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Long-term follow-up for incident cirrhosis among pediatric cancer survivors with hepatitis C virus infection

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Abstract

Background—Pediatric cancer patients who received blood transfusions were potentially exposed to hepatitis C virus (HCV) prior to second-generation HCV screening of blood products in 1992. Limited evidence is available about long-term incident cirrhosis in this population.

Objectives—We aimed to estimate the overall and sex-specific incidence of cirrhosis among HCV-seropositive survivors of pediatric cancer.

Study design—We identified 113 HCV-seropositive pediatric cancer patients treated at St. Jude Children's Research Hospital between 1962 and 1997, who survived ≥ 5 years post-diagnosis, and were followed through 2014. Our outcome was cirrhosis determined by liver biopsy or diagnostic imaging. We used a competing-risk framework to estimate the overall and sex-specific cumulative incidence and 95% confidence limits (CL) of cirrhosis at 10-year follow-up intervals.

Results—The median duration of follow-up was 30 years (interquartile range=28 – 36) post-cancer diagnosis. Cumulative incidence of cirrhosis increased at each 10-year interval from 0% after 10 years to 13% after 40 years ($P_{\text{trend}} < 0.001$). The median age at diagnosis of cirrhosis was 30 years (interquartile range=24 – 38). We observed a linear trend in incidence for males ($P_{\text{trend}} < 0.001$), with a cumulative incidence of 18% (95% CL: 6.1%, 34%) after 40 years. The cumulative incidence for females was 6.5% (95% CL: 0.42%, 26%) after 40 years, but we did not observe a linear trend ($P_{\text{trend}} = 0.99$).

Conclusion—Our results suggest that the incidence of cirrhosis is similar between HCV-seropositive pediatric cancer survivors and the general population given similar duration of follow-up, but survivors may be diagnosed with cirrhosis at an earlier age.

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CONFLICT OF INTEREST

None declared.

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BACKGROUND

Pediatric cancer survivors who received blood transfusions were potentially exposed to hepatitis C virus (HCV) prior to second-generation screening of blood products in July 1992. Alternatively, this population may have been exposed to HCV through other mechanisms, such as intravenous drug use (1). Symptoms of HCV infection are often indistinguishable from other chronic diseases, but adverse outcomes of chronic HCV infection are common. For example, 5 – 25% of individuals with chronic HCV infection in the general, non-cancer population develop cirrhosis after 25 – 30 years (2). Rapid progression to cirrhosis is a concern for cancer survivors because of immunosuppression from cancer-related treatment (3). Nevertheless, limited evidence is available about long-term incidence of cirrhosis in this population.

OBJECTIVES

We aimed to estimate long-term incidence of cirrhosis among HCV-seropositive pediatric cancer survivors. Given evidence of heterogeneity in the incidence of cirrhosis by sex among HCV-seropositive individuals in the general, non-cancer population (4, 5) and immunocompromised populations (e.g. HIV (6)), we also aimed to compare the incidence of cirrhosis by sex.

STUDY DESIGN

Study population

This longitudinal cohort study was approved by the institutional review board and has been previously described (7). Briefly, eligible individuals were aged <20 years at cancer diagnosis, treated at St. Jude Children's Research Hospital between 1962 and April 1997, survived ≥ 5 years post-cancer diagnosis, and diagnosed with HCV (regardless of exposure mechanism). For consenting participants, HCV infection status was initially determined at study baseline in 1995 by second-generation enzyme immunoassay (Abbott HCV EIA 2.0; Abbott Laboratories, Abbott Park, IL) and recombinant immunoblot assay (RIBA HCV 2.0 Strip Immunoblot assay; Chiron, Emeryville, CA) or polymerase chain reaction (Roche Amplicor Monitor HCV; Roche Diagnostic Systems, Somerville, NJ). We extended follow-up of this cohort through August 2014.

Variables

Serum biomarkers (FibroSURE; Quest Diagnostics, Burlington, NC) were used for cirrhosis screening or fibrosis staging, but cirrhosis was diagnosed by liver biopsy or abdominal ultrasound. Liver biopsies were systematically conducted prior to initiating antiviral therapy and graded according to the modified histologic activity index (8). Cirrhosis diagnosed by abdominal ultrasound was characterized by coarse echogenicity of the liver, increased liver density, and reverse portal flow, often accompanied by splenomegaly. Treatment for progressive fibrosis with interferon alpha (3 million units, 3 times per week), combination interferon with ribavirin (600 mg, twice daily), or pegylated interferon (0.5 µg/kg, weekly) with ribavirin (600 mg, twice daily) was based on availability and physician discretion.

Data analysis

We used a competing-risk framework (9) to estimate cumulative incidence and corresponding 95% confidence limits (CL) of cirrhosis at 10-year follow-up intervals. In addition, we estimated the subdistribution hazard ratio (HR) (9) and corresponding 95% CL for the association between sex and cirrhosis. The estimation of cumulative incidence and HRs accounted for left truncation (i.e. variability in age at study entry) using age as the time scale (10), where age at cancer diagnosis was assumed to be the age at HCV diagnosis given that transfusion of blood products would have occurred at this time. Individuals contributed person-time to the cohort until the event of interest (cirrhosis), the competing event (death), loss to follow-up, or end of follow-up (August 2014).

RESULTS

Table 1 summarizes demographic and clinical characteristics of the 113 HCV-seropositive survivors in our study population. Briefly, 50% were female and 82% were White. The median age at cancer diagnosis was 5.6 years (interquartile range [IQR]=3.1 – 13), and the most common cancer diagnosis was leukemia (73%). Of 88 individuals tested, 75% had HCV genotype 1. Antiviral therapy was administered to 43% of our cohort, of whom 59% achieved sustained virologic response. Median follow-up was 30 years (interquartile range [IQR]=28 – 36) post-cancer diagnosis.

Cirrhosis was diagnosed in 15 HCV-seropositive survivors, of whom 73% were diagnosed by liver biopsy and 27% by abdominal ultrasound. All cirrhosis diagnoses occurred among Whites. Antiviral therapy was administered to 80% of survivors with cirrhosis, of whom 25% achieved sustained virologic response and 75% discontinued therapy due to adverse symptoms or non-response. One survivor with cirrhosis received a liver transplant. During the study period, 6 individuals with cirrhosis died, of which 4 deaths were attributable to liver-related causes.

Figure 1 illustrates overall cumulative incidence of cirrhosis from time of cancer diagnosis. We observed a linear trend for cumulative incidence at each 10-year interval from cancer diagnosis (10 years: cumulative incidence=0%; 20 years: cumulative incidence=1.6%, 95% CL: 0.13%, 7.4%; 30 years: cumulative incidence=4.4%, 95% CL: 1.2%, 11%; 40 years: cumulative incidence=13%, 95% CL: 4.8%, 24%; $P_{\text{trend}} < 0.001$). The median age at cirrhosis diagnosis was 30 years [IQR=24 – 38], and the median time to cirrhosis diagnosis was 23 years [IQR=18 – 32]. We observed a linear trend in incidence for males ($P_{\text{trend}} < 0.001$) but not females ($P_{\text{trend}} = 0.99$), with a cumulative incidence of 18% (95% CL: 6.1%, 34%) for males and 6.5% (95% CL: 0.42%, 26%) for females after 40 years. The relative hazard of cirrhosis was higher for males (HR=4.5, 95% CL: 0.53, 37), but imprecise estimates preclude meaningful inference for this comparison.

DISCUSSION

Our results suggest that the incidence of cirrhosis among HCV-seropositive pediatric cancer survivors is comparable to the general, non-cancer population given similar duration of follow-up. Nevertheless, the median age at cirrhosis (30 years) in our cohort is considerably

lower than the median age at cirrhosis (65 years) (11) in the general, non-cancer population. This finding is consistent with emerging evidence suggesting that pediatric cancer survivors may have adverse health outcomes at an early age (12–14), but in this context may be a consequence of earlier age at exposure to HCV. In addition, 59% (53/90) of the remaining HCV-seropositive survivors in this cohort were diagnosed with hepatic fibrosis, and thus the magnitude of cirrhosis may increase with continued follow-up.

Prior studies of HCV-seropositive pediatric cancer survivors reported diverse estimates for incident cirrhosis (Table 2). For example, a study of 31 HCV-seropositive pediatric cancer survivors in Egypt reported no cases of cirrhosis with a mean follow-up of 2.6 years (15). Using information reported in a multi-institution cohort study of 105 HCV-seropositive pediatric cancer survivors in Italy and Austria (16), the estimated incidence proportion of cirrhosis was 0.95% (95% CL: 0.02%, 5.2%) with a median follow-up of 18 years. The incidence proportion of cirrhosis estimated in a separate study of 77 HCV-seropositive pediatric cancer survivors in Italy (17) was 5.2% (95% CL: 1.4%, 13%) with a median follow-up of 21 years. The higher estimated incidence in our study population may be attributable to longer follow-up (median 30 years). In addition, information reported in prior studies only allowed for the calculation of incidence proportion (i.e. number of individuals with cirrhosis divided by the population at risk of cirrhosis) (18), which is misleading when follow-up time varies between individuals and competing events are ignored (18, 19).

Our results should be interpreted in the context of certain limitations. A select subset of our study population underwent liver biopsy, the most accurate diagnostic measure of cirrhosis, and thus outcome status may be misclassified for the subset of survivors who underwent liver imaging (sensitivity=68%, specificity=88% compared with liver biopsy) (20), or no assessment because symptoms of cirrhosis were not clinically apparent. This misclassification would underestimate the cumulative incidence of cirrhosis in our study and prior studies (16, 17) given the use of similar approaches for outcome classification. Furthermore, given lack of information about age at HCV exposure for survivors with non-transfusion acquired HCV, age at HCV exposure for these individuals was defined as time of cancer diagnosis, which may be inaccurate. Nevertheless, only 3 survivors had non-transfusion-acquired HCV, and thus the impact on our incidence estimate is likely nominal.

Our findings are useful for raising awareness of the potential for early development of cirrhosis among HCV-seropositive pediatric cancer survivors. HCV screening by polymerase chain reaction, which is more accurate than HCV antibody testing, should be emphasized for pediatric cancer survivors who received blood transfusions as part of cancer-directed therapy prior to July 1992, particularly considering that only 29% of survivors at risk of transfusion-acquired HCV have been definitively tested (21). In addition, for HCV-seropositive pediatric cancer survivors, screening for cirrhosis should be prioritized. A potential consideration for more systematic screening of HCV-seropositive survivors is the use of less invasive but reasonably accurate approaches for staging fibrosis and diagnosing cirrhosis such as imaging with Fibroscan (22) and biomarker testing with FibroSURE or AST-to-platelet ratio index (20).

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Highlights

- We estimated incidence of cirrhosis for HCV-seropositive pediatric cancer survivors.
- The incidence of cirrhosis in our cohort is 13% after 40 years of follow-up.
- Median age at cirrhosis in our cohort was 30 years (interquartile range=24 – 38).
- Survivors may have earlier development of cirrhosis than the general population.

Figure 1. Cumulative incidence of cirrhosis among pediatric cancer survivors with hepatitis C infection.
Note: Dashed lines represent 95% confidence limits

Table 1

Demographic and clinical characteristics of pediatric cancer survivors with hepatitis C virus (HCV) infection at St. Jude Children's Research Hospital, 1962 – 2014.

Characteristic	HCV-seropositive patients (n=113) n (%)
<i>Sex</i>	
Male	57 (50)
Female	56 (50)
<i>Race</i>	
Non-White	20 (18)
White	93 (82)
<i>Primary cancer</i>	
Leukemia	82 (73)
Lymphoma	6 (5.3)
Central nervous system tumors	11 (9.7)
Other solid tumors	14 (12)
<i>Route of HCV infection</i>	
Transfusion-acquired	110 (97)
Other	3 (2.7)
<i>HCV genotype^a</i>	
1	66 (75)
2	17 (19)
3	4 (4.5)
4	1 (1.1)
<i>Co-infection with other viruses</i>	
Hepatitis B	3 (2.7)
Human immunodeficiency virus	1 (0.88)
<i>Fibrosis staging^{b,c}</i>	
None (0 / F0)	22 (30)
Mild (1 – 2 / F0 – F1)	26 (35)
Moderate (3 – 5 / F1– F2 / F3)	26 (35)
<i>Antiviral therapy</i>	
Yes	49 (43)
No	64 (57)
<i>Vital status at last follow-up</i>	
Alive	99 (88)
Dead	14 (12)

^a HCV genotype testing for 88 patients

^b Fibrosis assessment for 76 patients without cirrhosis; 2 patients with fibrosis had insufficient staging information

^c Liver biopsy staged according to the modified histologic activity index (8) and FibroSURE test staged according to the manufacturer's index (Quest Diagnostics; Lab Corp of America, Burlington, NC)

Table 2
Studies of incident cirrhosis among pediatric cancer survivors with hepatitis C infection.

Authors	Year	Location	Study population (n)	Follow-up duration (years)	Incidence of cirrhosis (95% CI)
El-Raziky <i>et al.</i> (15)	2015	Egypt	31	Mean=2.6	0% (0%, 11%)
Fioredda <i>et al.</i> (16)	2009	Italy and Austria	105	Median=18	0.95% (0.02%, 5.2%)
Cesaro <i>et al.</i> (17)	2010	Italy	77	Median=21	5.2% (1.4%, 13%)
Current study	2015	USA	113	Median=30	13% (4.8%, 24%)