Clinical and Genetic Determinants of Cardiomyopathy Risk among Hematopoietic Cell Transplantation Survivors

Kasey J. Leger [1], Kara Cushing-Haugen [2], John A. Hansen [3,4], Wenhong Fan [2], Wendy M. Leisenring [2,3], Paul J. Martin [3,4], Lue Ping Zhao [2], Eric J. Chow [1,2,3,*]

[1] Department of Pediatrics, University of Washington, Seattle Children's Hospital, Seattle, Washington
[2] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
[3] Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
[4] Department of Medicine, University of Washington, Seattle, Washington

A B S T R A C T

Cardiomyopathy has been recognized as a complication after hematopoietic cell transplantation (HCT). Using a nested case-cohort design, we examined the relationships between demographic, therapeutic, and selected cardiovascular disease risk factors among ≥1-year HCT survivors who developed cardiomyopathy before (n = 43) or after (n = 89) 1 year from HCT as compared to a randomly selected subcohort of survivors without cardiomyopathy (n = 444). Genomic data were available for 79 cases and 267 noncases. Clinical and genetic covariates were examined for association with the risk of early or late cardiomyopathy. Clinical risk factors associated with both early- and late-onset cardiomyopathy included anthracycline exposure ≥250 mg/m^2 and pre-existing hypertension. Among late-onset cardiomyopathy cases, the development of diabetes and ischemic heart disease further increased risk. We replicated several previously reported genetic associations among early-onset cardiomyopathy cases, including rs1786814 in CELF4, rs2232228 in HAS3, and rs17863783 in UGT1A6. None of these markers were associated with risk of late-onset cardiomyopathy. A combination of demographic, treatment, and clinical covariates predicted early-onset cardiomyopathy with reasonable accuracy (area under the curve [AUC], .76; 95% confidence interval [CI], .68 to .83), but prediction of late cardiomyopathy was poor (AUC, .59; 95% CI .53 to .67). The addition of genetic polymorphisms with marginal associations (odds ratios ≥1.3) did not enhance prediction for either early- or late-onset cardiomyopathy. Conventional cardiovascular risk factors influence the risk of both early- and late-onset cardiomyopathy in HCT survivors. Although certain genetic markers may influence the risk of early-onset disease, further work is required to validate previously reported findings and to determine how genetic information should be incorporated into clinically useful risk prediction models.

© 2016 American Society for Blood and Marrow Transplantation.

INTRODUCTION

Improvements in hematopoietic cell transplantation (HCT) outcomes have resulted in an expanding population of long-term survivors, many of whom experience significant late effects secondary to pretransplantation- and transplantation-related treatment exposures [1]. Among these, cardiovascular disease has been increasingly recognized as a significant cause of morbidity and mortality after HCT [2]. Previously, our group described the increased incidence of late post-transplantation cardiovascular mortality and morbidity related to ischemic heart disease, stroke, and cardiomyopathy or heart failure when compared with the incidence in the normal population [3]. Additionally, we observed a significantly higher incidence of related conditions that predispose toward more serious cardiovascular disease, including hypertension, dyslipidemia, and diabetes. More recently, we and others described the impact of these and other conventional cardiac risk factors on the risk for significant cardiac events, including ischemic heart disease, stroke, cardiomyopathy, and cardiac mortality [4-7].

Although treatment exposures and the presence of conventional cardiovascular risk factors may help determine the degree of long-term cardiac risk, these factors do not entirely account for the interindividual variability in cardiomyopathy risk. Numerous genetic polymorphisms have been reported to influence cardiomyopathy risk [8-18].

Many of these studies are based on relatively small numbers of cardiomyopathy cases, and the polymorphisms reported have been inconsistently replicated across studies. In this updated analysis, we expand upon the number of cardiomyopathy cases available from our prior analyses and assess the influence of treatment exposures, conventional cardiovascular risk factors (hypertension, dyslipidemia, and diabetes), and select genetic polymorphisms reported in the literature to be influential.

METHODS

Study Population

A variety of data sources previously described in detail were used to ascertain potential cardiomyopathy cases among all ≥1-year survivors of autologous and allogeneic HCT treated at the Fred Hutchinson Cancer Research Center (FHCRC) from 1970 through 2010 (n = 6903). These data sources included the following: (1) a National Death Index linkage of deaths from 1979 to 2006 [19], (2) linkage to Washington State hospital discharge and death registry records from 1987 to 2008 (of HCT recipients who were state residents at time of transplantation) [3], and (3) responses to a patient survey on cardiovascular health sent to all living HCT survivors in 2010 and 2011 [7]. Potential cardiomyopathy cases from the National Death Index and Washington State registry data were identified based on selected International Classification of Diseases-ninth revision codes (Appendix Table 1) or equivalent 10th revision codes. Cases defined by these administrative data or by patient self-report alone were further reviewed using available medical records and included in the analysis only if clinical documentation supported the diagnosis. If medical records were unavailable, cases were accepted if the patient was taking medication(s) used to treat heart failure (as distinct from treatment for other conditions, such as hypertension alone) or if administrative records corroborated patient self-report. We excluded cardiomyopathy attributable to a transient event (eg, sepsis) with subsequent recovery of heart function, cardiomyopathy due to diastolic dysfunction alone, and cardiomyopathy with a history of amyloidosis. Although imaging (eg, echocardiogram) data were not required for our case definition, such information along with medication information and initial date of cardiomyopathy onset were abstracted when available.

Individuals who did not respond to the survey, or were not Washington state residents, or had not died would not have been ascertained by these data sources. Therefore, we also reviewed available medical records of 415 additional individuals who otherwise met our eligibility criteria and who had existing genome-wide association study (GWAS) data available [20]. Overall, through these methods, we were able to determine the cardiomyopathy status of 4026 of 6903 ≥1-year survivors (58.3%) (Figure 1) and we verified 132 cardiomyopathy cases for analysis. Of these, 25 were diagnosed

before HCT and 18 were diagnosed within the first year after HCT. Given limited resources that precluded an ability to perform detailed medical record review for exposure assessment on all 4026 members of this cohort, we used an alternative nested case-cohort study design [21]. The final analytic population thus included all validated cardiomyopathy cases (n = 132) plus a random 10% sample selected from each of our 4 data sources to serve as the study subcohort (n = 444, after excluding overlap with 17 cases) (Figure 1).

Exposure Information

As previously described [6], standard transplantation exposures (donor type, stem cell source, and conditioning regimen including total body or lymphoid irradiation) were supplemented with pretransplantation exposures ascertained from the medical records. These included anthracyclines, radiotherapy, and baseline medication use for hypertension, dyslipidemia, or diabetes. Recognizing that there is some uncertainty regarding the most appropriate equivalence formula, to be consistent with prior analyses, anthracycline doses were converted to the equivalent doxorubicin dose: daunorubicin × .83, epirubicin × .67, idarubicin × 5, and mitoxantrone × 4 [22,23]. Radiotherapy records were abstracted and exposures classified by the body area exposed: brain, chest, and abdomen/pelvis. Fields that spanned multiple body areas, eg, spine (chest and/or abdomen/pelvis depending on extent), had all relevant areas coded as exposed. Post-transplantation exposures included systemic immunosuppressive therapy for chronic graft-versus-host disease; disease relapse; use of medications for hypertension, dyslipidemia, and diabetes after transplantation based on the medical records; and the development of ischemic heart disease (angina, coronary artery disease, myocardial infarct) per the medical records.

Identification of Published Single Nucleotide Polymorphisms Associated with Cardiomyopathy and Heart Failure

To identify candidate single nucleotide polymorphisms (SNPs) for replication, we reviewed PUBMED for articles published on "cardiomyopathy," "heart failure," or "systolic dysfunction" among HCT survivors or cancer survivors as of June 2014. Results from 1 subsequent abstract presented at a national meeting (and since published) were also included [18]. Studies were then graded in relation to their similarity with our study population (Appendix Table 2). Category 1 studies were those that featured HCT survivors with similar case ascertainment [16]. Category 2 studies were those that featured non-HCT cancer survivors with similar case ascertainment [8,9,11-14,17,18]. Category 3 studies were those that featured non-HCT cancer survivors with case status based primarily on echocardiographic changes [10,15]. Separately, we also identified a fourth category of studies consisting of GWAS focused on cardiomyopathy occurring in the general Caucasian population, restricted to phenotypes distinct from hypertrophic and ischemia-associated cardiomyopathies [24-29].
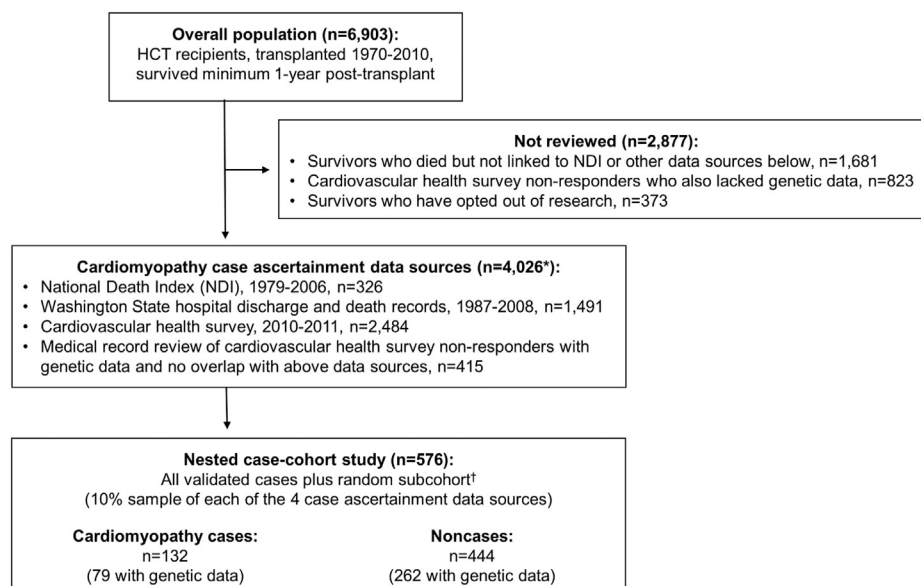
Figure 1. Study population and data sources for nested case-cohort study of cardiomyopathy among ≥1-year hematopoietic cell transplantation survivors. *Totals below exceed 4,026 as data sources overlap. †Random subcohort contained 461 individuals including 17 cases.