Effect of Hepatitis C Virus Infection in Patients With Cancer: Addressing a Neglected Population

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Abstract

Background: Hepatitis C virus (HCV) infection is a neglected disease in patients with cancer. Therefore, this study examined the impact of HCV infections in these patients. **Methods:** The records of HCV-infected patients with cancer seen at The University of Texas MD Anderson Cancer Center (2008–2011) were reviewed. The outcomes of those who underwent HCV treatment were analyzed. **Results:** Of 1291 patients who had positive test results for an antibody to HCV (anti-HCV), 744 (58%) were tested for HCV-RNA; 642 (86%) of which had chronic HCV infections. Most had solid tumors (72%) and genotype-1 (G-1) infections (66%). HCV therapy was administered in 348 patients (98 of them after cancer diagnosis). Sustained virologic response (SVR) occurred in 27 (35%) of the 78 patients treated for whom outcome data were available. Compared with patients who experienced an SVR, more patients who did not were black (29% vs 4%; *P*=.007), had G-1 infections (72% vs 6%; *P*<.0001), and had higher baseline aspartate aminotransferase (78 vs 47 IU/L; *P*=.006) and alanine aminotransferase levels (71.1 vs 43.3 IU/L; *P*=.009). Overall, progression to cirrhosis (hazard ratio [HR], 0.38; *P*=.03) and portal hypertension (HR, 0.19; *P*=.009) was less common in those treated, irrespective of the treatment outcome (SVR or non-SVR). Hepatocellular carcinoma (HCC) developed as a second primary malignancy in 7% of patients with non-HCC cancer. **Conclusions:** This is the largest series to analyze HCV infections in patients with cancer. HCV therapy is feasible and prevents liver disease progression in this forgotten population. A treatment algorithm is provided. (J Natl Compr Canc Netw 2015;13:41–50)

Background

Approximately 130 to 170 million persons globally are infected with hepatitis C virus (HCV).[1] In the United States, approximately 2.7 to 3.9 million persons (1.0%–1.5%) are infected.[2] Chronic HCV increases the risk for mortality from hepatic and extrahepatic diseases.[3]

The prevalence of HCV infection in patients with cancer ranges from 1.5% to 32.0%.[4–7] Despite the recent interest in HCV,[8] it is a neglected infection in patients with cancer, with little known about its natural history, management, and outcome. Professional societies have published guidelines for the diagnosis, management, and treatment of HCV infection,[9] specific sections of which address immunocompromised patients, such as HIV coinfected patients and solid organ transplant recipients, but no recommendations were made for patients with cancer. The FDA-designated HCV-infected special populations include children, HIV-positive pa-

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Author contributions: Dr. Torres designed the study, provided study patients, analyzed and interpreted the data, and wrote the manuscript; Dr. Mahale performed research, analyzed and interpreted the data, performed statistical analysis, designed tables and figures, and wrote the manuscript; Drs. Blechacz, Miller, Herlong, Kaseb, Fowler, Raad, and Kontoyiannis provided patients, analyzed and interpreted the data, and wrote the manuscript; and Dr. Jiang analyzed and interpreted the data, and performed statistical analyses.

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tients, patients with bleeding disorders, liver transplant recipients, and injection drug users, but not patients with cancer.

The most likely reason why no data exist on HCV treatment in patients with cancer is that clinical trials of antiviral or cancer therapy typically exclude these infected patients, partly because their baseline hematologic abnormalities (ie, neutropenia) can be exacerbated by interferon (IFN) alfa and ribavirin-containing HCV therapy.[10] Other reasons for excluding these patients is the potential for HCV to affect the toxicity and/or efficacy of the investigational chemotherapy agents. However, studies have demonstrated the feasibility of using pegylated IFN (pegIFN) alfa plus ribavirin in a subset of patients with cancer, such as hepatocellular carcinoma (HCC) survivors,[11] or recipients of hematopoietic cell transplants (HCTs).[12–14] Clinical trials of antiviral treatment exclude HCV-infected patients with cancer, likely because of the impact in long-term outcomes of the underlying malignancy, and limited clinical understanding of potential drug-drug interactions between antivirals and chemotherapy or other immunosuppressive agents in these patients.

Patients with chronic HCV may be at a higher risk of dying from nonliver cancers than the general population. For instance, age-adjusted cancer-related mortality was analyzed for 12,126 chronic HCV-infected patients in the Centers for Disease Control and Prevention's (CDC) Chronic Hepatitis Cohort Study and compared with Multiple Cause-of-Death mortality data for 2006 to 2010 from the National Center for Health Statistics. Of 1496 deaths, 372 (25%) were from cancer. Compared with the general population, HCV-infected individuals were more likely to die not only from HCC (relative risk [RR], 29.59) but also from nonliver cancers, such as non-Hodgkin's lymphoma (RR, 2.27) and rectal (RR, 2.60), pancreatic (RR, 1.63), and oral cavity or pharyngeal cancers (RR, 5.22).[15]

Patients with cancer may benefit from HCVf-therapy because persistent transaminase elevation as a result of chronic infection can make cancer treatment complicated.[16] In addition, successful HCV therapy can cure HCV, prevent its reactivation,[17] delay progression to cirrhosis,[12–14] and improve overall mortality rates, as observed in the general population of HCV-monoinfected and HIV-HCV–coinfected patients.[18,19] Few data exist on patients with cancer, but HCV treatment is recommended for all HCT recipients who meet certain criteria,[20] because HCV infection is associated with a higher risk for non–relapse-related mortality after allogeneic HCT.[21]

In 2009, The University of Texas MD Anderson Cancer Center established the first US clinic specifically devoted to managing HCV infections in patients with cancer.[22] In this study, we determined the treatment outcome of HCV infections in patients with cancer. They hypothesized that HCV infections affect these patients' clinical outcome and that cancer survivors can be safely treated to reduce the risk of liver-related clinical events.

Methods

Study Design and Patient Population

In this retrospective study, the medical records of patients with cancer and HCV infections who were seen at The University of Texas MD Anderson Cancer Center between January 1, 2008, and December 31, 2011, were examined. All patients who had positive test results for an antibody to HCV (anti-HCV) were identified through a search of the institutional database. Only patients with positive test results for anti-HCV and who had chronic HCV infections (ie, documented HCV-RNA in serum without clinical presentation suggestive of acute infection, or with a history of HCV therapy) were included. The information collected included demographic data, underlying cancer and stage, HCV infection risk factors, cancer therapy, coinfections (eg, hepatitis B virus), clinical presentation, HCV therapy, and outcome. Patients received HCV therapy either at MD Anderson or before referral to the center. Most patients who received HCV therapy at MD Anderson were cancer survivors (ie, persons whose cancer has been in complete remission for >6 months since their last cancer treatment and were under surveillance for recurrence). The protocol was approved by the MD Anderson Institutional Review Board.

Patients were tested for anti-HCV using the ABBOTT PRISM HCV assay (Abbott Park, IL). HCV-RNA in serum was quantified using a commercially available polymerase chain reaction method (COBAS TaqMan HCV test, version 1; Roche Molecular Systems, Branchburg, NJ). Information on underlying liver disease was sought through available liver biopsy reports. When these reports were not available, CT

scans or liver ultrasound imaging reports were used. All patients with no evidence of cirrhosis at baseline were followed up for evidence of liver disease progression (ie, development of cirrhosis or portal hypertension).

Treatment data were collected until 2011, a pre–direct-acting antivirals (DAAs) era, reflecting the use of dual combination of pegIFN and ribavirin, or, in a few cases, standard IFN or pegIFN monotherapy. These agents were administered following practice guidelines available at that time for noncancer patients, with the goal of preventing complications and death from HCV infection.[9]

Statistical Analyses

To determine the predictors of response to HCV therapy, the characteristics of cancer survivors who attained a sustained virologic response (SVR; ie, absence of HCV RNA in the serum 6 months after discontinuing HCV therapy[9]) were compared with those of patients who did not. Categorical variables were compared using the Pearson Chi-square test or Fischer exact test, and continuous variables were compared using an independent 2-sample Student *t* test or Wilcoxon rank sum test, as appropriate. Logistic regression was used to determine significant predictors of treatment response, after adjusting for other potential confounders. All variables with a *P* value less than .2 were included in a multivariable logistic regression model.

The association between HCV therapy and liver disease progression was estimated using Cox regression analysis. The probability of developing cirrhosis or portal hypertension among those who did and did not undergo HCV therapy was estimated using Kaplan-Meier curves; the statistical significance of the difference between the 2 groups was determined using the log-rank test. Unadjusted univariate analyses were conducted, and all variables with a *P* value less than .2 were included in a multivariable Cox regression model.

All statistical tests were 2-sided and conducted using STATA IC software, version 12.0 (StataCorp LP, College Station, TX). A *P* value less than .05 was considered statistically significant.

Results

Study Population

During the study period, 1291 patients with cancer had positive anti-HCV test results. Of 744 patients tested for HCV-RNA, 642 (86%) had chronic HCV infections. Most of the 642 patients were men (68%), non-Hispanic white (65%), and had genotype 1 (G-1) infections (66%; Table 1). Solid tumors were the predominant underlying cancer (n=462; 72%); 26% of patients had HCC. Of 173 patients (27%) with hematologic cancer, 61% had lymphoma. Complete remission of cancer was achieved in 223 patients (35%). A history of drug abuse was the most common risk factor for HCV (60%) and was more common in men than women (65% vs 50%; *P*=.005; Table 1). Only 35 patients (5%) were tested for interleukin-28B polymorphism, with a predominance of the CT genotype noted (n=17; 49%).

HCV Treatment

Of 642 patients with HCV infections, 348 (54%) underwent HCV therapy before (n=250) or after

Table 1 General Characteristics of Patients With Proven HCV Infection (N=642)*

Characteristic	Result
Male sex, n (%)	435 (68)
Mean age, y ± SD	58.3 ± 9.4
Race or ethnicity, n (%)	
Non-Hispanic white	414 (65)
Black	110 (17)
Hispanic	66 (10)
Asian	30 (5)
Middle Eastern	15 (2)
Native American	2 (1)
Baseline liver biopsy, METAVIR stage, n/total (%)[a]	
Unknown	45/206 (22)
0 (no fibrosis)	14/206 (7)
1 (periportal fibrotic expansion)	21/206 (10)
2 (periportal septae)	40/206 (19)
3 (porto-central septae)	46/206 (22)
4 (cirrhosis)	40/206 (19)
Baseline cirrhosis, n (%)[a]	73 (17)
Baseline portal hypertension, n (%)[a]	31 (8)
Cancer type, n (%)	
Hematologic malignancies	173 (27)
Solid tumors	462 (72)
Mixed tumors[b]	7 (1)
Hematopoietic cell transplant, n/total (%)	40 (23)
Mean baseline body mass index (kg/m^2) ± SD	27.4 ± 6.1
Basal HCV viral load >600,000 IU/mL	298 (69)
Mean baseline serum cholesterol (mg/dL) ± SD	167.1 ± 40.5
Mean baseline serum triglycerides (mg/dL) ± SD	150.5 ± 98.9
Coinfection, n (%)[a]	
Hepatitis B	
Exposure[c]	197 (39)
Infection[d]	7 (1)
HIV	10 (2)

Abbreviation: HCV, hepatitis C virus.
[a]For those with data available.
[b]Solid and hematologic malignancies.
[c]Hepatitis B core antigen positivity.
[d]Hepatitis B surface antigen positivity.
**Expanded version of Table 1 is available online, with this article, at JNCCN.org.*

Table 2 Details of HCV Treatment in Cancer Survivors (N=98)

Characteristic	Result
HCV treatment regimens, n (%)	98 (15)
Monotherapy	21 (21)
IFN	21 (21)
Ribavirin	0 (0)
Combination therapy	77 (79)
IFN + ribavirin[a]	76 (99)
IFN + ribavirin + nitazoxanide	1 (1)
Median treatment duration, wk (range)	24 (2–72)
Toxicity from HCV treatment,[b] n/total (%)	53/98 (54)
Constitutional	39/53 (74)
Hematologic	39/53 (74)
Psychiatric	21/53 (40)
Gastrointestinal	19/53 (36)
Dermatologic	11/53 (21)
Dose reduction of HCV therapy, n/total (%)	17/32 (53)
Growth factor used, n/total (%)[c]	21/39 (54)
Erythropoiesis-stimulating agent	18/21 (86)
Granulocyte colony-stimulating factor	7/21 (34)
Thrombopoietic agent	4/21 (19)
Treatment interrupted,[d] n/total (%)	40/61 (66)
Reasons for treatment interruption, n/total (%)	
Hematologic toxicity	17/40 (43)
Constitutional symptoms	2/40 (5)
Depression	4/40 (10)
Chemotherapy initiation	3/40 (8)
Renal insufficiency	2/40 (5)
Other[e]	4/40 (10)
Unknown side effects of HCV therapy	8/40 (20)
Treatment response known, n/total (%)	78 (81)
Sustained virologic response, n/total (%)	27 (35)

Abbreviations: HCV, hepatitis C virus; IFN, interferon; pegIFN, pegylated interferon.
[a]Includes non-pegIFN + ribavirin (n=19 [19%]), pegIFN alfa 2a + ribavirin (n=49 [50%]), and pegIFN alfa 2b + ribavirin (n=8 [9%]).
[b]More than one type of toxicity occurred in 41 of 53 patients (77%).
[c]More than one type of growth factor was administered in 9 of 21 patients (43%).
[d]For those with data available.
[e]Other reasons for treatment interruption include pericardial effusion, hypothyroidism, tumor progression, and elective surgery (1 each).

(n=98) their cancer diagnosis. The details of HCV therapy after cancer diagnosis are depicted in Table 2). Of the cancer survivors who underwent HCV therapy, most underwent combination therapy with pegIFN alfa 2a and ribavirin; none received DAAs. HCV therapy was frequently associated with adverse events (54%), mainly hematologic (74%) (Table 2). Most patients (77%) had more than one adverse event. HCV therapy was interrupted in 66% patients, mostly because of hematologic toxicity (43%). Of the 78 patients with known treatment responses, SVR occurred in 27 (35%; Table 2). The SVR rate was 4% (1 of 27 patients) for G-1; 59% (10 of 17) for genotype 2; and 57% (4 of 7) for genotype 3 infections (Table 3). Patients did not experience SVR due to either treatment interruption because of side effects (24%) or treatment nonresponse (20%).

Most treated patients were cancer survivors experiencing complete remission. No cancer survivors experienced a recurrence of the underlying cancer during HCV therapy. No patient experienced cancer progression within 1 year of HCV therapy and only 1 experienced cancer relapse within 2 years after therapy. Selected chemotherapy agents, mainly hormonal, were concomitantly used with HCV treatment (Table 3).

SVR Predictors

Among patients for whom treatment outcome data were available (Table 3), most of those who did not experience a response to HCV therapy were black (29% vs 4%; P=.007) and had more G-1 infections (72% vs 6%; P<.0001), higher baseline aspartate aminotransferase levels (mean, 77.6 vs 46.7 IU/L; P=.006), higher baseline alanine aminotransferase levels (mean, 71.1 vs 43.3 IU/L; P=.009), lower WBC counts (total WBC count <4000 cells/mcL; 25% vs 4%; P=.05), and shorter treatment durations (mean, 22.4 vs 27.8 weeks; P=.04) than those who experienced an SVR. A trend was seen toward treatment failure among men (65% vs 44%; P=.09) and patients with neutropenia (absolute neutrophil count <1500 cells/mcL; 16% vs 0%; P=.09). Multivariable logistic regression analysis revealed that those without G-1 infections (odds ratio, 7.2; 95% CI, 2.2–55.6; P<.001) were more likely to experience an SVR.

Underlying Liver Disease Progression

Kaplan-Meier curves were plotted to determine the probability of cirrhosis and portal hypertension among those who were and were not treated (Figures 1 and 2). Patients who were treated for HCV infection were analyzed, irrespective of the time of cancer diagnosis (Figure 1; Table 4). A separate analysis was also conducted by including those who were treated after cancer diagnosis (Figure 2; Table 4).

Overall, unadjusted Cox regression analyses revealed that among those who did not have cirrhosis or portal hypertension at baseline, the hazard of progression to cirrhosis (hazard ratio [HR], 0.31; 95% CI, 0.18–0.52; P<.001) and portal hypertension (HR, 0.26; 95% CI, 0.13–0.5; P<.001) were lower in the treated group, irrespective of the treatment outcome

Table 3 Treatment Outcomes of Patients With Cancer Who Underwent Treatment for HCV Infection (N=78)*

Characteristic	SVR (n=27)	Non-SVR (n=51)	*P* Value
Age, y (mean ± SD)	58.6 ± 1.9	59.4 ± 1.0	.37
Male sex, n/total (%)	12/27 (44)	33/51 (65)	.09
Race or ethnicity, n/total (%)			.02
Non-Hispanic white	19/27 (73)	28/51 (55)	
Black	1/27 (4)	15/51 (29)	
Hispanic	2/27 (8)	4/51 (8)	
Middle Eastern	0/27 (0)	2/51 (4)	
Asian	4/27 (15)	2/51 (4)	
Cancer type, n/total (%)			.24
Hematologic malignancies	9/27 (33)	22/51 (43)	
Solid tumors	18/27 (67)	29/51 (57)	
Hematopoietic stem cell transplant, n/total (%)	2/9 (22)	7/22 (32)	.92
Radiotherapy, n/total (%)	13/27 (48)	14/51 (27)	.06
Chemotherapy, n/total (%)[a]	17/27 (63)	40/51 (78)	.23
HCV genotype, n/total (%)[b]			<.001
1	1/17 (6)	26/36 (72)	
2	10/17 (59)	7/36 (20)	
3	4/17 (23)	3/36 (8)	
6	2/17 (12)	0/36 (0)	
Baseline cirrhosis, n/total (%)[b]	2/23 (9)	9/42 (21)	.30
Basal HCV RNA >600,000 IU/mL[b]	11/17 (65)	36/48 (75)	.42
Mean baseline body mass index (kg/m^2)[b] ± SD	26.5 ± 1.1	27.9 ± 1.0	.47
Concomitant chemotherapy, n/total (%)	3/27 (11)	4/51 (8)	1.0
Baseline laboratory values ± SD[b]			
Aspartate aminotransferase (IU/L)	46.7 ± 6.1	77.6 ± 9.6	.006
Alanine aminotransferase (IU/L)	43.3 ± 7.2	71.1 ± 9.1	.009
WBC count (cells/mcL)	11,300 ± 2700	6700 ± 600	.05
Absolute neutrophil count (cells/mcL)	5761 ± 953	3504 ± 306	.007
Coinfection, n (%)[b]			
Hepatitis B exposure/infection[c]	10 (43)	20 (45)	1.0
HIV infection[d]	3 (4)	7 (5)	1.0
HCV treatment			
Monotherapy with IFN, n (%)	7 (26)	5 (10)	.06
Combination therapy, n (%)[e]	20 (74)	46 (90)	
Mean treatment duration (wk) ± SD[b]	27.8 ± 2.2	22.4 ± 2.8	.04
Genotype 1[f]	–	24.3 ± 18.7	
Genotype 2 or 3	24.9 ± 7.4	9.6 ± 8.7	
Treatment interruption, n/total (%)[b]	3/19 (16)	35/39 (90)	<.0001
Toxicity from HCV treatment, n (%)[b]	19 (70)	31 (61)	.40

Abbreviations: HCV, hepatitis C virus; IFN, interferon; pegIFN, pegylated interferon; SVR, sustained virologic response.

[a]A patient may have received more than one type of chemotherapeutic agent

[b]For those with data available.

[c]Hepatitis B core antigen positivity.

[d]Hepatitis B surface antigen positivity.

[e]In patients with SVR, includes standard IFN + ribavirin (n=3 [11%]), pegIFN alfa 2a + ribavirin (n=15 [56%]), and pegIFN alfa 2b + ribavirin (n=2 [7%]). In patients without SVR, includes standard IFN + ribavirin (n=13 [25%]), pegIFN alfa 2a + ribavirin (n=27 [53%]), pegIFN alfa 2b + ribavirin (n=5 [10%]), and pegIFN alfa 2a + ribavirin + nitazoxanide (n=1 [2%])

[f]The treatment duration was unavailable for the only cancer survivor with a genotype 1 infection who experienced an SVR.

Expanded version of Table 3 is available online, with this article, at JNCCN.org.

(SVR or no SVR; Table 4). These lower hazards persisted in the multivariable Cox regression model (HR, 0.38; 95% CI, 0.16–0.93; *P*=.03 vs HR, 0.19; 95% CI, 0.05–0.66; *P*=.009, respectively; Table 4).

When only those who were treated for HCV infection after cancer diagnosis were included, the hazards of progression to cirrhosis (HR, 0.45; 95% CI, 0.22–0.91; *P*<.028) and portal hypertension (HR, 0.26; 95% CI, 0.09–0.75; *P*<.013) were lower in the treated group than in the untreated group, irrespective of the treatment outcome (SVR or no SVR; Table 4). These lower hazards persisted in the multivariable Cox regression model

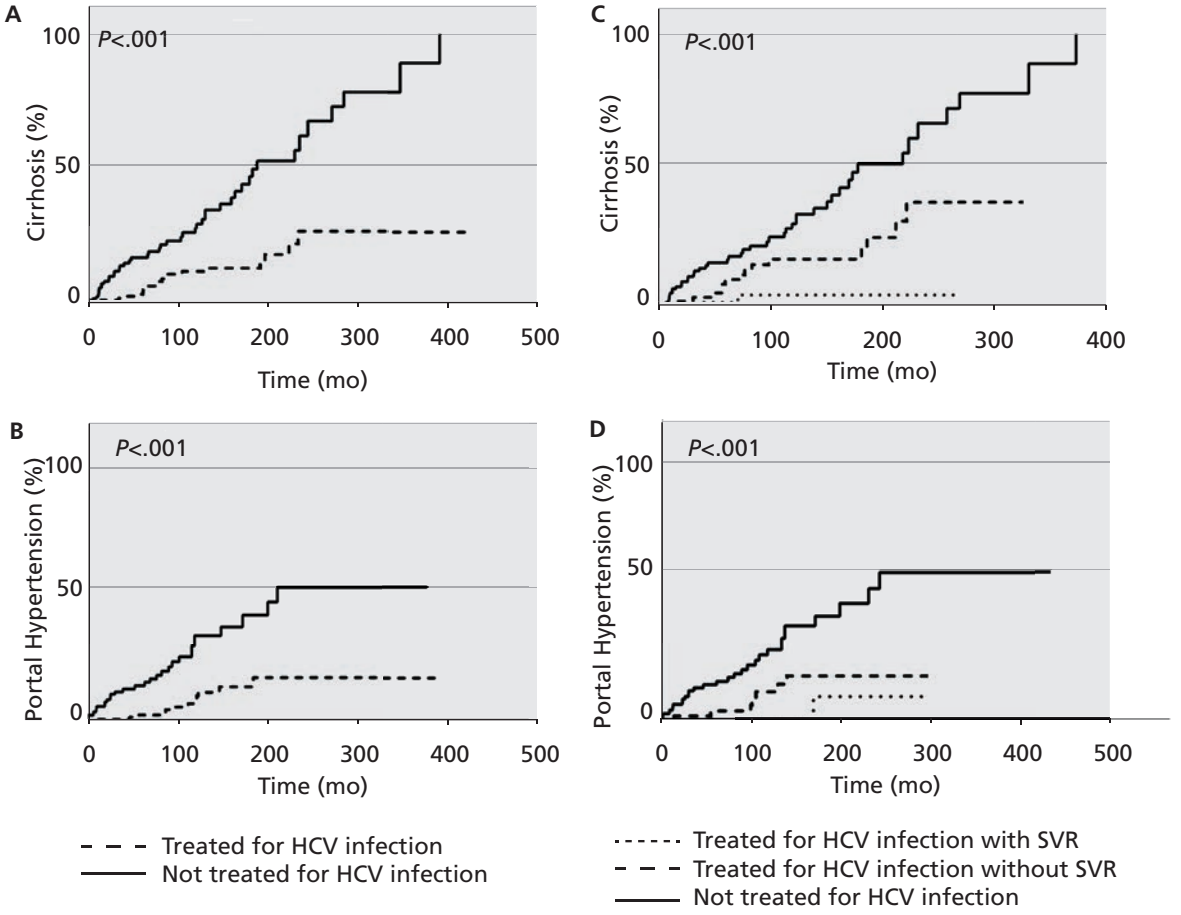

Figure 1 Kaplan-Meier curves for progression to cirrhosis and portal hypertension in hepatitis C virus (HCV)–infected patients with cancer, according to use of HCV therapy. The probability of cirrhosis and portal hypertension increased over time but was significantly higher (*P*<.001) in patients who did not undergo HCV therapy than in those who did (A and B). Likewise, the probability of underlying liver disease progression differed significantly (*P*<.001) based on treatment outcome, with those who did not experience a sustained virologic response (SVR) having a higher probability than those who did (C and D).

for progression to portal hypertension (HR, 0.23; 95% CI, 0.06–0.82; *P*=.02) but not cirrhosis (HR, 0.66; 95% CI, 0.28–1.52; *P*=.33; Table 4). The final parsimonious regression models are detailed in Supplemental eTables 1 and 2 (available with this article at JNCCN.org). HCC developed as a secondary cancer in 32 of the 476 (7%) patients with non-HCC cancers.

Discussion

To our knowledge, this is the largest analysis of the natural history and treatment outcomes of HCV infections in patients with cancer. Infected patients safely underwent HCV therapy after remission. Compared with the general population, SVR was much lower in those with G-1 infections. HCV therapy reduced the risk of liver disease progression in patients with cancer. Developing HCC as a second primary malignancy is not uncommon among those with baseline non-HCC cancer.

Based on epidemiologic investigations, biological studies, and therapeutic observations, HCV infections seem to be associated with HCC and lymphoma.[23–26] However, we found that HCV is not uncommon in patients with other cancers. In a recently reported large community-based cohort study, patients with chronic HCV infections had higher incidences of esophageal, prostate, and thyroid cancers.[3] The present findings indicate that HCV screening should not be limited to specific groups but should be performed in all patients with cancer.

Overall, a lack of treatment was associated with a higher hazard of progression to cirrhosis or portal hypertension in chronically infected patients, and

Table 4 Progression of Liver Disease by HCV Treatment Status

	Treated[a]		Not Treated		Unadjusted		Adjusted[b]	
Outcome	No. of Events	Observation Period (Person-mo)	No. of Events	Observation Period (Person-mo)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
A. In All Treated Patients (n=348)								
Progression to cirrhosis[c]	20	17,153	47	12,209	0.31 (0.18–0.52)	<.001	0.38 (0.16–0.93)	.03
Progression to portal hypertension[d]	12	17,579	32	12,503	0.26 (0.13–0.50)	<.001	0.19 (0.05–0.66)	.009
B. In Patients Treated for HCV Infection After Cancer Diagnosis[e] (n=98)								
Progression to cirrhosis[c]	9	5723	47	12,209	0.45 (0.22–0.91)	.028	0.66 (0.28–1.52)	.33
Progression to portal hypertension[d]	4	6104	30	12,375	0.26 (0.09–0.75)	.013	0.23 (0.06–0.82)	.02

Abbreviations: HCV, hepatitis C virus; HR, hazard ratio; SVR, sustained virologic response.
[a]Including those who did or did not experience an SVR.
[b]Multivariable Cox proportional hazards regression models adjusted for potential confounders, including age, gender, race, genotype, cancer type, cancer status, baseline laboratory values, coinfections, and baseline METAVIR stage. The proportional hazards assumption was tested with Schoenfeld residuals and through generating an interaction term between the covariate and the log-transformed follow-up time.
[c]Progression to cirrhosis was assessed in patients who did not have cirrhosis at the time of HCV diagnosis (for section A, n=352; for section B, n=268).
[d]Progression to portal hypertension was assessed in patients who did not have portal hypertension at the time of HCV diagnosis (for section A, n=371; for section B, n=296).
[e]Final parsimonious Cox proportional hazards regression models adjusted for potential confounders are described in Supplemental eTables 1 and 2 (available with this article at JNCCN.org).

HCV therapy tends to prevent this progression, even in those who were treated after cancer diagnosis. This finding is important because liver dysfunction is often associated with abnormal clearance of anticancer agents, and the metabolism of many classes of chemotherapy agents is altered in cirrhosis.[27,28] A previous study in patients without cancer showed a 44% improvement in liver histology (inflammation and fibrosis) among nonresponders to pegIFN plus ribavirin,[29] but the benefit on clinical outcomes in these patients is less clear.

Our findings also suggest that HCV-infected cancer survivors should not be excluded from participating in clinical trials of antiviral therapies while under surveillance for cancer recurrence. This is particularly true for patients with G-1 infections because their SVR rate was only 4% compared with 30% to 50% in the general population[9] and 14% to 38% in HIV-coinfected patients treated with pegIFN plus ribavirin.[30] The SVR rate in the present study was also remarkably lower than the 82% reported in 11 Taiwanese patients with G-1 infections and non-HCC cancer,[11] although the different sample sizes in these studies may account for the differences in treatment response. Why G-1–infected patients had such a poor SVR rate is unclear, but certainly these patients may benefit the most from new antiviral agents.

In the present study, treatment data were collected until 2011, the year when DAAs such as the first-generation protease inhibitors (PIs) telaprevir and boceprevir were approved by the FDA.[8] In our experience, a triple combination—one of these 2 PIs combined with pegIFN and ribavirin—resulted in substantially higher SVR rates but also had a higher incidence of side effects than dual therapy, as reported in patients without cancer.[31] PegIFN alfa 2 plus ribavirin are still used in cancer survivors with G-1 infection, especially if combined with recently approved DAAs, such as sofosbuvir or simeprevir.[32] In this population of patients, the use of IFN may be encouraged by some oncologists because of its anticancer activity.[33,34]

We believe that HCV therapy should be offered to patients with cancer in whom this treatment is not contraindicated. Viral eradication may normalize liver function, allowing access to multiple cancer chemotherapies, including agents with hepatic metabolism.[35] It may also prevent HCV reactivation, which can occur after chemotherapy and can lead to the discontinuation or dose reduction of potentially

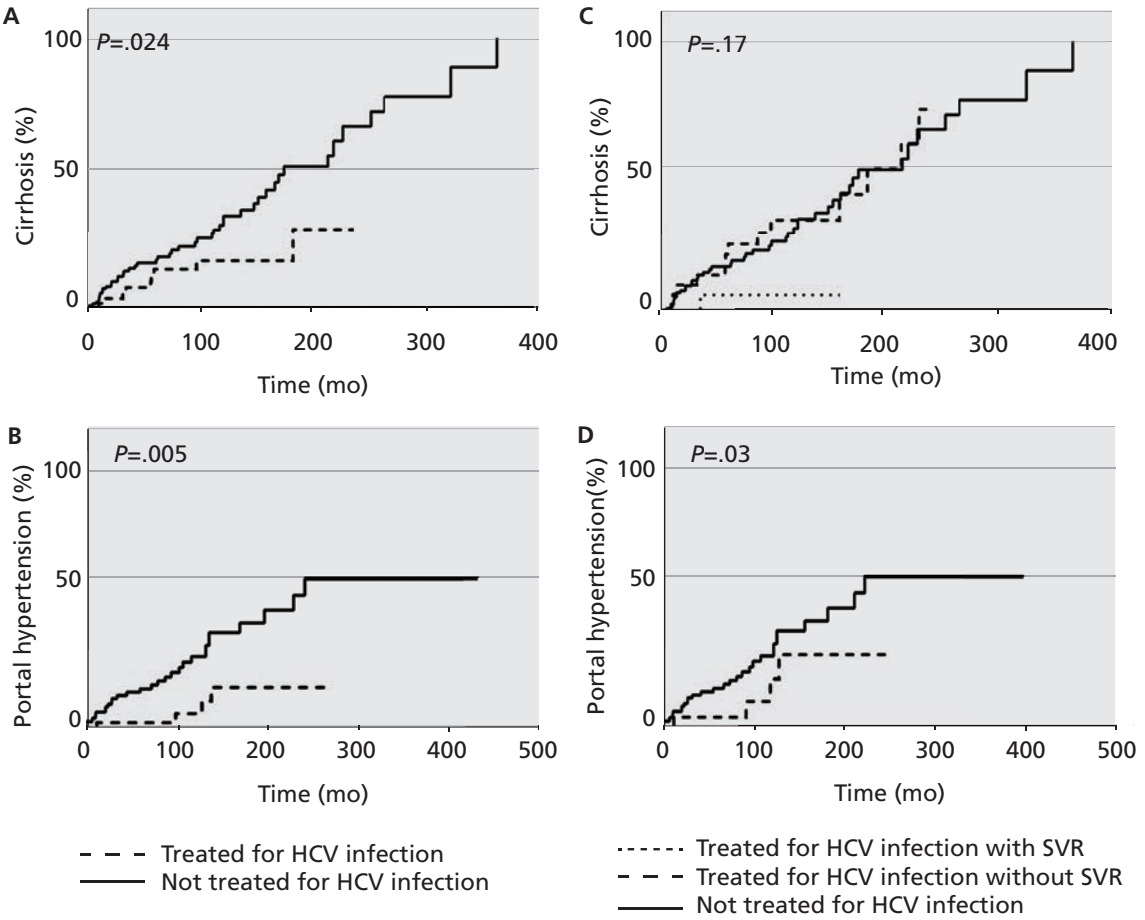

Figure 2 Kaplan-Meier curves for progression to cirrhosis and portal hypertension in hepatitis C virus (HCV)–infected patients with cancer, according to use of HCV therapy after cancer diagnosis. The probability of cirrhosis increased over time and was significantly higher (*P*=.024) in patients who did not undergo HCV therapy than in those who did (A). However, stratifying based on treatment outcome (sustained virologic response [SVR] vs no SVR) eliminated this statistical significance (*P*=.17; C). The probability of progression to portal hypertension was significantly higher in those who were not treated for HCV infection (*P*=.005; B) even after stratification on SVR status (*P*=.03; D).

life-saving chemotherapy[36]; it may also delay or prevent progression to cirrhosis or hepatic decompensation in patients with cancer, as reported in other patients (eg, normal hosts, solid organ transplant or HCT recipients).[9,12–14] Furthermore, HCV therapy may reduce the risk of second primary cancers, such as HCC, as described in other infected patients,[37] and improve the recurrence-free and overall survival rates of patients with selected cancers, such as those with HCV-related HCC.[38,39]

The overall safety and tolerability of HCV treatment in these patients were similar to those reported for other difficult-to-treat patients (eg, those with HIV coinfection).[30] Concerns exist about IFN therapy in patients with cancer and HCT recipients, including drug-induced toxicity, cancer relapse, graft compromise, and graft-versus-host disease exacerbation.[40,41] However, IFN-based HCV therapy has been safely used in HCT recipients, including those with underlying hematologic malignancies.[12–14] In the present study, only one patient experienced cancer relapse within 2 years of HCV therapy.

This study is limited by its retrospective nature, the heterogeneity of the cancer groups analyzed, the lack of treatment protocols, and the small number of patients treated with antivirals after their cancer diagnosis. A referral bias was also possible, wherein only patients likely to survive their cancer were referred for HCV treatment. Because most of treatment data were collected from available medical records, information on several variables was missing for patients who received treatment outside of MD Anderson. However, using a standardized approach since 2009, we have shown that HCV therapy is feasible in many patients

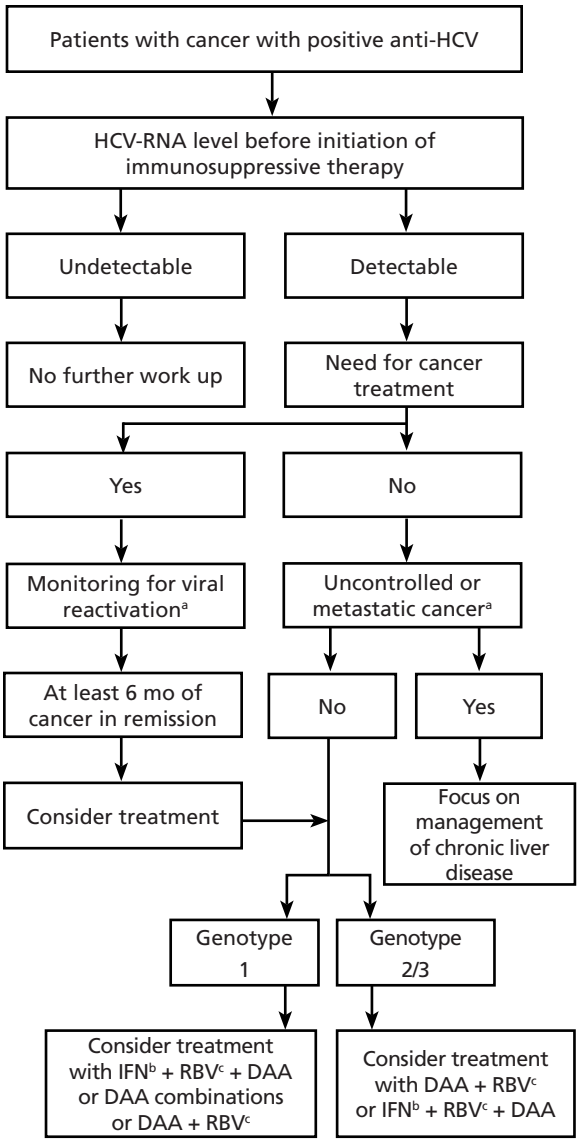

Figure 3 Management algorithm for patients with cancer and chronic HCV infection in 2014. The standard approach is to wait ≥6 months after cancer remission before initiating myelosuppressive HCV treatment with pegylated IFN (pegIFN) and RBV to allow patients' bone marrow to recover. HCV treatment can be administered to HCT recipients who meet the following criteria: complete remission of the original disease, ≥2 y since HCT, no evidence of protracted acute or chronic GVHD, no immunosuppressive therapy for 6 months, and normal blood counts and serum creatinine levels.[20] The use of pegIFN plus RBV may be encouraged by oncologists because of IFN's anti-cancer activity[33,34]; however, newer antivirals are urgently needed for patients with genotype 1 infections. The use of DAAs combinations is prudent and recommended in several scenarios (eg, need for IFN-free regimens).[32]
Abbreviations: DAAs, direct-acting antivirals; GVHD, graft-versus-host disease; HCV, hepatitis C virus; HCT, hematopoietic cell transplant; IFN, interferon; RBV, ribavirin.
[a]As recommended.[17]
[b]If not contraindicated.[9]
[c]As recommended for patients without cancer.[9,32]

with cancer.[22] The current management algorithm for HCV-infected patients with cancer seen at MD Anderson is depicted in Figure 3.

Conclusions

This is the largest series to analyze the natural history and outcomes of HCV in patients with cancer. Results showed that HCV therapy is feasible in patients with cancer, and should be administered as recommended. HCV therapy prevents liver disease progression in patients with cancer.

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