Original Study

Trends and Disparities in Cardiovascular Mortality Among Survivors of Hodgkin Lymphoma

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Abstract

To investigate trends and disparities among patients with Hodgkin lymphoma, we used the Surveillance, Epidemiology, and End Results database to show that the incidence of cardiovascular mortality (CVM) has been decreasing over the past 2 decades. We also show that black race, male gender, older age at diagnosis, and advanced disease stage were associated with higher CVM.

Background: Over the past decades, survival of patients with Hodgkin lymphoma (HL) has increased but remains curtailed by cardiovascular mortality (CVM). HL survivors at greatest risk for cardiovascular death have not been clearly identified. We sought to report trends of CVM identify HL survivors at highest risk. **Methods:** The Surveillance, Epidemiology, and End Results (SEER) database was queried for all adult patients diagnosed with HL (age 20-49 years) between 1990 and 2011. The trend of CVM and disparities are presented. **Results:** Of 19,781 HL patients, 53% were male and 83% were white; patients had a mean age of 33 ± 8.3 years at diagnosis. Eighteen percent had stage I disease, 45% stage II, 18% stage III, and 15% stage IV. The risk for CVM was higher in blacks (adjusted hazard ratio [HR], 1.97; $P = .002$), men (adjusted HR, 2.2; $P < .001$), and patients with older age at diagnosis (adjusted HR, 1.073 per year; $P < .001$). CVM has decreased, with 5-year cumulative incidence decreasing from 1.17% in 1990 to 0.18% in 2006, averaging 7% per year (adjusted HR, 0.927; $P < .001$). This trend was seen only in patients with early disease ($P < .001$) but not with advanced disease ($P = NS$). CVM as a proportion of all-cause mortality increases sharply at 50 years of age, constituting more than 30% of all causes of death. **Conclusion:** Despite an overall decrease in CVM in HL survivors over the last decades, older patients, black patients, and men, especially those who have advanced-stage disease at diagnosis, are at the highest risk of cardiovascular death. Cardiovascular screening and risk modification should be intensified in HL patients with these characteristics.

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Introduction

Hodgkin lymphoma (HL), one of the first malignancies to be cured by chemotherapy[1] and radiotherapy,[2] portends a 5-year overall survival of up to 88%.[3-5] However, compared to the general population, HL survivorship has been traditionally associated to a 6-fold increased risk of cardiovascular (CV) death,[6] largely attributable to chemotherapy- and radiation-related sequelae.[7]

For this reason, recent HL therapy trials have focused on decreasing short- and long-term toxicity rather than increasing cure rates, particularly in early-stage HL.[3] At the same time, onco-cardiology efforts have focused on CV screening and risk modification of cancer patients and survivors. Such efforts may be more cost-effective in higher-risk groups that remain unidentified. We therefore sought to identify HL patients at higher risk for CV-related mortality.

Methods

Study Cohort

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (http://seer.cancer.gov/) includes patient-level data on 8,208,917 cases of cancer (as of

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November 2013) collected from multicenter registries and is linked to death certificates. The SEER program prospectively collects data on patient demographics, tumor characteristics and staging, treatment, year of diagnosis, and mortality with cause of death for all incident cancers from selected population-based cancer registries in the United States that covered 26% of the entire US population by 2000. We queried the SEER 18 database (based on a November 2013 submission) for all patients diagnosed with classical HL at 20 to 49 years of age from between 1990 and 2011 (inclusive) using SEER*STAT. We defined cardiovascular mortality (CVM) to include the following International Classification of Disease (ICD) codes: ICD 9 (1979 to 1998): 390 to 398, 402, 404, 410 to 429; and ICD 10 (1999+):I00 to I09, I11, I13, I20 to I51.

Statistical Analyses

Data were imported into SPSS 20.0 (IBM). Categorical data are presented as numbers and percentages. No assumptions were made for the missing data. We used the Kaplan-Meier method with the log-rank test for analyses of cumulative incidence. The Cox proportional hazard model was constructed to identify disparities between patients. All tests were 2-sided, with $P < .05$ considered statistically significant.

Results

Patient Characteristics

A total of 19,781 patients were identified. Of those, 10,563 (53%) were men. The majority, 16,372 (83%), were white; 2329 (12%) were African American; and 883 (5%) were other minorities (Alaska natives, American Indians, or Asians). The median age at diagnosis was 32 years (range, 20-49 years). At the time of diagnosis, 3484 (17.6%) had stage I disease, 8795 (44.5%) stage II, 3539 (17.9%) stage III, and 2982 (15.1%) stage IV. Only 393 (2%) had a previous malignancy. A total of 7817 patients (40%) received radiotherapy, and 8158 (41%) had lymphoma-directed surgery.

Cause-Specific Mortality

At the end of the study period, 87% were still alive, 6% died of HL, and 0.8% died of cardiovascular disease (CVD). Patients who died from CVD had a median (95% confidence interval [CI]) survival of 7.7 years (6.3-9.8) after diagnosis of HL. Among patients who died, CVM comprised 6.5% of all causes of death; other major causes of death included HL (45%), other malignancies (18%), and infectious diseases (15%).

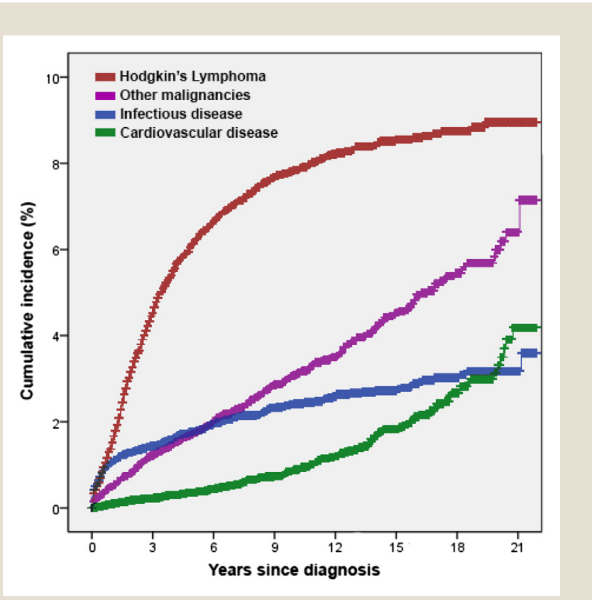
CVM

At 21 years of follow-up, CVM was the third cause of death, after HL and other malignancies (Figure 1). Median age at death from CVM was 46 years (range, 21-69 years), with 96% occurring before age 60 and 69% before age 50. CVM exceeds death from HL at 12 years after diagnosis (Figure 1).

Trends in CVM

The 5-year incidence of CV death has decreased from 1.17% in 1990 to 0.18% in 2006, with an average 7% decrease per year (hazard ratio [HR], 0.927; 95% CI, 0.894-0.962; $P < .001$). This decrease was seen only in patients with early-stage disease ($P < .001$) but not in patients with advanced-stage disease ($P = .497$) (Figure 2).

Figure 1 Cumulative Incidence of Major Causes of Death



Disparities in CVM

Overall, the risk for CVM was higher in men than in women (adjusted HR, 2.150; 95% CI, 1.522-3.038; $P < .001$) (Figure 3A) and in blacks than in whites (adjusted HR, 1.974; 95% CI, 1.297-3.008; $P = .002$) (Figure 3B). The incidence of CVM also increased with age at diagnosis (adjusted HR, 1.073; 95% CI, 1.053-1.094; $P < .001$) and was higher in patients with advanced disease compared with early disease (adjusted HR, 1.467; 95% CI, 1.044-2.062; $P = .027$). The proportion of CVM to all-cause mortality increased significantly in patients who died at age 52 or older (Figure 4).

Discussion

For the first time, we describe disparities in the risk of CVM across gender, race, and age in a large series of HL survivors.

We report that black HL survivors have a 2-fold increase in CVM compared to white patients, contrary to previous reports that showed no racial differences,[8] and much higher than the 30%[9] increased risk described in the general population. It appears that cancer potentiates CVM risk in blacks but less so in whites. This may be partially explained by the fact that black race has been shown to be an independent risk factor for anthracycline cardiotoxicity.[10,11] Whether cardiotoxicity from other forms of therapy, such as radiotherapy, have racial implications remains unknown.

Similarly, men in the community are at 40%[12] higher risk of CV death than women—much lower than the 120% increased risk observed in our study. Among HL survivors, male sex has been identified as an independent risk factor for development of coronary artery disease[13] and myocardial infarction.[14] However, in patients with HL treated with chest irradiation, there is a higher incidence of CV comorbidities and procedures in women than in men,[15] suggesting higher CV morbidity.

It is unlikely that our observed differences are merely due to more intensive lymphoma-directed therapies, as no guidelines have established different treatment strategies by race or gender. These