Hepatotoxicity during legacy cancer chemotherapy in patients infected with hepatitis C virus: A retrospective cohort study

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ABSTRACT

BACKGROUND: The rates and causes of significant hepatotoxicity with cancer chemotherapy (CCT) in patients infected with hepatitis C virus (HCV) are incompletely characterized. METHODS: We compared rates of grade 3 or 4 hepatotoxicity, defined as elevated transaminases, during CCT in patients who are mono-infected with HCV compared with rates in controls matched on demographics, diagnosis, and rituximab use. We excluded patients with hepatobiliary cancers, hepatitis B virus or human immunodeficiency virus infection. Hepatotoxicity was attributed to a medical cause, cancer progression, or CCT, including HCV flare. RESULTS: Patients with HCV (n = 196) had a higher rate of cirrhosis than the 1,130 matched controls (21.9% versus 4%; P < 0.001). Their higher rate of overall hepatotoxicity (8.7% versus 4.5% of controls, P = 0.01) was due to higher rate of CCT-related hepatotoxicity (4.1% versus 1.2%, P = 0.01). On multivariable analysis, the largest risk factor for overall hepatotoxicity was cirrhosis, and the only risk factor for CCT-related hepatotoxicity was HCV infection. Among those with HCV, the only significant risk factor for hepatotoxicity was rituximab use. Hepatotoxicity caused by CCT delayed or altered treatment in only 3 HCV patients and 1 control (1.5% versus 0.1%, P = 0.01). CONCLUSIONS: Most patients with HCV can safely be treated with cancer chemotherapy. Cirrhosis and HCV infection contributed to increased hepatotoxicity in subjects on CCT. Among HCV patients, rituximab use was the major risk factor for increased hepatotoxicity. Hepatotoxicity due to CCT itself rarely altered or delayed CCT. Nonetheless, HCV-positive patients should be monitored carefully during CCT.

KEYWORDS: chemotherapy; cirrhosis; hepatitis C virus; hepatotoxicity; reactivation; rituximab; transaminase

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INTRODUCTION

Hepatitis C virus (HCV) infection is common, affecting an estimated 3 to 5 million people in the United States (1) and 80 million worldwide (2). Many of these will eventually be diagnosed with some form of cancer and will be offered cancer chemotherapy (CCT).

In patients infected with hepatitis B virus (HBV), CCT can lead to clinically significant hepatotoxicity, much of which is due to HBV reactivation during immunosuppressive therapy, particularly with steroids or anti-CD20 monoclonal antibodies such as rituximab (3). This reactivation can lead to severe hepatitis, sometimes fatal, when immune reconstitution occurs, up to a year after the completion of CCT (3). In contrast, the impact of CCT on patients infected with HCV is less clear. Series before the use of rituximab generally showed a minimal impact of HCV on the incidence of hepatotoxicity, primarily elevated transaminases during the course of CCT (4–8), although there were isolated reports of significant hepatotoxicity, including deaths (9–11). After the advent of rituximab-containing regimens, studies have generally shown an increased incidence of hepatotoxicity during CCT in patients infected with HCV (12,13,14). However, most of these studies are limited by the absence of a control group without HCV infection and a systematic assessment of all causes of transaminase elevation during CCT. The respective roles of cirrhosis and HCV viremia are also unclear.

To address these questions, we performed a retrospective cohort study comparing HCV patients to matched controls in the incidence, causes and impact of elevated transaminases during CCT. This study was done before the general use of checkpoint inhibitors.

MATERIALS AND METHODS

We identified 50,695 subjects with invasive cancer who had received CCT between January 2000 and September 2010 (study entry period) and for whom electronic CCT administration records were available for review. Our study included only patients tested for HCV before CCT and who had tested negative for HBsAg and/or HBcAb. We also excluded patients listed in our comprehensive human immunodeficiency virus registry. The primary study subjects were the 196 patients viremic for HCV as determined by the last test performed between 1996 and the first day of the index CCT, either by qualitative or quantitative HCV assay or a positive test for genotype; this left 6,933 patients who tested negative for HCV and HBV before CCT. An initial comparison found significant differences between HCV-positive and HCV-negative patients in cancer diagnosis, rituximab use, and baseline demographics (see Appendix 1, Supplemental Table 1). Therefore, we matched each HCV-viremic patient with up to 6 control patients based on cancer diagnosis, rituximab use, gender, age, and race, resulting in a control group of 1,130 with average matching of 5.77 (Figure 1).

Drug administrations were grouped into courses of CCT, each defined as a series of treatments with a specific set of oncologic CCT agents. The index CCT was defined as the initial CCT course during the study entry period.

Invasive cancers were linked to 3-digit ICD-9-CM diagnosis codes and grouped into six categories: chronic lymphocytic leukemia/lymphoma (CLL-lymphoma), lung, breast, colon, hepatobiliary, and other tumours. As in other studies (15), patients treated for hepatobiliary cancers were excluded from further analysis because of difficulty distinguishing the tumour’s natural progression from elevated liver enzymes due to CCT.

Diagnosis of cirrhosis was based on ICD-9-CM diagnoses of cirrhosis (571.2, 571.5, 571.6), varices 456.0, 456.1), portal hypertension (572.3) or hepatic encephalopathy (572.2). This was validated by a structured review of electronic health records for each HCV and control patient looking for evidence of cirrhosis such as liver biopsy, endoscopy or imaging evidence of portal hypertension or nodular liver (see Appendix 1, Supplemental Table 2).

Definition of hepatotoxicity

Given that HCV hepatitis is overwhelmingly hepatocellular, our threshold for significant hepatotoxicity was a grade 3 or grade 4 elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), in accordance with the National Cancer Institute Common Toxicity Criteria (version 2.0), (16) with adaptation for underlying baseline liver enzyme elevation (see Appendix 1, Supplemental Table 3). Values were normalized to multiples of the upper limits of normal. We took grade 3 as the level of interest because a five-fold increase in transaminases is the minimal level needed to define a flare of HBV (17) or HCV (18).
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and is the threshold level recommended by the International Drug-Induced Liver Injury (DILI) Expert Working group (19). Baseline transaminase was the value immediately preceding CCT. We did not use alkaline phosphatase elevation as we found that grade 3 or 4 elevation was a marker of cancer progression in the liver.

Analysis of hepatotoxicity

Hepatotoxicity was analyzed from the time of onset of CCT until 12 months after treatment to allow for post-treatment toxicity to emerge with immune reconstitution. In relating hepatotoxicity to a chemotherapeutic agent, we reviewed all agents that had been given in the preceding 14 months. We selected for specific analysis the three chemotherapeutic agents most implicated in hepatotoxicity in patients with HBV: rituximab, prednisone, and anthracycline agents (3). Checkpoint inhibitors were not included as the study was completed before their general use. No patients were taking anti-HCV medications during the study period.

All cases of grade 3 or higher transaminases elevation in controls and HCV patients underwent structured chart review to eliminate causes clearly unrelated to chemotherapy, such as surgical resection, transarterial chemotherapeutic embolization, or non-hepatic origin of AST. The remaining cases were grouped into three mutually exclusive categories of causes. Medical causes related to treatment included causes such as sepsis, obstructive jaundice, and drug toxicity.

The treating oncologist ascribed drug toxicity since there was insufficient data to employ formal causality scales, although the electronic medical record (EMR) was reviewed to confirm there was no alternate explanation. Cancer progression was diagnosed by imaging at the time of hepatotoxicity. The remaining cases were considered related to the CCT per se, including cases of possible HCV flare. Details of death were captured in all those with hepatotoxicity.

We first analyzed the overall incidence of grade 3 or 4 hepatotoxicity in patients with HCV compared with controls and performed bivariate analysis assessing factors associated with hepatotoxicity. Demographic and clinical characteristics were examined using the Chi-square or Fisher’s exact tests for categorical variables and the non-parametric Wilcoxon–Mann-Whitney test for non-normally distributed continuous variables.

We determined risk factors for overall hepatotoxicity and specific CCT-related hepatotoxicity in both the total and the HCV cohorts and assessed whether the course of treatment was changed because of hepatotoxicity. Because of the small number of cases, stepwise logistic regression models were used to identify risk factors for all-cause hepatotoxicity and hepatotoxicity caused by CCT. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA), with the threshold of significance set at two-sided \( P < 0.05 \). The Kaiser Foundation Research Institute’s Institutional Review Board approved this observational data-only study with a waiver of consent.
RESULTS

Hepatotoxicity bivariate and multivariable analysis
The baseline characteristics of HCV-viremic subjects and matched controls are shown in Table 1. The only significant difference was that HCV patients had more cirrhosis (21.9% [43/196] versus 4% [45/1,130], P < 0.001) and had higher baseline transaminases.

After excluding instances of elevated transaminases due to causes unrelated to CCT (see Appendix 1, Supplemental Table 4), we found hepatotoxicity in 8.7% of HCV subjects

Table 1: Baseline demographic and clinical characteristics of HCV patients and matched* HCV- and HBV-negative patients who initiated chemotherapy January 2000–September 2010

| Characteristics, n (%) | HCV-viremic (n = 196) | Negative HCV and HBV (n = 1,130) |
|------------------------|------------------------|----------------------------------|
| Female                 | 75 (38.3)              | 416 (36.8)                       |
| Age ≥65 years          | 41 (20.9)              | 238 (21.1)                       |
| Race                   |                        |                                  |
| White, including Hispanic | 151 (77.0)           | 898 (79.5)                       |
| Asian-Pacific Islander | 8 (4.1)                | 42 (3.7)                         |
| African American       | 24 (12.2)              | 138 (12.2)                       |
| Other                  | 13 (6.6)               | 52 (4.6)                         |
| Cirrhosis†             | 43 (21.9)              | 45 (4.0)                         |
| Transaminase§ (ULN) †  |                       |                                  |
| 0–1                    | 107 (54.6)             | 855 (77.2)                       |
| 1.01–2.5               | 68 (34.7)              | 212 (19.2)                       |
| >2.5                   | 21 (10.7)              | 40 (3.6)                         |
| Cancer diagnosis       |                        |                                  |
| Breast                 | 24 (12.2)              | 138 (12.2)                       |
| CLL-lymphoma           | 43 (21.9)              | 238 (21.1)                       |
| Colon                  | 28 (14.3)              | 162 (14.3)                       |
| Lung                   | 39 (19.9)              | 228 (20.2)                       |
| Other‖                 | 62 (31.6)              | 364 (32.2)                       |
| Treatment              |                        |                                  |
| Rituximab              | 42 (21.4)              | 218 (19.3)                       |
| Steroid                | 12 (6.1)               | 70 (6.2)                         |
| Anthracycline          | 51 (26.0)              | 305 (27.0)                       |
| Other                  | 191 (97.5)             | 1083 (95.8)                      |
| Rituximab and steroid  | 11 (5.6)               | 58 (5.1)                         |
| Rituximab, steroid, and anthracycline | 9 (4.6) | 44 (3.9) |
| Anthracycline without rituximab or steroid | 24 (12.2) | 177 (15.7) |
| Other only             | 129 (65.8)             | 723 (64.0)                       |

* Up to 6 patients per HCV-viremic patient matched on cancer diagnosis, rituximab use, gender, age, and race
† Cirrhosis identified by ICD-9-CM codes and structured electronic health record review
‡ Denotes statistically significant difference between HCV-viremic and matched negative HCV/HBV groups (P < 0.05 Chi-square or Fisher’s exact tests as appropriate)
§ Missing data: Transaminase in HCV-/HBV-negative patients = 23
‖ Other includes chemotherapy agents other than rituximab, steroid, or anthracycline
HCV = Hepatitis C virus; HBV = Hepatitis B virus; ULN = Upper limit of normal; CLL = Chronic lymphocytic leukemia or lymphoma
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Table 2: Validated hepatotoxicity grade ≥3 and impact on treatment in HCV-viremic patients and matched HCV- and HBV-negative patients

| Characteristics, n (%) | HCV-viremic (n = 196) | Negative HCV and HBV* (n = 1,130) |
|------------------------|------------------------|----------------------------------|
| Hepatotoxicity†        |                        |                                  |
| All causes†            | 17 (8.7)               | 51 (4.5)                         |
| Chemotherapy-related†  | 8 (4.1)                | 14 (1.2)                         |
| Medical causes         | 8 (4.1)                | 28 (2.5)                         |
| Cancer-related         | 1 (0.5)                | 9 (0.8)                          |
| Hepatotoxicity impacted treatment |          |                                  |
| All causes†            | 7 (3.6)                | 11 (1.0)                         |
| Chemotherapy-related†  | 3 (1.5)                | 1 (0.1)                          |
| Medical causes         | 4 (2.0)                | 9 (0.8)                          |
| Cancer-related         | 0 (0.0)                | 1 (0.1)                          |

* Up to 6 patients per HCV-viremic patient matched on cancer diagnosis, rituximab use, gender, age, and race
† Hepatotoxicity grade ≥3 and cause confirmed via structured electronic health record review
‡ Denotes statistically significant difference between HCV-viremic and matched negative HCV/HBV groups (P <0.05 Chi-square or Fisher's exact tests as appropriate)
HCV = Hepatitis C virus; HBV = Hepatitis B virus

(17/196) and 4.5% of controls (51/1,130; P = 0.01) (Table 2). In multivariable analysis (Table 3), cirrhosis was the main risk factor for hepatotoxicity due to any cause (adjusted risk ratio [aRR] 2.56; 95% CI 1.23–5.31; P = 0.01), with older age and diagnosis of breast and colon cancer negative risk factors. Baseline transaminase was significant only for grade 1 hepatotoxicity (aRR 1.75; 95% CI 1.03–2.99; P = 0.04), not for higher or lower levels, raising doubts whether this was really a risk factor. Of note, HCV status was not a risk factor for overall hepatotoxicity. Thus, the increased all-cause hepatotoxicity in HCV patients was primarily due to increased cirrhosis at baseline.

The rates of elevated transaminases due to medical or cancer-related causes did not differ significantly in controls and HCV patients. Among the medical causes were 19 acute infections, 6 tumour-related obstructive jaundice, and 5 related to non-chemotherapy medications (4 in controls [one ibuprofen, one Lovenox overdose, 2 allopurinol] and isoniazid in an HCV patient). The HCV-viremic subjects with hepatotoxicity and the timing of hepatotoxicity are described in Table 4 and Figure 2.

This left 22 cases of hepatotoxicity likely related to a chemotherapy agent, 8/196 (4.1%) in the HCV group and 14/1,130 (1.2%) in the control group (Table 2), accounting for the difference in all-cause hepatotoxicity. In multivariable analysis, only HCV was an independent risk for hepatotoxicity attributable to chemotherapy (aRR 2.78; 95% CI 1.16–6.65; P = 0.02, Table 3). No specific agents contributed independent risk. Data on the evolution of viral loads during chemotherapy were limited and showed no clear relation to hepatotoxicity. Of the four patients with repeat viral load measurement available after hepatotoxicity was observed, two had a slight increase from baseline and two had a slight decrease (Table 4).

Hepatotoxicity within the HCV group

We then addressed a different question: if a patient had HCV viremia, what were the risk factors for hepatotoxicity? Although several factors had significance on bivariate analysis, with stepwise multivariable analysis, exposure to rituximab was the only risk factor for toxicity. This was true for both all-cause toxicity and toxicity due to CCT agent, with a risk ratio (RR) of 6.56 (95% CI 2.32–18.54) and 12.67 (95% CI 2.46–65.38), respectively (Table 5). This increased hepatotoxicity in HCV patients when exposed to rituximab is in contradistinction to the case in non-HCV cases, where rituximab toxicity occurred in 4.11% of those exposed to rituximab (9/219) compared with 4.6% of those not exposed (42/912) (Table 6).

Impact on treatment and deaths

Hepatotoxicity from CCT had minimal impact on planned therapy: only 3 HCV subjects (1.5%) had a brief delay in planned treatment, and a single control subject (0.1%) had a dose reduction (P = 0.01 for comparison) (Figure 3; Appendix 1, Supplemental Table 5). No deaths or hospitalizations were associated with CCT-related hepatotoxicity. This is in stark contrast to elevated transaminases associated with medical causes, which resulted in 9 deaths (25%)—3 in the HCV group and 6 among controls—and to elevations related to cancer progression, with 6 short-term
Table 3: Adjusted risk ratio for factors predictive of validated hepatotoxicity grade ≥3* of any cause and caused by chemotherapy in total cohort (N = 1,326, 196 HCV-viremic patients and 1,130 matched HCV- and HBV-negative patients)

| Factors                        | HT grade ≥3* due to any cause n = 68 (5.1%) | HT grade ≥3* due to chemotherapy n = 22 (1.7%) |
|--------------------------------|---------------------------------------------|-----------------------------------------------|
|                                | N (%) Adjusted RR (95% CI) P†               | N (%) Adjusted RR (95% CI) P†                  |
| HCV-viremic                    |                                             |                                               |
| 17 (8.7) 1.44 (0.78–2.65) 0.24 | 8 (4.1) 2.78 (1.16–6.65) 0.02                 |
| Age ≥65 years                  |                                             |                                               |
| 8 (2.9) 0.46 (0.22–0.94) 0.03  | 2 (0.7) 0.49 (0.14–1.66) 0.25                 |
| Cirrhosis‡                    |                                             |                                               |
| 11 (12.5) 2.56 (1.23–5.31) 0.01 | 3 (3.4) 1.43 (0.43–4.76) 0.56                 |
| Transaminase (ULN)             |                                             |                                               |
| 0–1                            | 42 (4.4) 1 (referent group) –               | 13 (1.4) 1 (referent group) –                 |
| 1.01–2.5                       | 23 (8.2) 1.75 (1.03–2.99) 0.04               | 9 (3.2) 2.00 (0.89–4.49) 0.09                 |
| >2.5                           | 3 (4.9) 1.09 (0.35–3.33) 0.89               | 0 (0.0) 0.46 (0.04–5.71) 0.54                 |
| Unknown                        | 0 (0.0) 0.56 (0.03–9.21) 0.68               | 0 (0.0) 1.44 (0.09–23.54) 0.80                 |
| Cancer diagnosis               |                                             |                                               |
| Breast                         | 6 (3.7) 0.34 (0.12–0.99) 0.047               | 3 (1.9) 0.55 (0.11–2.78) 0.47                 |
| CLL-lymphoma                   | 22 (7.8) 1.26 (0.41–3.84) 0.69               | 12 (4.3) 2.63 (0.56–12.29) 0.22                |
| Colon                          | 4 (2.1) 0.35 (0.13–0.97) 0.04                | 1 (0.5) 0.56 (0.10–3.11) 0.51                 |
| Lung                           | 11 (4.1) 0.86 (0.41–1.79) 0.69               | 1 (0.4) 0.53 (0.10–2.78) 0.45                 |
| Treatment                      |                                             |                                               |
| Rituximab                      | 19 (7.3) 0.79 (0.23–2.76) 0.71               | 9 (3.5) 0.54 (0.12–2.48) 0.43                 |
| Steroid                        | 6 (7.3) 0.89 (0.11–7.14) 0.92               | 4 (4.9) 2.18 (0.25–18.88) 0.48                 |
| Anthracycline                  | 25 (7.0) 0.70 (0.24–2.09) 0.52               | 14 (3.9) 2.45 (0.41–14.61) 0.33                |
| Other                          | 68 (5.3) 15.67 (0.93–265.42) 0.06 13.03–53.48 | 22 (4.3) 2.03 (0.11–38.48) 0.64                |
| Rituximab and steroid           | 5 (7.3) 0.75 (0.05–10.96) 0.83               | 3 (4.4) 1.77 (0.09–35.57) 0.71                 |
| Rituximab, steroid, and anthracycline | 4 (7.6) 1.26 (0.13–12.07) 0.84 | 2 (3.8) 0.19 (0.01–3.08) 0.24 | 0.73 |
| Other§ only                    | 36 (4.2) 0.38 (0.10–1.47) 0.16               | 6 (0.7) 0.68 (0.07–6.26) 0.73                 |

Notes: Factors in bold are significant at P <0.05 level
– indicates “not applicable”
* HT grade ≥3 and cause confirmed via structured electronic health record review
† Adjusted relative risk estimated using logistic regression with all variables in the table and racial groups (not shown in the table, not statistically significant at P < 0.05 level)
‡ Cirrhosis identified by ICD-9-CM codes and structured electronic health record review
§ Other includes chemotherapy agents other than rituximab, steroid, or anthracycline
HCV = Hepatitis C virus; HBV = Hepatitis B virus; HT = Hepatotoxicity; RR = Risk ratio; ULN = Upper limit of normal; CLL-lymphoma = Chronic lymphocytic leukemia or lymphoma

Deaths among 10 patients. Overall, there was a similar proportion of deaths in patients with and without HCV (see Appendix 1, Supplemental Table 6). This was true irrespective of the use of rituximab or CLL-lymphoma diagnosis. No deaths caused by HCV were identified during our study period.

**DISCUSSION**

Our study shows that before the era of checkpoint inhibitors, grade 3 or 4 increases in transaminases occurred in one of 20 patients (68/1,326; 5.13%) undergoing CCT. This was increased in those with cirrhosis, with HCV patients having more cirrhosis and more transaminase elevations. Having HCV
Table 4: Characteristics of individual HCV-viremic patients with hepatotoxicity grade ≥3 and time course

| Cancer diagnosis | Cirrhosis | CCT agent* | Baseline/peak | LAST CCT to HT interval (days) | Cause of HT | HT impact on chemotherapy | Viral load (log) change |
|------------------|-----------|------------|---------------|--------------------------------|-------------|--------------------------|------------------------|
| CLL-lymphoma     | No        | RAO        | 1.0/5.8       | 13                             | Chemotherapy | No                       | Increase 5.91 to 6.33  |
| CLL-lymphoma     | No        | RASO       | 2.4/12.9      | 21                             | Chemotherapy | No                       | Baseline VL only       |
| CLL-lymphoma     | No        | RSO        | 1.3/15.5      | 18                             | Chemotherapy | Yes, dose reduced for neutropenia, LFTs; paused later with neutropenia | Baseline VL only       |
| CLL-lymphoma     | Yes       | RAO        | 1.1/7.8       | 168                            | Chemotherapy | No, finished course before flare | Baseline VL only       |
| CLL-lymphoma     | No        | RAO        | 1.7/9.6       | 21                             | Chemotherapy | No                       | Baseline VL only       |
| CLL-lymphoma     | Yes       | RAO        | 2.0/10.6      | 14                             | Chemotherapy | Yes, also with cytopenias | Baseline VL only       |
| CLL-lymphoma     | No        | RO         | 1.2/11.7      | 189                            | Medical (sepsis) | Yes, lowered dose of meds when restarted | Decrease 6.72 week before, to 6.28 2 months later |
| CLL-lymphoma     | No        | RASO       | 1.8/14.2      | 13                             | Medical (sepsis) | No                       | Baseline VL only       |
| CLL-lymphoma     | Yes       | RAO        | 0.7/32.8      | 25                             | Medical (sepsis) | Died                     | Baseline VL only       |
| CLL-lymphoma     | Yes       | RO         | 0.9/5.4       | 9                              | Medical (sepsis) | No                       | Increase 5.62 to >6.88 |
| Other            | No        | AO         | 0.5/22.1      | 18                             | Chemotherapy | Yes, stopped maintenance 6MP, MTZ | Decrease 5.45 to 5.18 when LFTs down |
| Other            | No        | O          | 1.4/5.7       | 63                             | Chemotherapy | No                       | Baseline VL only       |
| Other            | No        | O          | 1.7/10.4      | 6                              | Medical (drug INH) | No, chemo continued | Baseline VL only       |
| Other            | Yes       | O          | 3.7/8.4       | 14                             | Medical (sepsis) | Died                     | Baseline VL only       |
| Other            | No        | O          | 0.9/47.6      | 157                            | Medical (sepsis 119 days after BMT) | Died | Baseline VL only |
| Other            | No        | O          | 1.2/11.1      | 6                              | Medical (sepsis) | No                       | Baseline VL only       |
| Other            | No        | AO         | 0.7/6.4       | 13                             | Cancer       | Stopped due to progression on therapy | Baseline VL only       |

Notes: – indicates “not applicable”

* CCT agent: R = Rituximab; A = Anthracycline; S = Steroid; O = Other
HCV = Hepatitis C virus; CCT = Cancer chemotherapy; ALKP = Alkaline phosphatase; ULN = Upper limit of normal; HT = Hepatotoxicity; CLL-lymphoma = Chronic lymphocytic leukemia or lymphoma; VL = Viral load; LFT = Liver function tests; 6MP = 6-mercaptopurine; MTZ = Methotrexate; INH = Isoniazid; BMT = Bone marrow transplant
**Figure 2:** Time course of hepatotoxicity grade ≥3 due to cancer chemotherapy in HCV-viremic patients

*Note: Y-axis represents the number of HCV-viremic patients with hepatotoxicity grade ≥3
HCV = Hepatitis C virus
* Hepatotoxicity grade ≥3 and cause confirmed via structured electronic health record review

**Table 5:** Adjusted risk ratio for factors predictive of validated hepatotoxicity grade ≥3 in 196 HCV-viremic patients

| Factors                      | HT grade ≥3* due to any cause† | HT grade ≥3* due to chemotherapy† |
|------------------------------|--------------------------------|-----------------------------------|
|                              | N (%)‡ | Adjusted RR (95% CI) | P       | N (%)‡ | Adjusted RR (95% CI) | P       |
| Age ≥65 years                | 3 (7.3) | 6.56 (2.32–18.54)     | <0.001  | 2 (4.9) | 12.67 (2.46–65.38)    | <0.01   |
| Cirrhosis                    | 6 (14.0)| 6 (14.0)              |        | 3 (7.0) | 6 (6.7)              |        |
| Transaminase >1 (ULN)        | 11 (12.4)| 6 (14.0)              |        | 6 (6.7) | 6 (6.7)              |        |
| Cancer diagnosis             |        |                      |        |        |                      |        |
| Breast cancer                | 0 (0.0) | 0 (0.0)               |        | 0 (0.0) | 0 (0.0)              |        |
| CLL-lymphoma                 | 10 (23.3) | 6 (14.0)              |        | 6 (14.0) | 6 (14.0)            |        |
| Colon cancer                 | 0 (0.0) | 0 (0.0)               |        | 0 (0.0) | 0 (0.0)              |        |
| Lung cancer                  | 0 (0.0) | 0 (0.0)               |        | 0 (0.0) | 0 (0.0)              |        |
| Other cancer                 | 7 (11.3) | 2 (3.2)               |        | 2 (3.2) | 2 (3.2)              |        |
| Treatment                    |        |                      |        |        |                      |        |
| Rituximab                    | 10 (23.8) | 6 (14.3)              |        | 6 (14.3) | 12.67 (2.46–65.38)    | <0.01   |
| Steroid                      | 3 (25.0) | 2 (16.7)              |        | 2 (16.7) | 2 (16.7)            |        |
| Anthracycline                | 9 (17.7) | 6 (11.8)              |        | 6 (11.8) | 6 (11.8)            |        |
| Other                        | 17 (8.9) | 8 (4.2)               |        | 8 (4.2) | 8 (4.2)              |        |
| Rituximab and steroid        | 3 (27.3) | 2 (18.2)              |        | 2 (18.2) | 2 (18.2)            |        |
| Rituximab, steroid, and anthracycline | 2 (22.2) | 1 (11.1)              |        | 1 (11.1) | 1 (11.1)            |        |
| Other only                   | 5 (3.9) | 1 (0.8)               |        | 1 (0.8) | 1 (0.8)              |        |

Notes: Racial groups and gender omitted, not significant
(%) in bold font represent bivariate comparisons of HT grade ≥3 with P < 0.05
* HT grade ≥3 and cause confirmed via structured electronic health record review
† Due to the small number of HCV-viremic patients with all-cause HT and HT caused by chemotherapy, ‘stepwise’ method was used in the multivariable regression models therefore, the results included in the table are limited to predictors with effects meeting the significance level of 0.05 to enter and remain in the model
‡ N
HCV = Hepatitis C virus; HT = Hepatotoxicity; RR = Risk ratio; ULN = Upper limit of normal; CLL-lymphoma = Chronic lymphocytic leukemia or lymphoma
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Infection was not associated with a statistically significant increase in hepatotoxicity due to medical or cancer causes, but it was the main risk factor for CCT-related hepatotoxicity, with the risk attributable to rituximab use. In those without HCV, rituximab use was not associated with hepatotoxicity. Steroids and anthracyclines were not risk factors for hepatotoxicity. Elevations due to medical or cancer causes were frequently associated with fatal outcomes, whereas those due to CCT itself were generally well tolerated and rarely impacted treatment course.

Before the use of rituximab, most but not all studies documented that severe hepatotoxicity due to CCT was uncommon in HCV (5,6,8,10). With the use of rituximab, primarily in hematological malignancies, higher rates of this hepatotoxicity in HCV patients were reported; however, the true degree is obscured by failure to account for baseline abnormalities, (12) imprecise exclusion and inclusion criteria (10,12,13,20), and case series limited to lymphoma diagnosis (5,10,15,6,7). The increased hepatotoxicity with rituximab use generally, but not always, was reported to be mild and did not correlate with viral loads (14,20). Most studies failed to show a large effect of HCV status on discontinuation or alteration of CCT (4,15,20), although there is variability pointing to variability in assessing the risk-benefit ratio of continuing chemotherapy. In our own study, the flares, when due to CCT itself (as opposed to other causes of hepatotoxicity) were usually mild and did not lead to decompensation in the 43 HCV-positive patients with cirrhosis, and only rarely led to altered treatment. This finding is reassuring and differs from the findings with HBV, where in the same overall population of patients receiving CCT, we identified seven patients who died from fulminant HBV hepatitis related to CCT (21).

The pathophysiology of increased hepatotoxicity with CCT in hepatitis C patients is not as clear as in those with hepatitis B. With HBV infection, a classic pattern is that of increased viral load during chemotherapy, followed by a biochemical flare either soon thereafter if the immune response is intact, or months later if the immune system needs

### Table 6: All-cause hepatotoxicity grade ≥3 in HCV patients and matched† HCV- and HBV-negative patients, with and without exposure to rituximab

|                     | HCV-viremic (n = 196) | Negative HCV and HBV (n = 1,130) |
|---------------------|-----------------------|---------------------------------|
| Rituximab           |                       |                                 |
| Yes, no. (%)        | 42 (21.4)             | 218 (19.3)                      |
| No, no. (%)         | 154 (78.6)            | 912 (80.7)                      |
| All-cause hepatotoxicity, no. (%) | 17 (8.7) | 51 (4.5) |
| If exposed to rituximab, no./n (%) | 10/42 (23.8) | 9/218 (4.1) |
| If not exposed to rituximab, no./n (%) | 7/154 (4.5) | 42/912 (4.6) |

† Up to 6 patients per HCV-viremic patient matched on cancer diagnosis, rituximab use, gender, age, and race

HCV = Hepatitis C virus; HBV = Hepatitis B virus

### Figure 3: Flow chart of hepatotoxicity in patients with HCV and controls

HCV = Hepatitis C virus; HBV = Hepatitis B virus
was the only agent that, on multivariable analysis, risk of reactivation of HBV during CCT: rituximab, so we selected the three agents that had the highest lyze the impact of every chemotherapeutic agent, to infections (12,31,32).

Cirrhosis, in part be due to increased susceptibility it did occur, was less well tolerated in those with findings in a large series that hepatotoxicity, when connected in that cirrhosis was the main risk factor for overall hepatotoxicity, and cirrhosis itself was significantly more common in those with HCV than in those without HCV. This is consistent with baseline ALT is already several-fold abnormal, may overstate the degree of liver damage and lead to misleading conclusions (19,35). For example, one early study that found grade 3 hepatotoxicity in 15 patients concluded that baseline transaminases were a risk factor for HT, but 7 of the cases met the criteria for grade 3 toxicity before any CCT was given (10). In our own study, 21/196 (10.7%) of our HCV patients had baseline transaminase levels that would have qualified as grade 2 or higher hepatotoxicity before any chemotherapy was administered. After we adjusted for baseline transaminase in the criteria for HT, baseline transaminase was no longer a risk factor on multivariable analysis.

Our cases of hepatotoxicity were too few to analyze the impact of every chemotherapeutic agent, so we selected the three agents that had the highest risk of reactivation of HBV during CCT: rituximab, anthracycline drugs, and steroids (3). Rituximab was the only agent that, on multivariable analysis, was associated with hepatotoxicity in HCV patients. Particularly, steroids did not confer increased risk, consistent with in vivo studies in healthy HCV volunteers that found greater than one log elevations of HCV RNA but only minimal elevations in ALT (33). In patients with hematological malignancies, four studies came to inconsistent conclusions on the effect of steroids on hepatotoxicity (6,12,15,34).

Our study has several strengths. First, to our knowledge, it has the largest number of HCV patients in the cancer literature. This is despite that, to isolate the effect of HCV infection, we employed rigorous inclusion and exclusion criteria, requiring negative tests for HBV and HIV. Most other studies have not done this (10,12,13,20). As a prospective study, we avoided bias introduced by testing after the fact, something not always made clear in other studies (13).

We present baseline ALT levels and use a threshold level of ALT elevation that is consistent with levels previously used to define flares of HBV (17) and HCV (18) and the threshold for defining drug-induced liver injury (19). As the DILI study group pointed out, setting too low a threshold, and failing to adjust the threshold in a situation in which baseline ALT is already several-fold abnormal, may overstate the degree of liver damage and lead to misleading conclusions (19,35). For example, one early study that found grade 3 hepatotoxicity in 15 patients concluded that baseline transaminases were a risk factor for HT, but 7 of the cases met the criteria for grade 3 toxicity before any CCT was given (10). In our own study, 21/196 (10.7%) of our HCV patients had baseline transaminase levels that would have qualified as grade 2 or higher hepatotoxicity before any chemotherapy was administered. After we adjusted for baseline transaminase in the criteria for HT, baseline transaminase was no longer a risk factor on multivariable analysis.

By using a matched control group and including all cases of elevated transaminases, we were able to ascertain the background level of hepatotoxicity in non-HCV infected individuals along with factors affecting the incidence of hepatotoxicity. In particular, this enabled us to highlight the impact of baseline cirrhosis on the risk of hepatotoxicity. To our knowledge, such a detailed assessment in control and study patients has not previously been done. We used strict criteria for cirrhosis that favoured specificity over sensitivity, requiring either biopsy confirmation, radiological evidence of cirrhosis or evidence of
decompensation. All patients underwent multiple imagings during treatment, so it is unlikely we missed clinically significant cirrhosis. Elastography was not available during our time period, and we did not use aspartate aminotransferase to platelet ratio index (APRI), given its false-positive rate of around 20% (36).

We did not limit ourselves to lymphomas but included all cancer diagnoses except for hepatobiliary cancers. We could thus demonstrate that HCV, not lymphoma, was a risk factor for HT due to cancer chemotherapy, particularly with rituximab.

Limitations of our study include those intrinsic to a retrospective study. We were reliant on physicians’ notes that did not always contain information in the detail of interest to us. For example, we were unable to retrospectively use formal DILI criteria in determining causation in the cases of drug-induced hepatotoxicity and had to rely on EMR review and physicians’ notes. There was no universal protocol for laboratory testing other than those embedded in the oncological protocols themselves. Thus, cases of hepatotoxicity or HCV activation may have been missed. However, most oncological protocols do include frequent transaminase assessment. Viral loads were not systematically obtained prospectively, so the exact relation of reactivation of HCV to hepatotoxicity cannot be determined. Such a study would most likely have to include viral loads at least monthly. Importantly, we do not have available data on HCV patients who did not undergo chemotherapy, so selection bias cannot be ascertained. It seems likely but unproven that decompensated cirrhotic patients were treated less aggressively.

Finally, since the end of our data collection, many new anticancer agents have come into widespread use that impact the immune system by exploiting a wide range of mechanisms of action. Nonetheless, our study has applicability in establishing a benchmark level of hepatotoxicity in controls and HCV patients. The classes of drugs in our study are mainstays of treatment for many cancers and other conditions. Moreover, a new generation of anti-CD20 monoclonal antibodies, such as ofatumumab, obinutuzumab, and ocrelizumab, are coming into use not only in treatment of cancers but also in a variety of immune mediated conditions such as autoimmune thrombocytopenia (37), autoimmune hemolysis (38), systemic lupus erythematosus (39), rheumatoid arthritis (40), multiple sclerosis (41), and many others. Our study highlights the need to exercise caution when using CD-20 antibodies for any indication in a patient infected with HCV.

CONCLUSION

Our study showed that cirrhosis was a significant risk factor for hepatotoxicity of all causes during chemotherapy, indicating that close monitoring of all patients with cirrhosis is warranted. Even when HCV is treated and cured, patients still need to be assessed for residual cirrhosis. Most causes of elevated transaminases during chemotherapy were due to the progression of cancer or to medical causes such as acute sepsis. A minority were due to chemotherapy itself, for which HCV infection was the risk factor. Among HCV patients, the risk factor for HT was rituximab use. Hepatotoxicity due to medical causes was often lethal, whereas hepatotoxicity attributed to CCT agents either did not affect treatment or rarely led to a temporary pause in treatment, even with compensated cirrhosis.

Nonetheless, careful monitoring of HCV-positive patients during and after CCT is warranted given the rare reports of severe hepatotoxicity and death even without rituximab (10,11). Function during chemotherapy, particularly with rituximab, should be evaluated in the context of baseline liver function, given the high incidence of baseline abnormalities in HCV patients. The use of new direct anti-HCV agents will likely decrease hepatotoxicity during CCT, but the low rate of alteration of hepatotoxicity in this study is reassuring in cases where chemotherapy cannot be delayed until HCV eradication.

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**APPENDIX 1**

**Supplemental Table 1:** Baseline demographic and clinical characteristics of patients who initiated chemotherapy January 2000–September 2010 (N = 7,129)

| Characteristics, n (%) | HCV-viremic* (n = 196 (2.8%)) | Negative HCV and HBV* (n = 6,933 (97.3%)) | P |
|------------------------|---------------------------------|---------------------------------|---|
| Female                 | 75 (38.3)                       | 3,966 (57.2)                    | <0.001 |
| Age (years), median [IQR] | 56.0 [51.0–62.5]                | 60.0 [50.0–68.0]                | 0.01  |
| Age ≥65 years          | 41 (20.9)                       | 2,468 (35.6)                    | <0.001 |
| Cirrhosis              | 43 (21.9)                       | 271 (3.9)                      | <0.001 |

(Continued)
### Hepatotoxicity during legacy cancer chemotherapy in patients infected with HCV

#### Characteristics, n (%)

| Characteristic | HCV-viremic*  
|----------------|------------------------------------------|
|                | HCV-viremic*  
|                | Negative HCV and HBV*  
|                | n = 196 (2.8%)  
|                | n = 6,933 (97.3%)  
| Transaminase† (ULN), median [IQR] | 0.9 [0.7-1.5]  
| Transaminase† (ULN) | 0.6 [0.4-1.0]  
| 0-1 | 107 (54.6)  
| 1.01-2.5 | 68 (34.7)  
| >2.5 | 21 (10.7)  
| Race | 0.001  
| White, including Hispanic | 151 (77.0)  
| Asian-Pacific Islander | 8 (4.1)  
| African American | 24 (12.2)  
| Other | 13 (6.6)  
| Cancer diagnosis | <0.001  
| Breast | 24 (12.2)  
| CLL-lymphoma | 43 (21.9)  
| Colon | 28 (14.3)  
| Lung | 39 (19.9)  
| Other | 62 (31.6)  
| Treatment |  <0.001  
| Rituximab | 42 (21.4)  
| Steroid | 12 (6.1)  
| Anthracycline | 51 (26.0)  
| Other† | 191 (97.5)  
| Notes: Data are n (%) unless otherwise specified. Comparisons were made using Chi-square tests for categorical variables and the Wilcoxon–Mann-Whitney test for continuous variables.  
* Based on hepatitis tests done on and before chemotherapy initiation  
† Missing data: Transaminase = 140. Transaminase refers to higher value of AST or ALT  
‡ Other includes chemotherapy agents other than rituximab, steroid, or anthracycline  
HCV = Hepatitis C virus; HBV = Hepatitis B virus; IQR = Interquartile range; ULN = Upper limit of normal; CLL-lymphoma = Chronic lymphocytic leukemia or lymphoma  

### Supplemental Table 2: Algorithm for identification of cirrhosis in 1,326 patients (196 HCV-viremic patients and 1,130 matched HCV- and HBV-negative controls) who initiated chemotherapy January 2000–September 2010

| Steps | Findings |
|-------|----------|
| Diagnosis codes for cirrhosis | 90 patients had cirrhosis coded in EHR:  
| | • 45 HCV-viremic patients  
| | • 45 matched controls  
| EHR review in all subjects for evidence of cirrhosis (clinical notes, imaging reports, and/or liver biopsy) |  
| a. Liver biopsy results were available in 64 HCV-viremic patients, with 15 stage 4 |  
| b. Liver biopsy results were available in 43 controls, with 3 stage 4 |  

(Continued)
Discrepancies in cirrhosis diagnosis were resolved by second EHR review

Five patients were added to coded diagnosis:

Biopsy showed cirrhosis in 3 patients

• Imaging showed cirrhosis in 2 patients (1 nodular shrunken liver)

Seven excluded as coding error:

• Five had data supporting the opposite, absence of cirrhosis
  (4 with biopsies, 1 with normal liver-spleen scan; none had other evidence of cirrhosis)

• Two had available data but none supported the diagnosis of cirrhosis

Final result

This left cirrhosis in 43 HCV-viremic patients and 45 controls

HCV = Hepatitis C virus; HBV = Hepatitis B virus; EHR = Electronic health record

Supplemental Table 3: Definitions of hepatotoxicity

| Grade | Adverse event |
|-------|---------------|
| 0     | SGOT (AST) WNL | >ULN–2.5× ULN, or <2× baseline |
| 1     | SGPT (ALT) WNL | >ULN–2.5× ULN, or <2× baseline |
| 2     | SGOT WNL       | >2.5–5.0× ULN, or 2–5× baseline |
| 3     | SGPT WNL       | >5.0–20.0× ULN, or 5–10× baseline |
| 4     |               | >20.0× ULN, or >10× baseline |

Standard grading scale

Modified grading scale for patients with baseline abnormal enzymes

SGOT = Serum glutamic oxaloacetic transaminase; AST = Aspartate transaminase; WNL = Within normal limits; SGPT = Serum glutamic pyruvic transaminase; ALT = Alanine transaminase

Supplemental Table 4: List of patients with hepatotoxicity unrelated to their cancer treatment, HCV-viremic and matched controls negative HCV and HBV

| Group   | Diagnosis       | Time from CCT to hepatotoxicity (days) | Details                                                                 |
|---------|-----------------|----------------------------------------|-------------------------------------------------------------------------|
| HCV-viremic | Breast        | 98                                     | TACE for liver metastases                                              |
| HCV-viremic | CLL-lymphoma  | 335                                    | TACE for second primary, HCC                                           |
| HCV-viremic | Colon         | 162                                    | DVT                                                                    |
| HCV-viremic | Breast        | 49                                     | Baseline artifact (patient was on interferon treatment with normalized transaminases when the cancer was diagnosed. When interferon was stopped, and chemotherapy was started the ALT rebounded to pre-interferon levels) |
| Control | Colon          | 104                                    | Surgery – liver metastases resection                                  |

(Continued)
Supplemental Table 5: Validated hepatotoxicity in HCV-viremic patients and matched negative HCV and HBV patients, by cancer type, cause, and effect on chemotherapy

| Characteristics     | HCV-viremic | Negative HCV and HBV |
|---------------------|-------------|----------------------|
|                     | Sample size | n = 196 | Yes, n (%) | Effect on chemotherapy & mortality | Sample size | n = 1,130 | Yes, n (%) | Effect on chemotherapy & mortality |
| CLL-lymphoma        | 43          | 10 (23.3) | Medical cause | 1 died, 1 delayed | 238          | 12 (5.0) |                     |
| CCT-related cause   | 6 (14.0)    | 2 delayed |                  |                     | 6 (2.5) | 1 died, 2 delayed |
| Other               | 62          | 7 (11.3)  | Medical cause | 2 died             | 364          | 18 (4.9) | 2 died, 1 delayed, 2 stopped as ineffective |
| CCT-related cause   | 2 (3.2)     | 1 delayed |                  |                     | 3 (0.8) | None |
| Cancer-related      | 1 (1.6)     | 1 ineffective |                |                     | 4 (1.1) | 2 stopped as ineffective |
| Breast              | 24          | 0 (0.0)   | Medical cause | NA                 | 138          | 6 (4.4) |                     |
| Lung                | 39          | 0 (0.0)   | CCT-related cause | NA                 | 228          | 11 (4.8) |                     |
| Other               | 28          | 0 (0.0)   | Medical cause | NA                 | 162          | 4 (2.5) |                     |
| Colon               | 28          | 0 (0.0)   | CCT-related cause | NA                 |                     | 1 (0.6) |                     |
|                     |             | Cancer-related | NA             |                     | 2 (1.2) | 2 ineffective |

HCV = Hepatitis C virus; HBV = Hepatitis B virus; CCT = Cancer chemotherapy; CLL = Chronic lymphocytic leukemia; TACE = Transarterial chemoembolization; DVT = Deep vein thrombosis; ALT = Alanine transaminase; TIPS = Transjugular intrahepatic portosystemic shunt; CBD = Common bile duct

*Group Diagnosis Time from CCT to hepatotoxicity (days) Details*

Control Colon 164 Surgery – liver metastases resection
Control Colon 72 Surgery – liver metastases resection
Control Colon 147 Surgery – rectal surgery
Control CLL-lymphoma 134 TIPS
Control CLL-lymphoma 66 Graft vs host disease
Control CLL-lymphoma 78 Acute cholecystitis
Control Other 20 CBD stone
Control Lung 39 CBD stone
Control Other 104 TACE
Control Colon 337 Different chemotherapy started 6 months after the end of our study period

*HCV = Hepatitis C virus; HBV = Hepatitis B virus; CCT = Cancer chemotherapy; CLL = Chronic lymphocytic leukemia; TACE = Transarterial chemoembolization; DVT = Deep vein thrombosis; ALT = Alanine transaminase; TIPS = Transjugular intrahepatic portosystemic shunt; CBD = Common bile duct*
**Supplemental Table 6:** Comparisons of mortality in HCV cohort (HCV-viremic and entire negative HCV and HBV based on hepatotoxicity grade ≥3 and/or chemotherapeutic agents received) \((N = 7,129)\)

| Characteristics                                      | Deaths, n/N (%) |  |
|------------------------------------------------------|-----------------|---|
|                                                      | HCV-viremic*    | Negative HCV and HBV* |
|                                                      | \(n = 196\)     | \(n = 6,933\)          |
| All                                                  | 94/196 (48.0)   | 3,000/6,933 (43.3)     |
| HT ≥3†                                               | 12/21 (57.1)    | 271/395 (68.6)         |
| Treated with rituximab and had HT ≥3†                | 4/11 (36.4)     | 25/46 (54.4)           |
| Not treated with rituximab and had HT ≥3†            | 8/10 (80.0)     | 246/349 (70.5)         |
| With CLL-lymphoma and had HT ≥3†                     | 4/11 (36.4)     | 37/86 (43.0)           |
| Without CLL-lymphoma and had HT ≥3†                  | 8/10 (80.0)     | 234/309 (75.7)         |

* Based on hepatitis tests done on and before chemotherapy initiation
† Hepatotoxicity grade ≥3 and cause confirmed via structured electronic health record review

HCV = Hepatitis C virus; HBV = Hepatitis B virus; HT = Hepatotoxicity; CLL = Chronic lymphocytic leukemia