Impact of hepatitis C virus seropositivity on survival after allogeneic hematopoietic stem cell transplantation for hematologic malignancies

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ABSTRACT

Background

Because hepatitis C virus infection causes hepatic and immunological dysfunction, we hypothesized that seropositivity for this virus could be associated with increased non-relapse mortality after allogeneic hematopoietic stem cell transplantation.

Design and Methods

We performed a case-control study of the outcomes of patients who were hepatitis C virus seropositive at the time of allogeneic hematopoietic stem cell transplantation (N=31). Patients positive for hepatitis C virus were considered candidates for stem cell transplantation only if they had no significant evidence of hepatic dysfunction. Matched controls (N=31) were seronegative for viral hepatitides and were paired according to age, diagnosis, disease stage, conditioning regimen and donor type. We also compared the hepatitis C virus seropositive patients to all seronegative patients (all controls, N=1800) transplanted during the same period, to adjust for other confounding effects.

Results

The median age of the seropositive patients was 49 (range 26-72); 15 had acute myeloid leukemia/myelodysplastic syndrome, 6 had chronic myeloid leukemia/myeloproliferative disease, 6 non-Hodgkin's lymphoma, 2 myeloma, 1 acute lymphocytic leukemia and 1 Hodgkin's lymphoma; 61% had poor risk disease; 68% had related donors; 68% received reduced intensity conditioning; 7 patients had mildly abnormal alanine transaminase levels (all less than three times the upper limit of normal) and 1 patient had minimally elevated bilirubin. These characteristics were similar to those of the matched control group. Median overall survival was 3, 18 and 20 months, and 1-year survival was 29%, 56% and 56%, in the hepatitis C virus, matched and all controls groups, respectively (hazard ratio for death 3.1, 95% confidence interval 1.9 - 5.6, $p<0.001$ in multivariate analysis). Non-relapse mortality at 1 year was 43%, 24% and 23%, respectively (hazard ratio 3.3, 95% confidence interval 1.8 - 7.1, $p<0.01$). Disease progression and graft-versus-host disease rates were comparable.

Conclusions

Hepatitis C virus seropositivity is a significant risk factor for non-relapse mortality after allogeneic hematopoietic stem cell transplantation even in patients with normal or minimally abnormal liver function tests.

Key words: hematopoietic stem cell transplantation, hepatitis C virus, transplant-related mortality.

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Introduction

Hepatitis C is the most common chronic blood-borne infection in the United States. It is estimated that 4.1 million people (1.6% of the population of the USA) test positive for antibodies to the hepatitis C virus (HCV).[1] Approximately 80% of individuals infected by HCV develop chronic hepatitis, making it a major cause of chronic liver disease. HCV infection used to be extremely common in the setting of allogeneic hematopoietic stem cell transplantation (HSCT) before the universal adoption of screening of blood products for the virus, with a study from the Seattle group calculating that one third of their patients undergoing allogeneic HSCT during the late 1980s were affected by HCV.[2] Although currently less frequent, HCV infection is still a relevant problem in this setting, with a prevalence at least as high as that in the general population.

The influence of chronic hepatitis C on the outcomes after allogeneic HSCT is not clearly defined. A few studies have suggested an increase in the rate of veno-occlusive disease (VOD, or sinusoidal obstruction syndrome[3]),[4-6] a finding which has not been corroborated in other series.[7-11] Longer follow-up studies have pointed towards an increased rate of progression to cirrhosis compared to that in non-transplant patients,[2,12,13] but none of the series has clearly demonstrated worse early outcomes in seropositive patients when compared to those in an otherwise similar seronegative population.

Because HCV is associated with immune dysregulation[14,15] and affects an organ that is the target for many post-transplant complications,[16] we hypothesized that chronic infection with HCV may be associated with an increase in non-relapse mortality (NRM) after allogeneic HSCT. We sought to address this issue by performing a retrospective comparison of outcomes after allogeneic HSCT of HCV-seropositive and seronegative patients. Herein we present the results of this analysis.

Design and Methods

Selection of patients

This retrospective study was approved by the University of Texas M. D. Anderson Cancer Center (UTMDACC) Office of Protocol Research (RCR07-0046). A waiver of informed consent was obtained given the study's characteristics. Between January 1998 and March 2007, 31 patients with positive serology for hepatitis C, as defined by the presence of antibodies against HCV (anti-HCV) in serum by a second generation enzyme-linked immunosorbent assay (ELISA), underwent an allogeneic bone marrow or peripheral blood stem cell transplant at the UTMDACC. During the same period, a total of 1800 patients with identical underlying hematologic diagnoses who were seronegative for viral hepatitides B and C received a first allogeneic HSCT from a seronegative donor. Information regarding patients' clinical characteristics, pre-transplant histories, transplant details and post-transplant courses is stored in a departmental database and was reviewed as appropriate during the analysis. Details regarding laboratory and pathology results were obtained from our institution's electronic medical records.

Conditioning regimens and graft-versus-host disease and infection prophylaxis

The conditioning regimen was chosen according to prospective clinical studies or according to standard clinical pathways when treatment was performed *off protocol*. Most patients were treated in a disease-specific clinical trial. Graft-versus-host disease (GVHD) prophylaxis was based on tacrolimus and mini-dose methotrexate, with the intention of tapering the former after an average of 6 months. Anti-fungal and anti-viral prophylaxis consisted of fluconazole or voriconazole and acyclovir or valacyclovir, administered according to our department's standard operating procedures. Anti-fungal prophylaxis was changed to an echinocandin if significant liver function test abnormalities were observed.

Definitions

Baseline laboratory values. Baseline laboratory values were defined as the latest values obtained in tests done between 7 and 14 days before the date of the transplant.

Vaso-occlusive disease. VOD was defined as the occurrence, within 21 days of transplantation, of hyperbilirubinemia (total serum bilirubin > 2 mg/dL) and two of the following three findings: hepatomegaly, ascites or sudden weight gain (≥ 5% of baseline body weight).[17] No other explanation for these signs and symptoms should be present at the time of diagnosis.[18]

Liver toxicity score. Liver function tests obtained after transplant for each of the anti-HCV positive and matched control patients (see below for definition of control groups) were analyzed. Peak values for alanine aminotransferase, alkaline phosphatase and total bilirubin were recorded during and after the first 100 days post-transplant. The corresponding Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) grades for these three parameters were added to give a score ranging from 0 to 12, which we designated the liver toxicity score, summarizing the degree of abnormalities in these parameters during the first 100 days (early period) and more than 100 days (late period) post-transplant.

Causes of death. The primary causes of death were determined by the attending physician and reviewed by at least one other investigator, taking into account the clinical course, laboratory data and autopsy results (available for 12% of the anti-HCV positive patients who died).

Statistical methods

Outcomes of the anti-HCV-positive group were compared to those of all other patients receiving an allogeneic HSCT for the same underlying diagnoses in our institution, during the same period (*all controls*). In addition, in order to facilitate the study of some parameters, we performed a matched case-control analysis in which each anti-HCV-positive patient was paired with one control subject selected from among all seronegative patients (defining a group of *matched controls*). Patients

were matched for age, underlying disease, disease stage category (low or high risk), type of conditioning regimen (myeloablative or reduced intensity) and donor type (sibling or unrelated), so as to control for confounding effects. If more than one potential match existed, matches were ranked by similarity so that a control patient with exactly the same disease stage, exactly the same treatment regimen and/or the same source of stem cells (bone marrow versus peripheral blood) as well as the closest age was selected. All these requirements ensured that the best available unique control was always selected for each case. A control patient could not be matched more than once. If more than one case was initially matched to the same control, the best matching pair was kept and the remaining cases were matched to their next best potential control. A computer algorithm developed in Microsoft Access software version 2007 (Microsoft Corporation, Redmond, WA, USA) was utilized for the matching procedure to avoid any human bias.

The primary end-points studied were overall survival and NRM. These were estimated using the Kaplan-Meier and the cumulative incidence methods,[19] respectively. Death attributed to disease recurrence or progression was considered as a competing risk in the estimation of NRM. The incidences of disease progression and acute GVHD were also estimated using the cumulative incidence method, considering death before the occurrence of the corresponding events as competing risk.

The outcomes of anti-HCV-positive patients (n=31), their matched controls (n=31), and all controls (n=1800) were compared using a Cox's proportional hazards model.[20] A Cox's regression model was also used to evaluate the prognostic factors for overall survival and NRM, including anti-HCV status, in the total cohort of patients (n=1831). Factors significant at the 0.1 level on univariate analysis were included in a multivariate model to adjust for confounding effects. Baseline clinical characteristics and post-transplant liver function parameters were compared using a t-test, a χ^2 test or a Mann-Whitney test as appropriate. Statistical significance was determined at the 0.05 level. Analyses were performed using STATA software release 7.0 (Stata Corporation, College Station, TX, USA).

Results

Baseline clinical characteristics

The clinical characteristics of the anti-HCV-positive patients and controls are summarized in Table 1. The median age of the anti-HCV-positive patients was 49 years, and most patients (21 out of 31) had a myeloid malignancy. The majority of patients (19 out of 31) had high-risk disease, defined as not being in remission for acute leukemias, as not being in first chronic phase for chronic myelogenous leukemia or as having chemoresistant disease for lymphomas, at the time of transplantation. Most patients (20 out of 31) received a peripheral blood graft, while the remainder were given bone marrow. Preparative regimens were of reduced intensity in 21 cases, mostly a combination of fludarabine and melphalan, our regimen of choice when the recipient was anti-HCV-positive. Myeloablative strategies included regimens both with and without busulfan or total body irradiation. Busulfan doses were adjusted according to the results of pharmacokinetic analysis.[21] The clinical characteristics of matched control patients were virtually identical to those of anti-HCV-positive patients, except for those characteristics for which the groups were not matched, such as gender.

All anti-HCV-positive patients were considered candidates for allogeneic HSCT only if they had alanine aminotransferase levels less than three times the upper limit of normal and essentially normal bilirubin levels at the time of transplantation (Table 1). Only two anti-HCV-positive patients had prolongation of the prothrombin time prior to their transplant, and these prolongations were minimal. There were no significant differences in any of these parameters between the anti-HCV-positive patients and the matched control patients. Approximately one third of the patients in both groups had hypoalbuminemia, a finding most likely related to their underlying malignancies rather than liver dysfunction. None of the patients had stigmata of chronic liver disease or evidence of portal hypertension.

Viral loads were known for ten (32%) of the anti-HCV-positive patients. In all cases the results confirmed the presence of active infection (median 5.95 logarithmic units, range 3.64 to 7.64, for quantitative tests). Liver biopsies were performed prior to transplantation in 14 patients (45% of anti-HCV-positive patients): in all but two there were findings consistent with chronic active hepatitis C grade 1 to 2, fibrosis stage 1 to 2, with the other cases showing non-specific changes. Six patients in the anti-HCV-positive group were also seropositive for hepatitis B core antibody (HBcAb), but negative for the surface antigen and (when available) had undetectable hepatitis B viral loads, i.e., they had no evidence of active hepatitis B.

Patients' outcomes

The median follow-up was 34 (range, 3 to 53), 27 (range, 4 to 74) and 29 months (range, 1 to 108) for the anti-HCV-positive group, matched controls and all controls, respectively. The median overall survival was 3, 18 and 20 months, respectively. The corresponding actuarial survival rates were 58%, 87% and 87% at 3 months, and 29%, 56% and 56% at 1 year. On univariate analysis using the matched controls group, overall survival post-allogeneic HSCT was significantly inferior in the anti-HCV-positive group (Figure 1), with a significantly higher hazard rate (HR) of death in the anti-HCV group compared to in the group of matched controls (HR 3.6 at 3 months, 95% CI 1.2 to 11, p=0.03; and HR 2.4 at 1 year, 95% CI 1.2 to 4.9, p=0.01). The higher mortality rate in the anti-HCV-positive group persisted on multivariate analysis adjusting for confounding effects using the entire dataset of 1831 patients (HR 3.9 at 3 months, 95% CI 2.2 to 6.8, p<0.001; HR 3.1 at 1 year, 95% CI 1.9 to 4.8, p<0.001). Additional significant predictors of survival were disease status at transplantation, intensity of the conditioning regimen, donor type and age of the patient (Table 2).

Table 1. Patients' characteristics.

	Anti-HCV +		Matched controls			All controls		
	N	%	N	%	*p*	N	%	*p*
Total	31		31			1800		
Sex					0.2			0.2
Male	22	71	17	55		747	41	
Female	9	29	14	45		1053	58	
Age median, years	49		48		0.9	47		0.2
(range)	(26-72)		(29-67)			(3-75)		
Diagnosis					0.9			0.7
AML/MDS	15	48	15	48		740	41	
CML/MPD	6	19	6	19		274	15	
Non-Hodgkin's lymphoma	6	19	6	19		423	24	
Hodgkin's lymphoma	1	3	1	3		91	5	
Multiple myeloma	2	6	2	6		87	5	
Acute lymphoblastic leukemia	1	3	1	3		185	10	
Risk category					0.9			0.2
High risk	19	61	19	61		905	50	
Low risk	12	39	12	39		895	50	
Cell type					0.9			0.4
Bone marrow	11	35	10	32		758	42	
Peripheral blood	20	64	21	68		1042	58	
Donor type					0.8			0.5
Related	21	68	21	68		1119	62	
HLA-identical	19	61	20	64		990	55	
1-antigen mismatched	2	6	1	3		85	5	
2-antigen mismatched						17	1	
Haploidentical						27	2	
Unrelated	10	32	10	32		681	38	
HLA-identical	10	32	9	29		651	36	
1-antigen mismatched			1	3		28	2	
2-antigen mismatched						2	0	
Conditioning regimen					0.9			*0.02
Reduced intensity	21	68	21	68		754	42	*0.004
High dose/TBI	1	3	1	3		241	13	
High dose/busulfan	6	19	6	19		648	36	0.06
High dose/other	3	10	3	10		157	9	
Abnormal laboratory studies								
ALT >ULN	7	23	5	16	0.8	ND		
(range, IU/dL)	(69-185)		(69-178)					
AST >ULN	7	23	4	13	0.5	ND		
(range, IU/dL)	(47-136)		(50-96)					
ALP >ULN	8	26	8	26	0.9	ND		
(range, IU/dL)	(127-160)		(127-326)					
Total bilirubin >ULN	1	3	0	-	0.9	ND		
(range, mg/dL)	(1.2)			-				
Albumin <LLN	9	29	10	32	0.9	ND		
(range, mg/dL)	(2.6-3.4)		(2.7-3.3)					
PT >ULN + 1 sec	2	6	0	-	0.5	ND		
(range, sec)	(15.1, 18.5)		-					
Median follow-up, months	34		27			29		
(range)	(3-53)		(4-74)			(1-108)		

**p value reflects the higher proportion of reduced intensity regimens in the anti-HCV group and of myeloablative busulfan-containing regimens in the all controls group. AML: acute myeloblastic leukemia; MDS: myelodysplastic syndrome; CML: chronic myelogenous leukemia; MPD: myeloproliferative disorder; HLA: human leukocyte antigen; TBI: total body irradiation; ULN: upper limit of normal; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; LLN: lower limit of normal; PT, prothrombin time; ND: not determined.*

In order to determine reasons for this difference in survival, we analyzed the incidence of treatment failure events. The cumulative rate of disease progression was comparable between groups, but NRM was significantly increased in the anti-HCV-positive group, regardless of the control group used (Figure 2). The cumulative incidence of NRM at 3 months was 29%, 13% and 10%, and at 1 year 43%, 24% and 23%, in the HCV, matched and all controls groups, respectively. Univariate analysis using the matched controls group demonstrated excess NRM in the anti-HCV-positive patients (HR 2.5 at 3 months, 95% CI 0.8 to 8.1, p=0.1; HR 2.9 at 1 year, 95% CI 1.1 to 7.7, p=0.03). The multivariate model for NRM, employing the dataset with 1831 patients (Table 2), confirmed anti-HCV positivity as the strongest predictor of mortality (HR 3.6 at 3 months, 95% CI 1.8 to 7.1, p<0.001; HR 3.3 at 1 year, 95% CI 1.9 to 5.9, p<0.001).

We then investigated causes for the observed higher NRM in the anti-HCV-positive group. We did not find a statistically significant difference in the incidence of acute GVHD (Figure 3). The cumulative incidence of grades II-IV and III-IV acute GVHD was 32% versus 26% (HR 1.3, 95% CI 0.5 to 3.2, p=0.6), and 13% versus 7%, (HR 1.9, 95% CI 0.3 to 10.7, p=0.4), in the anti-HCV and matched control groups, respectively. Because we were concerned about greater liver toxicity in the anti-HCV-positive group, we tried to ascertain whether there was any evidence for a greater propensity to hepatic complications in this group compared to among the matched controls. We documented the incidence of VOD, the frequency of prolonged prothrombin time (as a surrogate for synthetic liver failure) and the degree of abnormalities in tests commonly used to document hepatic injury, namely serum transaminases, alkaline phosphatase and bilirubin levels. There were no documented cases of VOD in either of the two cohorts and only two patients in each of them had prothrombin times more than 10 seconds above the upper limit of normal at any time after transplantation (p=0.9 and 0.4, respectively). The late post-transplant period liver toxicity score was comparable between groups (2.9 for the anti-HCV-positive group and 2.0 for the matched controls group, p=0.2), but there was a statistically significant difference in the early post-transplant period score (4.4 and 3.0, p=0.02) suggesting worse hepatic complications in the anti-HCV-positive group during the first 100 days. However, analysis of the primary causes of death (Table 3) did not show an obvious excess of deaths attributed to liver failure. Almost all cases of hepatic dysfunction before death occurred in the setting of multi-organ failure. Indeed, the only notable difference regarding causes of death was a slight trend towards an increased rate of infectious deaths.

No cases of HCV-associated disorders, cirrhosis or hepatocellular carcinoma were documented. We did not see any clear association of worsening liver function tests with discontinuation of immunosuppression.

Table 2. Multivariate analysis of overall survival and non-relapse mortality. The analysis was performed for the entire cohort of transplanted patients (n=1831).

	Overall survival*			Non-relapse mortality*		
Factor	HR	95% CI	p	HR	95% CI	p
Anti-HCV positivity	3.1	1.9-4.8	<0.001	3.3	1.9-5.9	<0.001
High-risk disease	1.9	1.7-2.3	<0.001	1.5	1.2-1.8	<0.001
Reduced intensity conditioning	0.7	0.6-0.8	<0.001	0.8	0.7-0.9	0.03
Matched sibling donor	0.6	0.5-0.7	<0.001	0.6	0.5-0.7	<0.001
Age > 50 years	1.2	1.0-1.3	0.04			NS

**The overall survival rate at 1 year was 29% for anti-HCV positive patients and 56% for all controls; non-relapse mortality was 43% and 23%, respectively. HR: hazard ratio; CI: confidence interval.*

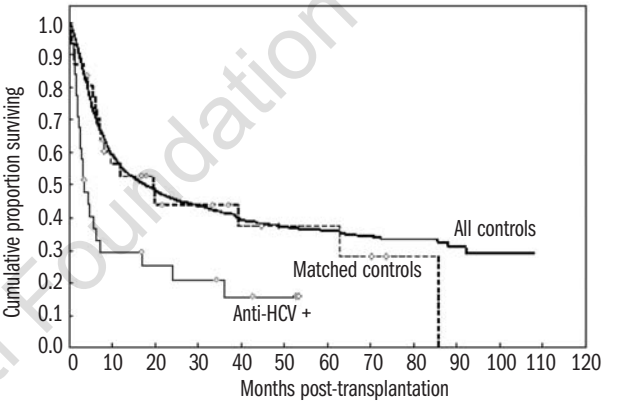

Figure 1. Overall survival of anti-HCV-positive patients and controls. Seropositive patients had worse survival due to an increase in NRM. The survival rate at 1 year was 56% for both control groups versus 29% for anti-HCV-positive patients (HR 3.1, 95% CI 1.9-4.8, p<0.001, in multivariate analysis).

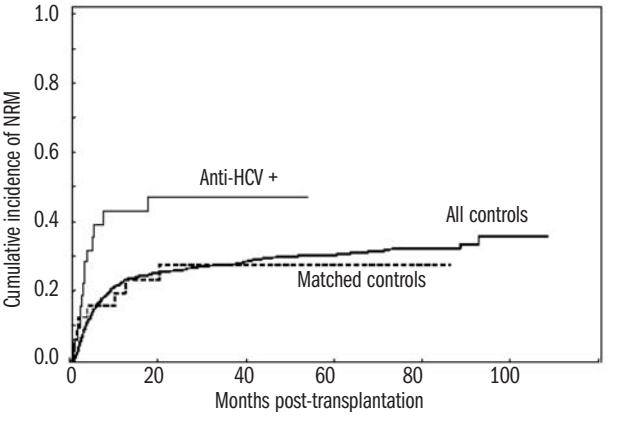

Figure 2. Cumulative incidence of non-relapse mortality (NRM) of anti-HCV-positive patients and controls. Death due to primary disease is the competing event for non-relapse mortality. Seropositivity for HCV was associated with a statistically significant increase in the cumulative incidence of NRM: 24% and 23% versus 43% at 1 year for matched controls, all controls and anti-HCV positive patients, respectively (HR 3.3, 95% CI 1.9 to 5.9, p< 0.01, in multivariate analysis).

Viral loads after transplantation were available for review for eight patients: in three patients they went from unknown to negative (non-quantitative tests); in one patient the viral load changed from 3.64 logarithmic units to undetectable; in four patients the viral loads remained positive with stable levels or a less than 2 logarithmic unit increase.

None of the patients with positive HBcAb had evidence of hepatitis B reactivation when viral serology was repeated to investigate abnormalities in liver function tests.

Of note, two patients in the anti-HCV-positive group had been treated with interferon-α and ribavirin: one of the patients was treated 16 years before allogeneic HSCT, had increased viral loads after the procedure and died of multi-organ failure; the other received therapy 1 year before allogeneic HSCT and is one of our long-term survivors.

Discussion

Our data demonstrate that patients with evidence of HCV infection prior to allogeneic HSCT have worse overall survival and NRM than seronegative controls. To our knowledge, this is the first time that such a difference in survival has been documented, a fact that may arise from several circumstances. Some of the previous studies looking at post-allogeneic HSCT outcomes in hepatitis C patients either excluded patients who survived less than 1 year or patients with HCV infection prior to transplantation.[2,6,8,12,13,22,23] Others analyzed the role of HCV as a risk factor for hepatic complications, but the number of infected patients was small or no control group with comparable characteristics was available for analysis.[9,10,24-26] In contrast to those studies, we used a robust matching algorithm to define a control cohort with identical clinical characteristics. Careful data collection by our department also allowed us to extend the comparison to the entire cohort of seronegative patients while controlling for other significant risk factors. The higher NRM rate among anti-HCV-positive patients is even more striking when one considers that patients with hepatitis C were given the option to undergo allogeneic HSCT only if they had no evidence of major liver dysfunction. In addition, patients were preferably treated with reduced-intensity regimens and spared busulfan-containing conditioning due to concerns over the high risk of VOD. As seen in other recent studies, the prevalence of anti-HCV in the allogeneic HSCT population is much lower than in the past, a finding reflecting the implementation of HCV screening of blood donors. The frequency of anti-HCV in our patients during the study period is approximately 1.4%. This value is almost identical to the most current estimates of the prevalence of anti-HCV in the general population.[1]

In contrast to other series, we did not observe any cases of VOD in the anti-HCV-positive group. Some previous studies showed an increase in the incidence of VOD in patients with chronic hepatitis C[5] (especially if associated with elevated levels of transaminases pre-transplantation),[6] or at least suggested that HCV was a contributing factor in the pathogenesis of VOD.[4,7,8] However, this finding is controversial, with work from other authors dispelling an association of HCV with VOD.[9-11,27] Very likely, active HCV infection increases the incidence of VOD when combined with other risk factors for this condition, such as specific chemotherapy regimens and the presence of marked hepatic fibrosis.[17,18,28] Possible explanations for why we did not see any VOD in our anti-HCV cohort include the large proportion of reduced intensity conditioning regimens employed (for 68% of the patients) and the routine use of pharmacokinetically adjusted doses of intravenous busulfan when this drug was administered.[21] Also contrary to other series, we did not observe any cases of liver cirrhosis or hepatocellular carcinoma. This is not unexpected, though, given the slow progression of chronic hepatitis C to cirrhosis[29] and the limitations of our follow-up time. Indeed, although HCV infection is associated with a faster progression to cirrhosis after allogeneic HSCT, even in that setting most cases seem to occur more than 10 years after transplantation.[2,12,13]

Our series and methodology of analysis have several strengths compared to other studies. We analyzed a large cohort at a single center with uniform standard operating procedures and a large number of patients treated in clinical trials. Moreover, our departmental database contains prospectively recorded data regarding patients' characteristics and clinical course, with elements that are consistently captured across treatment protocols. Finally, we have accumulated enough cases with identical or comparable treatment regimens and disease stages to allow us to select closely matched controls using an unbiased algorithm. This strategy made it possible to adjust our results for some differences in clinical characteristics between the study group and all controls, in particular a lower frequency of myeloablative conditioning regimens and a trend towards a higher rate of high-risk disease in the anti-HCV-positive group. Multivariate analysis of the entire cohort confirmed these results.

We recognize some limitations to our analysis. Selection of hepatitis C patients was based on a positive second generation ELISA test for anti-HCV, with a potential risk for false positive results. Several studies tried to confirm all the positive ELISA results with a polymerase chain reaction for the HCV genome or a recombinant immunoblot assay (RIBA) for specific HCV antigens.[8,12,13,23,30] While there was a low rate of false positive results, most studies showed an excellent agreement of the confirmatory tests with the second generation ELISA results. Furthermore, the operating characteristics of HCV ELISA have improved with newer technologies. Finally, when viral loads were measured in our patients, they confirmed active infection in all cases. Therefore, we are confident that most, if not all, of the anti-HCV patients had indeed been infected with HCV. We are also aware that seropositivity for HCV antibodies does not necessarily imply ongoing infection with HCV. In fact, the strict definition of active hepatitis C infection requires examination of a liver biopsy. However, several studies have shown that

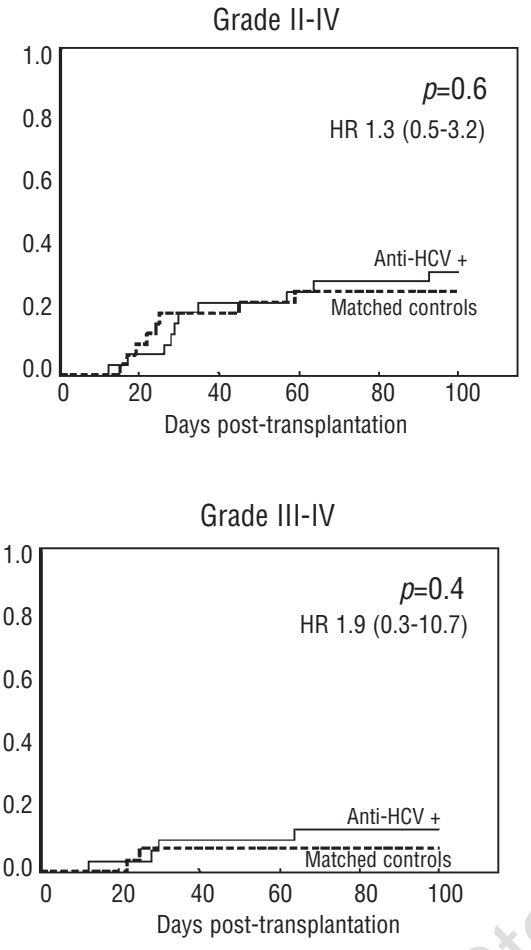

Figure 3. Cumulative incidence of acute graft-versus-host disease (GVHD) in anti-HCV-positive patients and matched controls. Death is the competing event. There was no significant difference in the incidence of acute GVHD between anti-HCV-positive patients and controls.

Table 3. Causes of death for anti-HCV-positive patients and matched controls. Matching criteria are described in the text.

	Anti-HCV* (N=31)		Matched controls (N=31)	
	N	%	N	%
Total deaths	24		19	
Causes of death				
Recurrence/persistence	9	38	10	53
Acute GVHD	4	17	2	11
Chronic GVHD	2	8	2	11
Graft rejection or failure	1	4	-	-
Infection	4	17	1	5
Hemorrhage	1	4	-	-
Liver failure (not VOD)	1	4	-	-
Heart failure	-	-	1	5
Multiorgan failure	1	4	2	11
Other/unknown	1	4	1	5

GVHD: graft-versus-host disease; VOD: veno-occlusive disease.

at least 80% of anti-HCV-positive individuals develop chronic infection,[31] so most patients in our anti-HCV-positive cohort were likely to have some degree of chronic hepatitis. Indeed, biopsies were available from approximately half of the patients and in 86% of the cases showed aspects consistent with chronic active hepatitis.

The underlying reasons for the increased NRM associated with HCV seropositivity are unclear and we can only speculate regarding potential mechanisms. We did document a worse liver toxicity score in the early post-transplant period, which is in line with previous reports of the association of HCV infection with transient hepatitis in the immediate post-allogeneic HSCT setting.[6,8,9,26] However, we did not observe an excess of deaths primarily attributed to liver failure. On the other hand, hepatitis C is associated with immune dysfunction, as attested by the frequent occurrence of autoimmune phenomena[15] and its association with lymphoid malignancies,[14] which may predispose HCV-infected patients to worse infectious complications. In this regard, we did see a trend towards an excess of infectious deaths. Furthermore, although we did not detect any association of HCV infection with acute hepatic GVHD, active replication of HCV may promote the development of an inflammatory cytokine milieu that may be conducive to multiorgan dysfunction. Finally, the differences in outcome between cases and matched controls could be due to uncontrolled confounding covariates, although this is unlikely given the results of the multivariate analysis of the whole cohort.

Although we have observed higher mortality after allogeneic HSCT in anti-HCV positive individuals, we do not feel that active hepatitis C with normal liver function or mild hepatic dysfunction should be a contraindication to allogeneic HSCT. All the anti-HCV-positive patients had a compelling indication for transplantation, without any effective therapeutic alternatives. Our recommendations at this point are the same as those that have been proposed by other authors,[30,32] namely to exclude advanced fibrosis or cirrhosis, to follow the patient closely for the development of chronic hepatitis after allogeneic HSCT and to consider antiviral therapy in long-term follow-up, apart from paying careful attention to the early post-transplant course. Along these lines, prevention of hepatitic flares in the immediate post-transplant period through the administration of specific antiviral agents, similar to what can already be done for hepatitis B, may become an important goal in the near future. Although the most active drug against HCV, interferon-α, is almost always contraindicated in the peri-transplant period, ribavirin has had some success.[33] Furthermore, other small molecule antiviral drugs, which may be more effective and less toxic in this setting, are currently being developed.[34-36] Regardless, patients should be advised that worse outcomes are significantly more likely in the presence of HCV seropositivity.

In conclusion, serological evidence of HCV infection at the time of allogeneic HSCT, even with normal or minimally abnormal liver tests, is associated with worse survival. The difference in survival is attributable to an increased number of non-relapse deaths. The similarity of our results regardless of the control group used validated the matching procedure employed in this work. Additional studies will be needed to ascertain what factors underlie the differences in survival, whether further risk stratification of these patients is possible using such tools as viral load, iron levels and immune markers, and whether any prophylactic measures should be offered to these patients prior to transplantation.

Authorship and Disclosures

CAR conceived and designed the study, cared for patients, collected and assembled data, analyzed and interpreted data, and wrote the manuscript; RMS analyzed and interpreted data, performed the statistical analysis and reviewed data; LP and OK collected and assembled data; EJS, SG, PAP, CMH, URP, IFK, YLN and REC were involved in caring for patients, and reviewing data; GR collected, assembled, and reviewed data; ML conceived and designed the study, cared for patients, analyzed and interpreted data. All authors reviewed and approved the manuscript. Figures and tables were created by CAR and RSS.

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