data collection forms, as well as cause(s) of death, differ by transplant center. The goal of adjudication was to reduce variability in ascertaining the cause-specific deaths in patients with similar sequences of events leading to death.

Cause of Death Adjudication

The consensus panel consisted of 2 adult HCT physicians (M.P., P.L.M.), a pediatric hematologist/oncologist (K.O.), and an HCT clinical epidemiologist (T.H.). Causes of death and additional action plans (eg, request for clinical information from the transplant center) were recorded for each case by an independent coinvestigator (X.Z.) using prespecified nomenclature and notation. Adjudication of Cohort 1 was completed over 8 months via 3 in-person meetings at the CIBMTR (Milwaukee, WI) and weekly teleconferences. Adjudication for Cohort 2 was completed over 2 days via an in-person session at the CIBMTR.

Case report form summaries were provided to the consensus panel and included detailed data summarized in Supplemental Table 1. Each clinical summary was discussed by the consensus panel using information available in submitted forms, autopsy reports, error correction forms, and source documents. Discussions continued until a unanimous consensus was reached regarding the causes of death or whether additional information was needed from the transplant center. When additional information was needed before adjudicating cause-specific death, up to 3 data queries requesting source documentation or forms data clarification were submitted to the transplant center.

Cause of Death Category Definitions

The primary cause of death was broadly defined as “disease-related mortality” (DRM; related to leukemia/MDS relapse/progression, including death due to toxicity or infection from post-HCT antileukemic therapy) or “transplant-related mortality” (TRM; any cause of death not included in DRM), similar to previous HCT studies [3-6]. TRM subtypes were further classified as GVHD, infection, organ failure, and other. Cause-specific deaths were categorized in a hierarchical manner: disease, GVHD, infection, organ failure, and then other, in descending priority.

Table 1 provides detailed definitions and description of clinical scenarios. Briefly, DRM included documented post-HCT disease progression, relapse, or death before day +30 post-HCT in patients with a high disease burden pretransplant. Autopsy-confirming presence of disease was coded as DRM. Treatments such as reinduction chemotherapy, donor lymphocyte infusion, and second HCT after the index HCT may have caused “TRM-like” deaths but were coded as DRM because of the hierarchical structure and priority for the cause-specific death definitions.

GVHD deaths included severe acute or chronic GVHD with active treatment at time of death. Infection deaths included bacterial, viral, fungal, and/or protozoan infections causing end organ damage. Organ failure deaths were defined as transplant-related toxicity *not* due to disease progression, GVHD, or infection and included, for example, veno-occlusive disease/sinusoidal obstructive syndrome, noninfectious interstitial pneumonitis, adult respiratory distress syndrome, myocardial infarction, and renal failure in the absence of infection and GVHD. “Other” causes of death included rare events: vascular events including hemorrhage or thrombosis (eg, pulmonary emboli, stroke), secondary malignancies, primary or secondary graft failure, accident, suicide, or unknown.

The consensus panel could include an unlimited number of secondary or contributing causes of death. Based on the hierarchical nature of the definitions, secondary causes were included only for TRM and were coded in the same categories as the primary cause (GVHD, infection, organ failure, other). Secondary causes contributed to death but were not as severe as the primary cause or were closer to the time of death. Rare exceptions (affecting $\leq$3 cases per category) to the rules were allowed for unusual patient circumstances.

Internal and External Validity

Internal validity was tested using 2 approaches [9]. First, 11 sequential cases from Cohort 1 were blindly re-reviewed 2 months later. Second, 25 nonsequential cases were randomly selected by a non–panel member (X.Z.) and blindly re-reviewed by the consensus panel after all cases were adjudicated.

External validity was measured using a fourth in-person meeting at the CIBMTR with 2 adult HCT physicians not involved in the study (J.A.H., P.J.M.). Twenty-one previously adjudicated simple and complex cases from Cohort 1 were selected by a consensus panel member (T.H.) and then adjudicated in the same manner as prior panel meetings.