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Cancer Specific Survival in Patients with Sickle Cell Disease

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Abstract

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Summary

Sickle cell disease (SCD) patients have a higher incidence of certain cancers, but no studies have determined the impact of cancer on survival among SCD patients. SCD patients (n=6,423), identified from statewide hospitalization data, were linked to the California Cancer Registry (1988–2014). Multivariable Cox proportional hazards regression was used to examine survival. Among SCD patients, a cancer diagnosis was associated with a 3-fold increased hazard of death. Compared to matched cancer patients without SCD, SCD was associated with worse overall survival, but not cancer-specific survival, suggesting that SCD cancer patients should be treated with similar therapeutic intent.

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Author Contributions

AB, TK, AM, SP, and TW designed the study. AB, TK, and TW acquired and analyzed the data. AB, TK, and TW drafted the manuscript. All authors made revisions and approved the final manuscript.

Introduction

Sickle cell disease (SCD), the most common inherited blood disorder in the United States, and is associated with a number of serious complications, including vaso-occlusive crisis, thrombosis, stroke, acute chest syndrome and osteonecrosis of the femoral head.(Adesina, *et al* 2017, Brunson, *et al* 2017b, Platt, *et al* 1991, Powars, *et al* 2005) We and others have found an increased incidence of certain cancers among SCD patients compared to general or hospitalized populations.(Brunson, *et al* 2017a, Seminog, *et al* 2016) Utilizing population-based California Cancer Registry data, we recently reported that California SCD patients have an over two-fold higher incidence of leukemia compared to the general population of California.(Brunson, *et al* 2017a) In addition, Seminog et al. reported increased cancer incidence of a number of hematologic cancers, including lymphoma, leukemia and myeloma, and some solid tumors among hospitalized SCD patients compared to controls with minor medical and surgical conditions.(Seminog, *et al* 2016) To our knowledge, no studies have evaluated survival outcomes among SCD patients after a cancer diagnosis. Therefore, we determined the impact of cancer on survival among SCD patients, and assessed overall and cancer-specific survival among those with SCD compared to a matched cohort of cancer patients without SCD.

Methods

As previously described, the SCD cohort was identified using longitudinal records from the California Patient Discharge Data (PDD) and the Emergency Department Utilization (EDU) databases from the Office of Statewide Health Planning and Development (OSHPD). (Adesina, *et al* 2017, Brunson, *et al* 2017a, Brunson, *et al* 2017b) Since July 1990, the State of California has required that non-Federal hospitals report up to 25 diagnoses and up to 21 procedures associated with each hospitalization, coded using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) through 2014. Since 2005, an Emergency Department Utilization (EDU) database of all hospital associated emergency department encounters has also been mandated. In addition to diagnostic and procedure information, patient demographic information including age, gender, race/ethnicity, and insurance coverage is collected. An encrypted form of the social security number, called the record linkage number, is used to identify unique individuals, allowing serial linking of multiple hospitalization records over time. This administrative database does not contain laboratory or medication information.

Patient sex, race/ethnicity, and entry year to the cohort were obtained from the patients' first PDD or EDU encounter. As done previously, patients with an average of ≥ 3 PDD or EDU encounters per year (across all study years in the cohort) were defined as having severe SCD; all other patients were defined as less severe SCD.(Adesina, *et al* 2017, Brunson, *et al* 2017a, Brunson, *et al* 2017b) SCD related complications were identified using specific ICD-9-CM codes in the PDD or EDU (Supplemental Table 1). Cancer occurrence was obtained through a linkage of the SCD cohort with the California Cancer Registry (CCR); this linkage was conducted by OSHPD using a deterministic strategy based on social security number and sex. The CCR is a statewide, population-based cancer surveillance system and National Cancer Institute SEER registry collecting cancer incidence

and mortality information since 1988.(Brant Mary 2017, CCR 2016, Mazreku Jenna 2017, Mazreku Jenna 2016) Cancer-specific data, including date of diagnosis, primary site and histology, stage at diagnosis, initial course of treatment, and patient demographics and follow-up are collected for all malignant and selected *in situ* cancers in California.

To determine the impact of cancer on overall survival among SCD patients, we used multivariable Cox proportional hazard regression, adjusting for SCD severity, gender, race/ethnicity, sex and other SCD related complications, and stratifying by entry year. All SCD complications were included as time dependent covariates using date at first occurrence. Analyses including acute chest syndrome were limited to follow-up only during 2003–2013, when acute chest syndrome coding became available. Event time was measured in days from entry into the SCD cohort to the date of death or end of study (12/31/2013), whichever occurred first. Death data was obtained from hospitalization and California vital records linkage.

To determine the effect of SCD on overall and cancer-specific survival after a cancer diagnosis, conditional multivariable Cox proportional hazards regression was used. Each SCD cancer patient was matched to 4 non-SCD cancer patients on age, year of diagnosis, gender, race/ethnicity, cancer site and histology. Event time was measured in days from cancer diagnosis to date of death (from CCR) or end of study (12/31/2014); models were adjusted for radiation treatment, neighborhood socioeconomic status(Yang J 2014, Yost, *et al*/2001) and health insurance at diagnosis/initial treatment, and stratified by chemotherapy and stage at diagnosis. SCD patients were classified as having severe or less severe SCD. In all models, the proportional hazards assumption was assessed using Schoenfeld residuals, (Allison 2010) with variables violating this assumption considered as stratifying variables. Results are presented as hazard ratios (HR) and 95% confidence intervals (CI). This study was approved by the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the University of California, Davis Institutional Review Boards.

Results/Discussion

Among 6,423 SCD patients, 1.8% (n=115) had cancer and 17.1% died as of December 2013. The median follow-up time and age of death was 13 and 40 years, respectively. The most common types of cancer diagnosed among SCD patients were breast (n=16), digestive system (n=16), respiratory system (n=16), lymphoma (n=15) and leukemia (n=12) (Supplemental Table 2). Among SCD patients, a cancer diagnosis (HR=3.18, 95% CI: 2.35–4.30) was associated with a 3-fold increased hazard of death in multivariable regression models (Table 1). When we considered survival by type of cancer diagnosis, SCD patients with hematologic malignancies (HR=10.87, 95% CI: 6.38–18.53) had a nearly 11-fold increased hazard of death, while SCD patients with solid tumors (HR=2.37, 95% CI: 1.66–3.38) had a 2-fold increased hazard of death compared to SCD patients without cancer (Supplemental Table 3). In addition, severe SCD and all SCD complications were associated with an increased mortality. Acute chest syndrome was associated with an increased mortality in analyses of 2003–2013 data, but the inclusion of this complication did not

attenuate the association of a cancer with overall survival for these study years (HR=3.36, CI: 2.34–4.82).

Compared to a matched cohort of cancer patients without SCD, SCD was associated with worse overall survival after a cancer diagnosis (HR=1.40, CI: 1.00–1.94). When SCD was categorized by disease severity, only severe SCD was associated with worse overall survival (Severe-HR=1.78, CI: 1.15–2.74; Less Severe- HR=1.12, CI: 0.71–1.75; vs. no SCD; p=0.0016) (Figure 1). There was no difference in cancer-specific survival among SCD patients compared to non-SCD cancer patients overall (HR=0.79, CI: 0.49–1.26) or by disease severity (Severe-HR=0.79, CI: 0.39–1.60; Less Severe - HR=0.79, CI: 0.44–1.42; vs. no SCD; p=0.1095). We also did not observe differences in cancer-specific survival in a sensitivity analysis where we classified all SCD-related deaths as cancer-related (Overall-HR=1.07, CI: 0.70–1.62; Severe-HR=1.23, CI: 0.67–2.25; Less Severe-HR=0.96, CI: 0.56–1.65).

In our large, population-based cohort of SCD patients in California, a diagnosis of cancer is associated with worse survival, even when adjusted for SCD severity and a number of other complications previously associated with worse survival.(Brunson, *et al* 2017b, Powars, *et al* 2005) The negative impact of a cancer diagnosis on survival was similar, if not stronger, than a number of other serious complications in SCD patients, an important finding given recent studies observing an increased risk of cancer in SCD patients.(Brunson, *et al* 2017a, Seminog, *et al* 2016) With improvements in the treatment and care of SCD, resulting in an increased life expectancy,(Platt, *et al* 1991, Powars, *et al* 2005) cancer will likely become an increasingly more frequent complication in SCD patients.

Compared to cancer patients without SCD, overall survival after a cancer diagnosis was significantly worse among SCD patients with severe disease, who comprised 43.3% of our SCD cohort. However, cancer-specific survival was similar to those without SCD, regardless of SCD severity, suggesting that SCD does not impact the outcome of cancer treatment. Instead, our findings indicate that the reason for worse overall survival after cancer in SCD patients compared to cancer patients without SCD is the underlying SCD. Taken together, these findings argue for aggressive management of both the cancer and underlying SCD for patients afflicted with both, and the possibility of cancer-specific outcomes similar to non-SCD patients. If these findings are confirmed, this implies that hematologists and oncologists should approach an SCD patient with cancer with similar therapeutic intent as with other patients without underlying SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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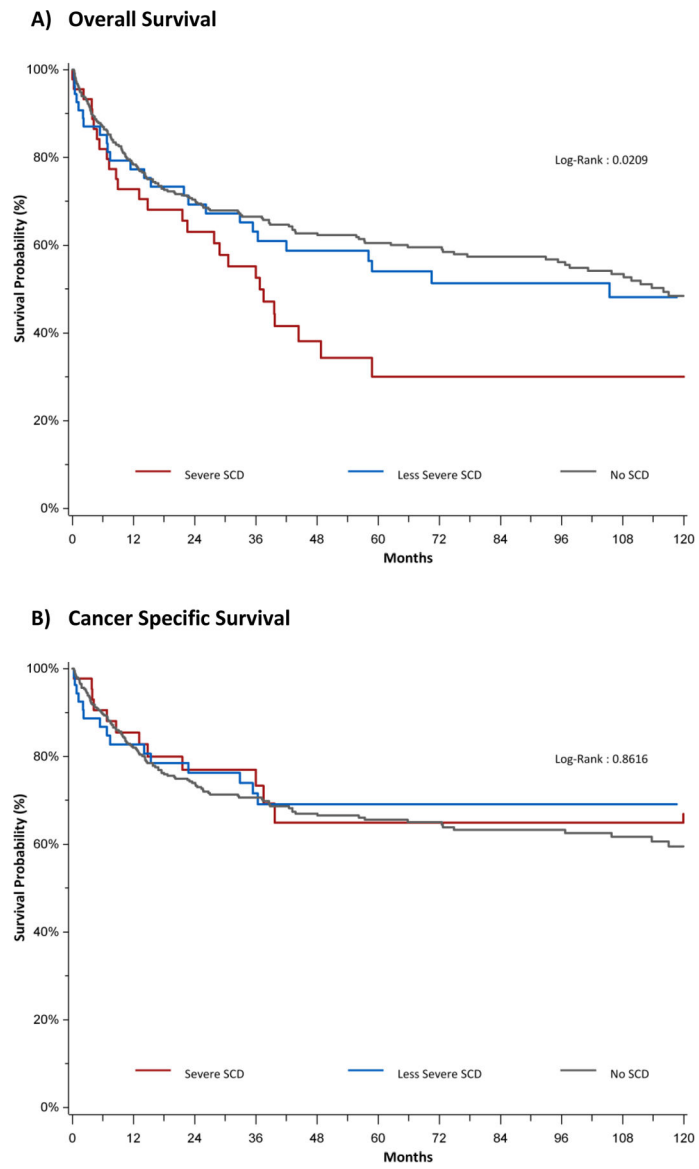


Figure 1—.
 Overall and cancer-specific survival among cancer patients with sickle cell disease matched to cancer patients without sickle cell disease.

Table 1:

Overall survival among SCD patients in California, 1991–2013

Variables	HR	95% CI	P-Value
SCD Severity			
Less Severe		<i>Reference</i>	
Severe SCD	1.38	(1.21, 1.57)	<.0001
Gender			
Female	0.85	(0.76, 0.96)	0.0108
Male		<i>Reference</i>	
Race/Ethnicity			
African American	0.95	(0.74, 1.20)	0.6485
non-African American		<i>Reference</i>	
Age at Entry			
< 18		<i>Reference</i>	
18–29	1.76	(1.48, 2.10)	<.0001
30–39	3.34	(2.79, 3.98)	<.0001
40–49	4.12	(3.37, 5.04)	<.0001
50–59	6.83	(5.16, 9.05)	<.0001
60–64	12.01	(7.38, 19.56)	<.0001
* Cancer Diagnosis			
Yes	3.18	(2.35, 4.30)	<.0001
No		<i>Reference</i>	
* Stroke			
Yes	2.55	(2.04, 3.19)	<.0001
No		<i>Reference</i>	
* Bleeding			
Yes	3.26	(2.83, 3.75)	<.0001
No		<i>Reference</i>	
* Acute Chest Syndrome[†] (limited to n=5,657 SCD patients; years 2003–2013)			
Yes	2.12	(1.74, 2.58)	<.0001
No		<i>Reference</i>	
* Venous Thromboembolism			
Yes	1.93	(1.61, 2.31)	<.0001
No		<i>Reference</i>	
* Osteonecrosis of the femoral head			
Yes	1.60	(1.39, 1.84)	<.0001
No		<i>Reference</i>	

Cox proportional hazard regression model stratified by entry year.

* covariate included as a time-dependent covariate

[†] Acute Chest Syndrome ICD-9-CM code available in years 2003