ARTICLE TITLE: The Oncologic Burden of Hepatitis C Virus Infection: A Clinical Perspective

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EDUCATIONAL OBJECTIVES:
After reading the article “The Oncologic Burden of Hepatitis C Virus Infection: A Clinical Perspective,” the learner should be able to:
1. Summarize hepatitis C virus (HCV) epidemiology and risk factors.
2. Highlight the carcinogenic potential of HCV; complications of HCV infection; and treatment of HCV infection, including the use of new direct-acting antivirals.
3. Relate current HCV screening recommendations for patients with and without cancer.

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The Oncologic Burden of Hepatitis C Virus Infection: A Clinical Perspective

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Additional supporting information may be found in the online version of this article.

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ABSTRACT: Chronic hepatitis C virus (HCV) infection affects millions of people worldwide and is associated with cancer. Direct-acting antivirals (DAAs) have changed HCV treatment paradigms, but little is known about the management of HCV infection in patients with cancer. The substantial burden of HCV infection and the inconclusive evidence regarding its detection and management in patients with cancer prompted the authors to review the literature and formulate recommendations. Patients for whom HCV screening is recommended included all patients with hematologic malignancies, hematopoietic cell transplantation candidates, and patients with liver cancer. There is a lack of consensus-based recommendations for the identification of HCV-infected patients with other types of cancer, but physicians may at least consider screening patients who belong to groups at heightened risk of HCV infection, including those born during 1945 through 1965 and those at high risk for infection. Patients with evidence of HCV infection should be assessed by an expert to evaluate liver disease severity, comorbidities associated with HCV infection, and treatment opportunities. DAA therapy should be tailored on the basis of patient prognosis, type of cancer, cancer treatment plan, and hepatic and virologic parameters. HCV-infected patients with cancer who have cirrhosis (or even advanced fibrosis) and those at risk for liver disease progression, especially patients with HCV-associated comorbidities, should have ongoing follow-up, regardless of whether there is a sustained virologic response, to ensure timely detection and treatment of hepatocellular carcinoma. HCV infection and its treatment should not be considered contraindications to cancer treatment and should not delay the initiation of an urgent cancer therapy. CA Cancer J Clin 2017;67:411-431. © 2017 American Cancer Society.

Keywords: cancer, direct-acting antiviral, hepatitis C virus (HCV), hepatocellular carcinoma, non-Hodgkin lymphoma, primary liver cancer

Practical Implications for Continuing Education

> Hepatitis C virus (HCV) is carcinogenic and is associated with the development of different types of malignancies.

> Chronic HCV infection causes significant morbidity and mortality in patients with cancer, and can interfere with cancer treatment. However, HCV infection should not be considered a contraindication to chemotherapy, and should not delay the initiation of an urgent cancer therapy.

> In most cases, direct-acting antiviral-based therapy in HCV-infected patients with cancer is associated with viral clearance, improved liver function, the prevention of HCV reactivation, and favorable oncologic outcomes for selected patients who have already developed HCV-associated malignancies (eg, B-cell non-Hodgkin lymphoma).

> Viral eradication with direct-acting antiviral-based therapy also may allow patients access to multiple clinical trials of cancer chemotherapies.

Introduction

Chronic hepatitis C virus (HCV) infection affects millions of people worldwide. The oncologic burden of HCV infection is substantial. First, HCV infection is
associated with the development of several different types of cancer.\textsuperscript{2,3} In 2012, a total of 170,000 new cancer cases, or approximately 7.8% of all new cancers, were attributable to HCV in GLOBOCAN 2012.\textsuperscript{4} Second, chronic HCV infection in patients with cancer causes significant additional morbidity and mortality and can interfere with cancer treatment.\textsuperscript{5–10}

The management of chronic HCV infection has historically been neglected in cancer centers, likely due to reservations about treating patients concomitantly with chemotherapy and older HCV therapy, such as interferon.\textsuperscript{6} Today, direct-acting antivirals (DAAs) have changed the treatment paradigm for chronic HCV infection and improved virologic outcomes, even in HCV-infected patients with cancer.\textsuperscript{11} Rates of sustained virologic response (SVR), regarded as indicating HCV cure, are now similar in HCV-infected patients with and without cancer.\textsuperscript{11} Differences in the presentation, natural history, and management of HCV infection in patients with and without cancer are presented in Table 1.\textsuperscript{5–7,12–15}

The burden of HCV in patients with cancer and the inconclusive evidence regarding the detection and management of HCV infection in such patients prompted us to review the literature and to summarize the available data on HCV epidemiology and risk factors; associations between HCV and cancer; the carcinogenic potential of HCV; HCV screening; complications of HCV infection; and the treatment of HCV infection, including the new DAAs.

We searched the PubMed and Web of Science databases for articles published from January 1, 1966, through March 24, 2017, using the terms “hepatitis C virus,” “HCV,” “prevalence,” “screening,” “cancer,” “chemotherapy,” and “reactivation.” We also searched the reference lists of articles identified by this search strategy and selected those references we judged relevant for each specific issue discussed. Abstracts were included only when they related directly to subsequently published work. We used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system to grade the quality of evidence.\textsuperscript{16}

### Global Epidemiology of HCV Infection

The main mode of HCV transmission was the use of contaminated medical materials. In high-income countries, widespread use of shared needles for medical treatments led to an epidemic of HCV infection in the 1940s. In the United States, contaminated blood products were also a mode of transmitting HCV infection before July 1992. Intravenous drug use has been and remains a leading contributor to the epidemic of HCV infection worldwide.\textsuperscript{17,18} In low-income to middle-income countries, iatrogenic factors are still key contributors to the epidemic of HCV infection.

Estimates of the prevalence of HCV antibodies worldwide range from 1.6%\textsuperscript{19} to 2.8%.\textsuperscript{20} The highest prevalence is reported in low-income countries, including Egypt (15%), Pakistan (4.7%), and Taiwan (4.4%),\textsuperscript{21} and is lower in North America (range, 1.1%-1.3%), Australia (1.7%), and Eastern and Western Europe (range, 0.5%-4.5%).\textsuperscript{19} The latest epidemiologic reports suggest that there are currently 80 million HCV–RNA–positive individuals around the globe.\textsuperscript{19,22}

In the United States, it is estimated that at least 3.5 million people (range, 2.5–4.7 million) live with HCV infection\textsuperscript{23} and that about one-half are unaware that they are infected.\textsuperscript{24}

### Table 1. Characteristics of Hepatitis C Virus Infection in Patients With and Without Cancer

| CHARACTERISTIC | HCV INFECTION IN PATIENTS WITH CANCER | HCV INFECTION IN PATIENTS WITHOUT CANCER |
|---------------|--------------------------------------|----------------------------------------|
| Findings on serologic assays for HCV antibodies | False-negative results possible (negative findings on screening for HCV antibodies with detectable HCV RNA in serum) | Reliable |
| Risk of developing fibrosis progression and early cirrhosis | High, particularly in HCT recipients | Low |
| Viral reactivation | Reported after certain types of cancer treatment | Uncommon in patients without immunosuppression |
| Standard-of-care anti-HCV therapy | Not defined | Well defined |
| Rate of sustained virologic response after treatment with DAAs | High | High |
| Risk of drug-drug interactions with DAAs | High | Low to moderate |
| Use of DAAs in patients with decompensated cirrhosis | Potentially contraindicated | Recommended but to be managed by providers with expertise in that condition, ideally in a liver transplant center |
| Provision of care | Frequently requires a transdisciplinary team | Frequently managed by single provider |

Abbreviations: DAAs, direct-acting antivirals; HCT, hematopoietic cell transplant; HCV, hepatitis C virus.
Individuals born from 1945 to 1965 have a 3% prevalence of HCV antibodies, which is 5 times the prevalence in adults born in other years. 

Natural History of HCV Infection

HCV infection evolves to chronic infection in more than two-thirds of cases, and 4% to 25% of patients with chronic HCV infection develop cirrhosis within 20 to 30 years after HCV infection is first diagnosed. Once cirrhosis develops in a patient with chronic HCV infection, the estimated risk of hepatocellular carcinoma (HCC) is from 1% to 4% annually, similar to the risk of end-stage liver disease. A small proportion of HCC cases, fewer than 10%, develop in patients who have HCV infection without cirrhosis. In the Global Burden of Disease Study 2013, in which liver-related deaths were classified as secondary to hepatitis B virus (HBV), HCV, or alcohol use, the annual number of HCV-attributable deaths worldwide increased from approximately 450,000 in 1990 to 520,000 in 2013.

Many factors affect the natural history of HCV infection. Liver disease progression in patients with chronic HCV infection is closely related to age at infection, sex, and HCV-associated comorbidities, including human immunodeficiency virus (HIV) and HBV co-infections, alcohol use disorders, and diabetes. For cohorts in which intravenous drug use was the main mode of HCV transmission, alcohol use disorders were reported in about 30% to 50% of individuals; among male military service veterans with HCV infection, the proportion with alcohol use disorders was even higher. In Sub-Saharan Africa, where alcohol abuse is rare, HCV transmission is associated with HBV infection. In Egypt and the Middle East, obesity and diabetes mellitus are endemic. Comorbidities associated with HCV infection probably underlie the unexpected observations of early HCC occurrence and recurrence among patients who are at risk for liver disease progression after HCV eradication with DAAs. These observations from uncontrolled studies contrast with previous models of liver disease progression supporting the widespread use of DAAs to reduce the burden of HCV infection. These discrepancies regarding the benefits of DAA therapy can most likely be explained by underestimation of the prevalence of HCV-associated comorbidities and their impact on liver disease progression; the historical practice of selecting healthier patients without comorbidities for interferon-based HCV treatments, a selection bias that does not apply to treatment with DAAs; and maximization of the benefits of HCV treatment with systematic implementation of care pathways and accompanying lifestyle modifications, which include curing HCV-associated comorbidities, in observational cohorts.

Some patients who have cancer with HCV infection will probably remain at risk for liver disease progression after an SVR, and the risk of progression is probably greatest in patients who have HCV-associated comorbidities, including alcohol use disorders. Alcohol use has not been included in most liver disease progression models, including those that support current cost-effectiveness strategies in industrialized countries; therefore, the benefits of treating HCV infection with DAAs may have been overestimated. In an individual patient, treating HCV-associated comorbidities could be as important as eradicating HCV in terms of improving outcomes, and there is enough evidence to recommend abstinence from alcohol together with treatment of HCV-associated comorbidities in patients with advanced liver disease, regardless of whether or not they attain an SVR.

Associations Between HCV Infection and Cancer

Among adults with cancer who were newly registered at The University of Texas MD Anderson Cancer Center (MD Anderson Cancer Center) from January 2004 through April 2011, the prevalence of HCV antibodies was 1.5% overall, and it was much higher in certain subtypes—eg, it was 10.6% in those who had selected solid tumors other than HCC. In some regions of Europe and Asia, HCV antibodies have been reported in up to 2.8% of patients with solid tumors and in 30% of those with hematologic malignancies.

Such data are limited, however, in that they come from single cancer centers and were derived using various study methodologies, cancer subpopulations, and diagnostic tests (antibody or nucleic acid testing). Original studies that reported associations between HCV infection and hepatic and extrahepatic malignancies are summarized in Supporting Information Table 1. The strength of the evidence supporting associations between HCV infection and cancer is presented in Table 2 and in previous meta-analyses.

HCV and Primary Liver Cancer

The strongest reported association between HCV infection and cancer is that between HCV and primary liver cancer, including HCC and intrahepatic cholangiocarcinoma. The association between HCV and HCC was first described in 1989 in reports of 2 European case-control studies. Both studies demonstrated the synergistic carcinogenic effects of HCV infection and HCV-associated comorbidities, including alcohol use and HBV infection.
Between 2005 and 2015, deaths from HCV-attributable HCC increased by 21.1%, and deaths from alcohol-attributable HCC increased by 26.1%, during which time deaths from HCC attributable to all other causes, including HBV, remained stable. From 2001 to 2012, 38.4% of patients in New York City with newly diagnosed HCC had HCV infection, 17.9% had HBV infection, and 2.2% had both.

The association between HCV and intrahepatic cholangiocarcinoma was first suggested in a case-control study from Korea published in 1996 and was confirmed in a case-control study from Italy published in 2001. Two meta-analyses and a cohort study demonstrated that the odds ratio (OR) for intrahepatic cholangiocarcinoma in patients with versus without HCV infection ranged from 3.42 (95% confidence interval [95% CI], 1.96–5.99) to 4.84 (95% CI, 2.41–9.71). In contrast, no significant association has been reported between HCV infection and extrahepatic cholangiocarcinoma.

### HCV and Hematologic Malignancies

The second most robust association between HCV infection and cancer is that between HCV and B-cell non-Hodgkin lymphoma (NHL). The association was first reported in 1994 in a large multicenter case-control study from Italy. In another large European multicenter case-control study, HCV infection was associated with increased risks of diffuse large B-cell NHL (OR, 2.24; 95% CI, 1.68–2.99), marginal zone lymphoma (OR, 2.47; 95% CI, 1.44–4.23), and lympho-plasmacytic lymphoma (OR, 2.57; 95% CI, 1.14–5.79). In a large population-based study in the United States, HCV infection was associated with increased risks of Burkitt

### Table 2: Summary of Evidence on the Association Between Hepatitis C Virus and Cancer

| TYPE OF CANCER          | TYPE(S) OF STUDIES*                          | NO. OF STUDIES ANALYZED | NO. OF PATIENTS WITH HCV INFECTION/TOTAL NO. OF PATIENTSA | QUALITY OF EVIDENCEb |
|-------------------------|---------------------------------------------|-------------------------|----------------------------------------------------------|---------------------|
| Primary liver cancer    |                                             |                         |                                                          |                     |
| Hepatocellular carcinoma| Retrospective and prospective cohort, case-control, and case series | 10                      | 19,185/128,049                                          | High               |
| Intrahepatic cholangiocarcinoma| Retrospective and prospective cohort, case-control, and case series | 11                      | 5415/426,561                                            | High               |
| Hematologic malignancy  |                                             |                         |                                                          |                     |
| NHL                     | Retrospective and prospective cohort, case-control, and case series | 30                      | 115,999/1,379,245                                       | High               |
| Myelodysplastic syndrome| Case-control                               | 1                       | 17,320/217,320                                          | Very low           |
| Waldenstrom macroglobulinemia| Retrospective cohort                         | 1                       | 165/719,687                                              | Very low           |
| Digestive cancers       |                                             |                         |                                                          |                     |
| Pancreas                | Retrospective and prospective cohort and case-control | 6                       | 52,045/1,065,206                                        | Low                |
| Esophagus               | Retrospective cohort                         | 3                       | 36/155,023                                               | Very low           |
| Rectum                  | Retrospective cohort                         | 1                       | 12/12,126                                                | Very low           |
| Anus                    | Case-control                                 | 1                       | 4015/204,015                                             | Very low           |
| Head and neck           | Retrospective and prospective cohort and case-control | 5                       | 637/185,522                                             | Low                |
| Thyroid                 | Retrospective and prospective cohort and case-control | 7                       | 11,613/1,01,516                                         | Very low           |
| Kidney                  | Retrospective and prospective cohort and case-control | 7                       | 36,633/398,051                                          | Very low           |
| Prostate                | Retrospective cohort and case-control        | 3                       | 283,428/562,556                                         | Very low           |
| Lung                    | Retrospective cohort                         | 1                       | 67/12,126                                                | Very low           |
| Nonepithelial skin      | Retrospective cohort and case-control        | 1                       | 6650/206,650                                             | Very low           |

Abbreviations: HCV, hepatitis C virus; NHL, non-Hodgkin lymphoma. *All studies are detailed in Supporting Information Table 1. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al16). With this approach, the quality of evidence is rated as high, moderate, low, or very low, depending on the presence of 5 factors: type of evidence; quality of evidence; consistency of evidence; directness of evidence; and effect size based on the reported odds ratio, relative risk, or hazard ratio for comparison and the amplitude of the ratio. Meta-analyses were not taken into account when the quality of evidence was rated.
lymphoma (OR, 5.21; 95% CI, 1.62-16.8) and follicular lymphoma (OR, 1.88; 95% CI, 1.17-3.02). Only weak associations between HCV and other hematologic malignancies have been reported (Table 2 and Supporting Information Table 1).

HCV and Extrahepatic Solid Tumors

Literature on the correlation between HCV infection and extrahepatic solid tumors is inconclusive. In a large cohort study from the United States, HCV infection was associated with carcinomas of the pancreas (standardized rate ratio [SRR], 2.5; 95% CI, 1.7-3.2), rectum (SRR, 2.1; 95% CI, 1.3-2.8), kidney (SRR, 1.7; 95% CI, 1.1-2.2), and lung (SRR, 1.6; 95% CI, 1.3-1.9); however, that study was unadjusted for major confounders, including alcohol and tobacco use. In fact, alcohol-related and tobacco-related cancers were overrepresented in the cohort, suggesting that HCV could be a lifestyle marker. A prospective, community-based cohort study from Taiwan showed that chronic HCV infection was associated with increased risks of esophageal, prostate, and thyroid cancers. In another case-control study, HCV infection was associated with nonoropharyngeal (except nasopharyngeal) and human papillomavirus-positive oropharyngeal head and neck cancers (OR, 2.97; 95% CI, 1.31-6.76).

Mechanisms by Which HCV Contributes to the Development of Cancer

HCV Infection and Primary Liver Cancer

Currently, evidence of a direct oncogenic effect of HCV on liver cells is scant, although HCV core protein has transforming effects and impairs oxidative stress metabolism in animal models. In a cellular model of HCV, NS3/4A (an HCV viral protease) and NS5B (an RNA-dependent RNA polymerase) impeded DNA repair via interaction with the ataxia telangiectasia mutated (ATM)-driven response pathway. Selected genotypes of HCV also might be associated with the risk of developing HCC: greater carcinogenic potential has been reported for some variants, mostly genotypes 1 (1b) and 3, although definitive studies are lacking.

The main mechanism by which HCV contributes to the development of HCC seems to be related to chronic inflammation, which mediates cycles of death and regeneration and eventually can lead to cirrhosis and to HCC. Most cases of HCC arise from hepatocytes or liver stem cells in cirrhotic nodules that have accumulated enough mutations to re-enter the cell cycle, reactivate telomerase, and progress through cancer checkpoints. This pattern accounts for the clinical and molecular heterogeneity of HCC and probably explains the limited benefit of targeted therapies. Reactive oxygen species are also thought to play a central role in the development of HCV-associated HCC. A small proportion of HCCs develop in patients who have HCV infection without cirrhosis; in almost all such cases, the patients also previously had or currently have HBV infection.

Genetic studies suggest that mutations accumulate in the premalignant stage of HCC and that mutation of the telomerase reverse transcriptase (TERT) promoter is an early genetic event. The other genes most commonly mutated in HCC are tumor protein 53 (TP53) and β-catenin (CTNBN1). Recurrent mutations in the epigenetic modifier genes AT-rich interaction domains 1A (ARID1A) and 2 (ARID2) are also often present. These and other genetic defects impact telomere maintenance and oxidative stress. Other pathways that are dysregulated in HCC include the phosphatidylinositol-3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR), rat sarcoma/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase pathway (RAS/RAF/ MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways.

Confounders hinder determination of the precise impact of HCV infection on the development of HCC. Common risk factors for the development of HCC include environmental exposures to hepatotoxins (eg, alcohol and aflatoxins), misdirected host-immune and DNA-damage responses, coinfections (eg, with HBV and HIV), advanced age, male sex, and metabolic factors (nonalcoholic fatty liver disease, obesity, metabolic syndrome, and type 2 diabetes). Diabetes and the metabolic syndrome with steatosis are important risk factors for HCC and are associated with alcohol use disorders and with the worldwide obesity epidemic. Furthermore, evidence is accumulating that even past heavy alcoholism in people who have since stopped drinking can contribute to liver disease progression, cirrhosis, and liver cancer in HCV-infected patients, including those who attain an SVR.

Just as evidence of a direct oncogenic effect of HCV on liver cells is scant, there is no clear evidence of a direct oncogenic effect of HCV on biliary cells, and intrahepatic cholangiocarcinoma seems to be associated more with chronic liver disease and cirrhosis, regardless of its origin, than specifically with HCV infection. Overall, the main risk factor for intrahepatic cholangiocarcinoma seems to be liver regeneration and hepatic progenitor-cell turnover with selection of transformed cells.

HCV Infection and Other Extrahepatic Solid Tumors

For other extrahepatic cancers, it is important to keep in mind that correlation does not imply causation. As mentioned above, most epidemiologic studies that demonstrate associations between HCV and extrahepatic cancers are...
unadjusted for potential confounders, including alcohol use disorders and tobacco smoking.

There could be a mechanistic link with HCV for oral and head and neck cancers, especially oropharyngeal cancers, because HCV is found in precancerous lesions.91 Potential synergism between HCV and human papillomavirus has also been suggested in the development of oral and head and neck cancers.47 To date, the potentiation of human papillomavirus by HCV has not been reported in other cancers.

HCV Infection and Hematologic Malignancies

Evidence for a mechanistic contribution of HCV to cancer is strongest for B-cell NHL. A subset of HCV-associated lymphomas produces immunoglobulins against E2 (an HCV envelope glycoprotein), suggesting that these malignancies originate from B cells activated by HCV recognition.92 The mechanism or mechanisms of HCV-related lymphomagenesis remain to be elucidated, but emerging data are now reported regarding the genetic basis for lymphotropism of HCV.93 Mechanisms that have been postulated to explain the HCV-induced transformation process include cryoglobulinemia, translocation t(14;18), chronic lymphocytic proliferation stimulated by viral antigens, HCV replication in B cells mediated by viral proteins, and virus-induced B-cell damage.94,95 Treatment of HCV is thought to reduce the risk of developing NHL and may aid in the treatment of some HCV-associated NHLs.95 The best evidence of a direct relationship between HCV and B-cell NHL is the demonstration of regression of B-cell NHL resulting from anti-HCV therapy with interferon, which has antiproliferative properties.96 Early reports of the use of interferon-free regimens also suggested benefit.97–99

Natural History of HCV Infection in Patients With Cancer

The natural course of HCV infection can be altered by cancer treatment. Patients with HCV infection are at risk for liver disease progression, including decompensated cirrhosis and HCC.8,100 Hepatitis flare occurs in 26% to 45% of HCV-infected patients with cancer and can lead to liver dysfunction, which necessitates discontinuation or dose reduction of potentially lifesaving chemotherapy.5,101

Hepatitis flare is defined as an increase in alanine aminotransferase (ALT) levels to at least 3 times the upper limit of normal in the absence of liver infiltration by tumor, the use of hepatotoxic drugs other than chemotherapeutics,102 or other active systemic infection (bacterial or fungal infection or infection with hepatitis A virus, HBV, hepatitis E virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella–zoster virus, adenovirus, or HIV).5

Both HCV reactivation and hepatitis flare have been described in association with various chemotherapy regimens.5,101 However, except for rituximab and high-dose steroids, the level of evidence is low. At the MD Anderson Cancer Center HCV clinic, HCV RNA is ordered as a confirmatory test for patients who have a positive anti-HCV–antibody test during screening. Among patients with proven infection (detectable HCV RNA), HCV specialists monitor for hepatitis flare, checking the ALT level before initiating chemotherapy (baseline) and every 2 to 8 weeks during chemotherapy. The HCV-RNA level is also checked before initiating chemotherapy (baseline), every 12 weeks during chemotherapy, and at the time of suspected hepatitis flare, looking for simultaneous viral reactivation.

The risk of liver failure or liver-related death associated with HCV reactivation or hepatitis flare is low, including the risk from chemotherapy regimens that incorporate rituximab.5,101 Therefore, because chemotherapy and hematopoietic cell transplantation (HCT) are potentially lifesaving, the presence of HCV infection should not be considered a contraindication to cancer treatment and should not delay the initiation of an urgent cancer treatment.

Patients With Hematologic Malignancies

The highest risks of HCV reactivation, hepatitis flare, and increased rate of liver disease progression have been reported among patients with hematologic malignancies. Among HCV-infected patients with hematologic malignancies, HCT recipients have faster progression to cirrhosis than patients who do not undergo HCT.12 Among HCT recipients, patients with HCV are at higher risk for fatal sinusoidal obstruction syndrome (previously known as veno-occlusive disease),103 hepatitis flare,103,104 liver decompensation,105 and fatal fibrosing cholestatic hepatitis C (rare) than patients without HCV.106 The use of mycophenolate mofetil has been linked to the development of fibrosing cholestatic hepatitis C in patients undergoing HCT.106,107

HCV reactivation is more common among patients with lymphoma and in those who receive treatment with rituximab than in patients who have other types of cancer. HCV reactivation is defined as an increase in the HCV-RNA level of at least 1 log₁₀ IU/mL over baseline after administration of chemotherapy,5 because chronically infected patients generally have stable HCV-RNA levels that vary within 0.5 log₁₀ IU/mL.108 HCV reactivation due to chemotherapy is less common than HBV reactivation.109 HCV reactivation is rarely fatal,110 and most patients have an indolent course.5,101 HCV reactivation mainly occurs during the weeks of chemotherapy treatment and frequently regresses upon treatment cessation.5,101
Patients With Solid Tumors
Evidence concerning the potential for HCV reactivation and hepatitis flare in HCV-infected patients who are receiving chemotherapy is weaker for those with solid tumors than for those with hematologic malignancies and is based on only limited published data.8,10

Natural History of Cancer in Patients With HCV Infection
A recent epidemiological study in the New York City population found that viral hepatitis was the primary risk factor for HCC (>50% of patients) and that the median survival for HCV-infected patients who developed HCC was 13.1 months from the time of HCC diagnosis. Of note, this median survival time was significantly shorter than that for HBV-infected patients who developed HCC (22.3 months).65 Similar results were reported from a nationwide study in France.112

To date, there have been no randomized clinical studies directly comparing the impact of cancer therapy in patients with HCV-related and HBV-related HCC. However, subanalyses from the pivotal trials of systemic therapy with sorafenib and local therapy with transarterial chemoembolization have been reported that address the question. The key results, which are summarized in Supporting Information Table 2, suggest that both treatments may be more effective in HCV-related than in HBV-related HCC. Given the heterogeneity of these studies with respect to patient populations and performance status, the small numbers of patients studied in some groups, and the fact that HBV-related HCC is more lethal than HCV-related HCC, the impact of cancer therapy in HCV-related versus HBV-related HCC merits further study. Because HCV-driven cirrhosis progression can make a patient with HCC ineligible for treatment, viral eradication before sorafenib treatment could improve oncologic outcomes, such as post-progression survival and overall survival, among patients with HCV-associated advanced HCC.113 HCV-infected patients are at risk for development of a second primary, HCV-associated cancer after cancer treatment, including HCC and B-cell NHL, if the infection is left untreated.8,10

HCV Screening in Patients With Cancer
The diagnosis of HCV infection in patients with cancer is a neglected topic.6 The objective of HCV screening in these patients is to ensure that those with HCV infection are identified, helping to prevent the spread of this infection while also increasing opportunities for preventive care and potentially reducing HCV-associated morbidity and mortality in infected individuals. These patients can receive proper care for the infection that could slow the progression of liver disease12,100,114 and give them maximum access to cancer drugs.11

In the United States, the Centers for Disease Control and Prevention recommends one-time HCV testing for persons born between 1945 and 1965 (so-called baby boomers), without prior ascertainment of risk.25 Worldwide, one-time HCV testing is recommended by professional societies for individuals with past behaviors, exposures, and conditions associated with an increased risk of HCV infection (eg, injection-drug use, long-term hemodialysis, prior recipients of transfusions or organ transplantation before July 1992, HIV infection, etc).15,115,116 Periodic testing is also recommended for persons with ongoing risk factors for exposure to HCV.

The importance of screening the 1945 to 1965 birth cohort is illustrated in the Annual Report to the Nation on the Status of Cancer (1975–2012), which indicates that HCV-associated and liver cancer-associated death rates were highest among persons born during 1945 through 1965.117 Data in the National Cancer Institute’s Surveillance, Epidemiology, and End Results program from 1975 through 2013 show that 50.6% of all new cancers in the United States are diagnosed among individuals ages 55 to 74 years.118 In 2017, the baby boomers, who have a high rate of HCV infection, will be in approximately that age range (ages 52-72 years) (Fig. 1, gray box), which means that the number of HCV-infected patients with cancer in the United States may peak around this time. Certainly, birth cohort–based HCV screening of patients with newly diagnosed cancer would identify a substantial proportion of HCV-infected patients but would leave many with undiagnosed HCV infection.

![FIGURE 1. Relationship Between Ages of Baby Boomers in 2017 and Ages at Which Cancer Is Most Commonly Diagnosed. This bar graph illustrates the percentage of new cancer cases by age at diagnosis (Surveillance, Epidemiology, and End Results 18 registries, 2009-2013; any site, all races, both sexes). In 2017, baby boomers (individuals born during 1945-1965), the targets of birth-cohort-based hepatitis C virus (HCV) screening, will be 52 to 72 years old. Birth-cohort-based HCV screening of patients with newly diagnosed cancer would identify a substantial proportion of HCV-infected patients but would leave many with undiagnosed HCV infection.](image-url)
for HCV at the MD Anderson Cancer Center from January 2004 to April 2011. Predictors of HCV screening included not only birth after 1965 and traditional HCV risk factors but also Asian race and receipt of rituximab therapy, indicating that decisions about screening for HCV were extrapolated from HBV screening recommendations.

Of interest, a more recent community-based study demonstrated that screening only patients in the 1945 to 1965 birth cohort would mean missing HCV infection in approximately 25% of HCV-infected patients. The risk of such selective screening in a cancer center was illustrated in a 2008 to 2011 retrospective cohort of adult patients with hematologic malignancies. Of the HCV-infected patients, only 75% had at least one HCV risk factor identified by the oncologists or were born during 1945 through 1965, which means that 25% of the seropositive patients with cancer would have been missed without universal screening. A prospective study from France also indicated that selective screening using a questionnaire on HCV risk factors had low sensitivity for the identification of HCV-infected patients who were receiving chemotherapy for solid tumors. As a result of those findings, the authors recommended that HCV screening be conducted routinely and systematically in every patient with cancer.

For over a decade, universal HCV screening has been standard practice among the hematologic services at the MD Anderson Cancer Center. Professional societies, such as the American Society for Blood and Marrow Transplantation, the European Conference on Infection in Leukemia (a joint initiative of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation), the European Organization for Research and Treatment of Cancer, the Immunosuppressed Host Society, and European LeukemiaNet, have generated guidance documents for the diagnosis and treatment of HCV infection in patients with hematologic malignancies and HCT recipients; and universal screening is recommended in this population. In terms of those with solid tumors, all patients with liver cancer should undergo screening for HCV, but the optimal screening strategy for patients with other solid tumors is less clear. One-time HCV screening in patients with cancer who belong to the 1945 to 1965 birth cohort and other patients based on exposures, behaviors, and conditions that increase risk for HCV infection will be in alignment with recommendations of the Centers for Disease Control and Prevention and the US Preventive Services Task Force in patients without cancer. Another possible approach to identifying such infected patients with cancer is combining risk-based and birth cohort-based strategies with education for oncologists. Since 2016, the standard practice at the MD Anderson Cancer Center of universal HCV screening in the hematologic patient population has been expanded to all other patients with cancer.

The rationale to that approach is that identification and elimination of HCV from infected patients have the potential for virologic, hepatic, and oncologic benefits not only in patients with hematologic malignancies but also in those with solid tumors. For instance, viral eradication may normalize transaminases, allowing access to chemotherapeutic agents that would otherwise be contraindicated; prevent liver disease progression or the development of HCC or NHL as a secondary cancer; and allow access to multiple clinical trials of cancer chemotherapies (for more details, see Potential Benefits of Antiviral Therapy, below). Exceptions to screening could be patients who have contraindications for DAAs (eg, uncontrolled cancer with limited life expectancy or decompensated cirrhosis), patient decline, or other medical reasons. HCV infection in patients with cancer warrants better awareness and well-designed research to identify the optimal screening strategy.

The US Food and Drug Administration has approved 2 methods for diagnosing HCV: serologic assays that detect antibodies are used for screening, and molecular assays that detect HCV RNA (eg, nucleic acid testing) are used to confirm HCV infection. The specificity of current serologic assays is greater than 99%. Guidelines from the US Public Health Service, the Infectious Diseases Society of America, the Veterans Affairs Hepatitis C Resource Center Program, and the National Hepatitis C Program Office recommend HCV antibody screening in immunocompromised patients, such as those with HIV infection. However, little is known about the optimal approach to diagnosis of HCV infection in patients with cancer, particularly those who are immunocompromised, such as patients with hematologic malignancies and HCT recipients. Previous studies have established that the prevalence of seronegative HCV infection in HIV-infected patients is as high as 6.9%, but no similar data exist for patients with cancer. Furthermore, serologic assays could be unreliable for diagnosing HCV infection in HCT recipients. One study demonstrated that 13% of HCV-infected HCT recipients had false-negative anti-HCV antibody test results after transplantation. Therefore, molecular diagnostic methods (eg, nucleic acid testing) could be more reliable than serologic assays in HCT recipients. Professional societies recommend that all HCT candidates should be screened for HCV.

**Evaluation and Treatment of HCV-Infected Patients With Cancer**

HCV infection is a supplementary burden in patients with newly diagnosed cancer. HCV-infected patients with cancer are at risk for serious adverse effects of cancer treatment, including sinusoidal obstruction syndrome and chemotherapy-
associated steatohepatitis resulting from oxaliplatin or irinotecan.\textsuperscript{127,128} Ischemic hepatitis, cholangiopathy, impaired liver regeneration, sinusoidal obstruction syndrome, and death during HCT and liver surgery have also been reported in HCV-infected patients with cancer.\textsuperscript{129,130} Moreover, patients with chronic viral hepatitis are often excluded from cancer trials: approximately 48% of early phase cancer clinical trials at the MD Anderson Cancer Center exclude HCV-infected patients.

New entry into the health care system with close follow-up and subsequent lifestyle modifications can improve outcomes of patients with HCV infection.\textsuperscript{42} Treatment and eradication of HCV infection with subsequent normalization of liver function tests might also open access to cancer clinical trials for patients who originally were excluded because of HCV infection.\textsuperscript{11}

**Evaluation of the HCV-Infected Patient**

As mentioned above, patients with HCV infection are at risk for liver fibrosis and cirrhosis, which are both associated with serious adverse events during cancer treatment, including HCT. Cirrhosis can also be associated with abnormal clearance and metabolism of anticancer agents.\textsuperscript{131} Therefore, evaluation of liver fibrosis in HCV-infected patients with cancer is mandatory, regardless of whether or not there is an SVR.

Liver stiffness, as measured by transient elastography, is a surrogate marker for cirrhosis in HCV-RNA–positive patients. A liver stiffness value below 7.1 kilopascals (kPa) rules out significant liver fibrosis, whereas a liver stiffness value above 12.5 kPa is very predictive of cirrhosis.\textsuperscript{132} Between these thresholds, the liver stiffness value is inconclusive, and liver biopsy should remain a standard. Transient elastography also performs poorly, as do all other noninvasive tests, in HCV-infected patients who have an SVR to treatment, and decisions regarding care should not be based on such measurements.\textsuperscript{133} Therefore, liver biopsy should remain the standard for diagnosing cirrhosis in HCV-RNA–negative patients.\textsuperscript{134}

The simplest method for the classification of patients with HCV infection and cirrhosis is to classify them according to whether they have compensated or decompensated cirrhosis. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy, and/or jaundice.\textsuperscript{135} Median survival is significantly longer in patients with compensated cirrhosis than in those with decompensated cirrhosis (\textgreater{}12 vs 2 years).\textsuperscript{136} Because the outcome of HCV-infected patients with cancer who have decompensated cirrhosis is related more to liver dysfunction than to cancer, these patients are generally not candidates for cytotoxic treatments.

A more precise method for the classification of patients with HCV infection and cirrhosis is based on the Child-Pugh score, which is based on bilirubin and albumin levels, prothrombin time, and the presence or absence of ascites and encephalopathy. Patients with Child-Pugh C disease usually are not eligible for cancer treatment. For patients with Child-Pugh B disease, it is essential to carefully evaluate both the effective degree of hepatic dysfunction as well as tumor and patient characteristics (eg, chemosensitivity, site of disease, kind and degree of symptoms).

Despite the fundamental role of the liver in drug metabolism, the impact of late-stage cirrhosis on the metabolism and clearance of cancer drugs is not understood. The pharmacokinetics of hepatically cleared chemotherapy may be affected by multiple factors, including altered clearance due to decreased hepatocyte uptake or impaired liver blood flow, altered biliary excretion, altered metabolic capacity, decreased albumin level leading to increased free drug, or altered oral drug absorption from portal hypertension.\textsuperscript{137} No single method allows estimation of the pharmacokinetics and pharmacodynamics of a drug in an individual patient with cirrhosis. However, the evidence supporting systematic drug dose reduction in patients with compensated cirrhosis is very weak, and most patients with normal liver function can receive cancer drugs without liver damage. Care for such patients should be managed by physicians and doctors of pharmacy with expertise in treating patients who have compensated cirrhosis to avoid systematic dose reduction that could be associated with poor cancer outcome.

Patients who have cirrhosis and portal hypertension are at risk for postoperative hepatic decompensation after liver resection or bleeding caused by treatment with an antiangiogenic agent.\textsuperscript{138,139} Measurement of hepatic venous pressure gradient or gastrointestinal endoscopy may be used to rule out esophagogastric varices and clinically significant portal hypertension. A low platelet count (<100,000/mL) or the presence of large varices on preoperative imaging rules out patients with cirrhosis as candidates for major liver resection. Patients who have a liver stiffness value less than 20 kPa with a platelet count greater than 150,000/mL have a very low risk of clinically significant portal hypertension, but whether this holds true among HCV-infected patients who have an SVR to treatment has not been validated.\textsuperscript{140} The future liver remnant volume after liver resection should always be assessed before surgery by experts in liver volume manipulations.\textsuperscript{130}

**Patient Selection for Treatment**

Data on the treatment of HCV infection in patients with cancer are limited, largely because studies of anti-HCV therapy typically exclude them. There is currently no standard-of-care antiviral therapy; however, data are becoming available, and SVR rates seem to be similar to those...
FIGURE 2. Management Algorithm for Patients With Cancer and Hepatitis C Virus (HCV) Infection. Abbreviations: ALT indicates alanine aminotransferase; anti-HBc, hepatitis B surface antibody; anti-HBs, hepatitis B surface antibody; AST, aspartate aminotransferase; DAA, direct-acting antivirals; GGT, \( \gamma \)-glutamyl transferase; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HAV, hepatitis A virus; HBV, hepatitis B virus; HCT, hematopoietic cell transplantation; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; SOS, sinusoidal obstruction syndrome.

a) Patient had spontaneous resolution of acute HCV infection, false-positive anti-HCV test result, or sustained virologic response after treatment. Patients with previous antiviral therapy should undergo fibrosis assessment per Box 1.

b) Patients with cirrhosis will need follow-up with specialists in hepatology or gastroenterology.

c) Specialist in infectious disease, hepatology, or gastroenterology.

d) Check ALT level before the initiation of chemotherapy (baseline) and every 2–8 weeks during chemotherapy. Check HCV RNA level before the initiation of chemotherapy (baseline), at 12-week intervals after the initiation of chemotherapy, and at the time of hepatitis flare.

e) As recommended as of May 2017 (AASLD-IDSA. hvguidelines.org) for selected patients without cancer.

f) Screen for HCC regardless of virologic outcome, particularly in patients with other risk factors for liver disease progression.

g) Patients at risk for chronic HEV infection include immunocompromised cancer patients (HCT recipients and patients with hematologic malignancies, low CD4+ lymphocyte count, or low lymphocyte count).
observed in HCV-infected patients without cancer. Unlike interferon-based regimens, DAA therapy can be used in patients who have cancer with bone marrow compromise or cytopenias without dose adjustments or discontinuation. Our algorithm for the treatment of HCV-infected patients with cancer is depicted in Figure 2.

Antiviral therapy should be offered to HCV-infected patients with cancer, except those who have contraindications to antiviral therapy, including uncontrolled cancer, comorbidity associated with a life expectancy of less than 12 months, pregnancy or a pregnant partner (if ribavirin is considered), anticipated major drug-drug interaction with a chemotherapy or immunosuppressive agent that cannot be temporarily discontinued, and/or known hypersensitivity or intolerance to DAAs. Antiviral therapy also could be contraindicated in HCV-infected patients who have cancer with Child-Pugh class B or C cirrhosis, because incurable extrahepatic malignancy is considered a contraindication to listing a patient for liver transplantation, which is the only available treatment for decompensated cirrhosis. In addition, decompensated cirrhosis is a contraindication to DAA therapy in oncologic patients because of an increased risk of lactic acidosis, which could be even higher with cancer treatment.

### Selection and Delivery of DAA Therapy

In general, HCV-infected patients with cancer can be treated in the same way as HCV-infected patients without cancer. However, the DAA regimen should be individualized on the basis of the patient’s prior antiviral therapy, HCV genotype, and degree of liver disease; the potential hematologic toxic effects of the DAA regimen; and the potential for drug-drug interactions (see below for details on interactions). If an HCV-infected patient with cancer is deemed to be a candidate for treatment with DAAs, then he or she should receive antiviral therapy according to the guidelines for patients without cancer. In some major cancer centers, HCV-treating physicians (infectious disease specialists and hepatologists),

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**TABLE 3. Metabolism and Transporter Effects of Direct-Acting Antivirals**

| DIRECT-ACTING ANTIVIRAL | METABOLISM | TRANSPORTER EFFECTS |
|-------------------------|------------|---------------------|
| Sofosbuvir              | Hepatic; forms active nucleoside analog triphosphate GS461203 | P-gp and BCRP substrate |
| Sofosbuvir-ledipasvir<sup>a</sup> | Slow oxidative metabolism via unknown mechanism | P-gp and BCRP substrate: Inhibits P-gp, BCRP, OATP1B1, OATP1B3, and bile salt export pump |
| Sofosbuvir-velpatasvir<sup>a</sup> | Hepatic via CYP286, CYP2C8, and CYP3A4 | P-gp and BCRP substrate: Inhibits P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1 |
| Ritonavir-boosted paritaprevir-ombitasvir-dasabuvir<sup>b</sup> | Ritonavir-boosted paritaprevir: Hepatic via CYP3A4 (primary) and CYP3A5 Ombitasvir: Hydrolysis Dasabuvir: Hepatic via CYP2C (primary) and CYP2C8 | Ritonavir-boosted paritaprevir P-gp, BCRP, and OATP1B3 substrate: Inhibits P-gp, BCRP, OATP1B1, and OATP1B3 Ombitasvir P-gp and BCRP substrate: Inhibits P-gp, BCRP, and OATP1B1 Dasabuvir P-gp and BCRP substrate: Inhibits P-gp, BCRP, and OATP1B1 |
| Grazoprevir-elbasvir | Hepatic via CYP3A4 (partial) | Grazoprevir: OATP1B1 and OATP1B3 substrate; Transported by P-gp; Inhibits BCRP (intestinal level), and CYP3A (weak) Elbasvir: Inhibits BCRP (intestinal level) |
| Daclatasvir | Hepatic via CYP3A | CYP3A4 and P-gp substrate: Inhibits BCRP, P-gp, OATP1B1, and OATP1B3 (moderate) |
| Simeprevir | Hepatic via CYP3A (primary), CYP2C8, and CYP2C19 | CYP3A4, P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1 substrate; Transported by OATP1B1 and OATP1B3, Inhibits OATP1B1, OATP1B3, P-gp, BCRP, BSEP, CYP1A2 (mild), and CYP3A4 (mild) |
| Ribavirin<sup>c</sup> | Hepatic and intracellular | Inhibits CYP1A2 and IMDH |

*Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CYP, cytochrome P450 enzymatic system; IMDH, inosine monophosphate dehydrogenase; OATP, organic anion transporting polypeptide; P-gp, p-glycoprotein. *Metabolism and transporter effects do not include sofosbuvir; refer to sofosbuvir for information. *Ritonavir has no activity against hepatitis C virus but is given as a low-dose CYP3A inhibitor to boost paritaprevir concentration. *Ribavirin is often used in combination with direct-acting antivirals; therefore, it is included to provide a comprehensive overview.*
HCV in most infected patients within 2 to 3 months with- not applicable to HCV infection, because DAAs eradicate infections, such as HBV infection, long-term antiviral ther- view. AdCoadministration was studied directly.

Additional drug-drug interactions and more extensive range of drugs, detailed pharmacokinetic interaction data, and dosage adjustments, refer to the (hep-druginteractions.org; University of Liverpool), Lexicomp Online (Lexi-Comp, Inc, Hudson, OH; November 2016), and medication package inser ts. For

**TABLE 4. Major Interactions Between Hepatitis C Virus Direct-Acting Antivirals and Standard Chemotherapy Drugs**

| CHEMOTHERAPY DRUG | SOFOSBUVIR | SOFOSBUVIR- LEDIPASVIR | SOFOSBUVIR- VELPATASVIR | RITONAVIR- BOOSTED PARITAPREVIR- OMBITASVIR- DASABUVIR | GRAZOPREVIR- ELBASVIR | DACLATASVIR | SIMEPREVIR | RIBAVIRIN |
|-------------------|------------|------------------------|-------------------------|---------------------------------------------------|----------------------|-------------|------------|----------|
| Alkylating agents |            |                        |                         |                                                   |                      |             |            |          |
| Chlorambucil      |            |                        |                         |                                                   |                      |             |            |          |
| Cyclophosphamide  |            |                        |                         |                                                   |                      |             |            |          |
| Antifolate        |            |                        |                         |                                                   |                      |             |            |          |
| Methotrexate      |            |                        |                         |                                                   |                      |             |            |          |
| Antitumor antibiotics |      |                        |                         |                                                   |                      |             |            |          |
| Doxorubicin       |            |                        |                         |                                                   |                      |             |            |          |
| Idarubicin        |            |                        |                         |                                                   |                      |             |            |          |
| Cytidine analog   |            |                        |                         |                                                   |                      |             |            |          |
| Gemcitabine       |            |                        |                         |                                                   |                      |             |            |          |
| 5-Fluoropyrimidine|            |                        |                         |                                                   |                      |             |            |          |
| Cepacitabine      |            |                        |                         |                                                   |                      |             |            |          |
| Microtubule agents|            |                        |                         |                                                   |                      |             |            |          |
| Docetaxel         |            |                        |                         |                                                   |                      |             |            |          |
| Paclitaxel        |            |                        |                         |                                                   |                      |             |            |          |
| Platinum analogs  |            |                        |                         |                                                   |                      |             |            |          |
| Carboplatin       |            |                        |                         |                                                   |                      |             |            |          |
| Cisplatin         |            |                        |                         |                                                   |                      |             |            |          |
| Oxaplatin         |            |                        |                         |                                                   |                      |             |            |          |
| Purine antimetabolites |        |                        |                         |                                                   |                      |             |            |          |
| Fludarabine       |            |                        |                         |                                                   |                      |             |            |          |
| Mercaptopurine    |            |                        |                         |                                                   |                      |             |            |          |
| Topoisomerase VII inhibitors | |                         |                         |                                                   |                      |             |            |          |
| Etoposide         |            |                        |                         |                                                   |                      |             |            |          |
| Irinotecan        |            |                        |                         |                                                   |                      |             |            |          |
| Topotecan         |            |                        |                         |                                                   |                      |             |            |          |
| Vinca alkaloids   |            |                        |                         |                                                   |                      |             |            |          |
| Vinblastine       |            |                        |                         |                                                   |                      |             |            |          |
| Vincristine       |            |                        |                         |                                                   |                      |             |            |          |
| Vinorelbine       |            |                        |                         |                                                   |                      |             |            |          |

*The table does not include all chemotherapeutic agents. Drug interactions are based on metabolism and clearance data rather than direct study of coadministration except where otherwise indicated. Symbols used to indicate clinical significance of drug interactions are based on HEP Drug Interactions (hep-druginteractions.org; University of Liverpool), Lexicomp Online (Lexi-Comp, Inc, Hudson, OH; November 2016), and medication package inserts. For additional drug-drug interactions and more extensive range of drugs, detailed pharmacokinetic interaction data, and dosage adjustments, refer to the above-mentioned Web sites, medication package inserts, and specific references (Peyrin-Biroulet et al, 171 Kraljacic et al,172 and Gilead Sciences Inc178).

**Legend:** ◆, no clinically significant interaction expected; ◆, potential interaction that may require a dosage adjustment, altered timing of administration, or additional monitoring; ◆, these drugs should not be coadministered; ◆, not included in HEP Drug Interactions; however, metabolism and clearance data suggest that an interaction is unlikely; ◆, not included in HEP Drug Interactions; however, metabolism and clearance data suggest that an interaction may occur. Ribavirin is often used in combination with direct-acting antivirals; therefore, it is included to provide a comprehensive drug-drug interaction overview. Coadministration was studied directly.

Oncologists, and pharmacists work together in the diagnostic work-up, monitoring, and treatment of HCV-infected patients.14

In HCV-infected patients without cancer, achieving an SVR at 12 weeks has a positive predictive value greater than 97% for an SVR at 24 weeks. However, confirmation of SVR by repeat HCV-RNA testing at 24 weeks is still appropriate, because late recurrences are reported after treatment with DAAs.146 For some chronic and incurable viral infections, such as HBV infection, long-term antiviral therapy is used to prevent viral reactivation. This approach is not applicable to HCV infection, because DAAs eradicate HCV in most infected patients within 2 to 3 months without viral recurrence after cancer therapy.147

About 40% of patients with HCV infection (more in areas with high HBV endemicity) harbor HBV markers and are at risk for HBV reactivation during cancer treatment.9,148 Reactivation of HBV infection in HCV-coinfected patients receiving DAAs has also been reported, and there are a few reported cases of fulminant hepatic failure requiring liver transplantation.149,150 Most of these reports were from patients with detectable HBV surface antigen (HBsAg), and none were receiving anti-HBV therapy.150 It is interesting to note that a few cases of reactivation of HBV infection in HCV-coinfected patients occurred in patients with isolated hepatitis B core antibody,149,151 even in the absence of immunomodulatory medications.152 However, on the basis of currently available data, the impact of HBV reactivation in HCV-coinfected patients receiving DAAs appears to be minor.151,152 Patients who have cancer with HBV and HCV coinfection are at risk for HBV reactivation, but it is expected that patients with detectable HBsAg will receive anti-HBV therapy during chemotherapy, which lowers the risk of
TABLE 5. Major Interactions Between Hepatitis C Virus Direct-Acting Antivirals and Monoclonal Antibodies, Targeted Chemotherapy, and Endocrine Therapy\(^a,b\)

| DRUG | SOFOSBUVIR | SOFOSBUVIR-LEDIPASVIR | SOFOSBUVIR-VELPATASVIR | RITONAVIR-BOOSTED PARITAPREVIR-OMBITASVIR-DASABUVIR | GRAZOPREVIR-ELBASVIR | DACLATASVIR | SIMEPREVIR | RIBAVIRIN\(^c\) |
|------|------------|------------------------|------------------------|-------------------------------------------------|----------------------|-------------|------------|--------------|
| Endocrine agents | | | | | | | | |
| Anastrozole | | | | | | | | |
| Exemestane | | | | | | | | |
| Letrozole | | | | | | | | |
| Tamoxifen | | | | | | | | |
| HDAC inhibitors | | | | | | | | |
| Vorinostat | | | | | | | | |
| Romidepsin | | | | | | | | |
| Immunotherapy | | | | | | | | |
| Ipilimumab | | | | | | | | |
| Nivolumab | | | | | | | | |
| Tocilizumab | | | | | | | | |
| Immunomodulators | | | | | | | | |
| Lenalidomide | | | | | | | | |
| Thalidomide | | | | | | | | |
| Monoclonal antibodies | | | | | | | | |
| Rituximab | | | | | | | | |
| Brentuximab | | | | | | | | |
| mTOR kinase inhibitor | | | | | | | | |
| Everolimus | | | | | | | | |
| Proteasome inhibitor | | | | | | | | |
| Bortezomib | | | | | | | | |
| TKIs | | | | | | | | |
| Dasatinib | | | | | | | | |
| Erlotinib | | | | | | | | |
| Gefitinib | | | | | | | | |
| Imatinib | | | | | | | | |
| Lapatinib | | | | | | | | |
| Nilotinib | | | | | | | | |
| Ponatinib | | | | | | | | |
| Sorafenib | | | | | | | | |
| Sunitinib | | | | | | | | |

Abbreviations: HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; TKIs, tyrosine kinase inhibitors. \(^a\)Drug interactions are based on metabolism and clearance data rather than on direct study of coadministration, except where otherwise indicated. Symbols used to indicate clinical significance of drug interactions are based on HEP Drug Interactions (hep-druginteractions.org; University of Liverpool), Lexicomp Online (Lexi-Comp, Inc, Hudson, OH; November 2016), and medication package inserts. For additional drug-drug interactions and more extensive range of drugs, detailed pharmacokinetic interaction data, interactions are based on HEP Drug Interactions (hep-druginteractions.org; University of Liverpool), Lexicomp Online (Lexi-Comp, Inc, Hudson, OH; November 2016), and medication package inserts. For additional drug-drug interactions and more extensive range of drugs, detailed pharmacokinetic interaction data, and dosage adjustments, refer to the above-mentioned Web sites, medication package inserts, and specific references (Mikazzio et al,\(^{196\text{-}197}\) Caseiro,\(^{117}\) Kraljacic \textit{et al},\(^{172}\) Fardouly \textit{et al},\(^{173}\) and Shi \textit{et al}\(^{174}\). \(^b\)Legend: \(\blacksquare\), no clear data; \(\blacktriangle\), no clinically significant interaction expected; \(\blacktriangledown\), potential interaction that may require a dosage adjustment, altered timing of administration, or additional monitoring; \(\triangledown\), these drugs should not be coadministered; \(\blacklozenge\), not included in HEP Drug Interactions; however, metabolism and clearance data suggest that an interaction is unlikely; \(\blacklozenge\), not included in HEP Drug Interactions; however, metabolism and clearance data suggest that an interaction may occur. \(^c\)Ribavirin is often used in combination with direct-acting antivirals; therefore, it is included to provide a comprehensive drug-drug interaction overview. \(^d\)Coadministration was studied directly.

HBV reactivation.\(^{153}\) We recommend periodic monitoring of ALT, HBsAg, and HBV DNA according to the guidelines for HBV-monoinfected patients who have cancer\(^{154}\) for the early detection of hepatitis flare and HBV reactivation in those who have cancer with HBV and HCV coinfection and are receiving DAAs. Recommendations are less clear for patients who have cancer with isolated hepatitis B core antibody, but close observation is still advised, because most of those patients do not routinely receive anti-HBV therapy.\(^{153,154}\)

**Potential Benefits of Antiviral Therapy**

The benefit of holistic treatment of HCV-infected patients, including close follow-up with subsequent lifestyle modifications and interferon-based treatment, has been demonstrated.\(^{42}\) Eradication of HCV with interferon-based treatment was associated with a 75% reduction in the risk of liver cancer.\(^{117,155,156}\)

DAA therapy with close follow-up has been reported to improve liver function in patients with decompensated cirrhosis,\(^{114,157}\) although there have also been cases of DAA-associated lactic acidosis and sudden hepatic decompensation.\(^{143,144,158}\) Decompensated cirrhosis is the main cause of death among HCV-infected patients with cancer in complete remission.\(^{100}\) The benefit of DAA therapy in infected patients who have cancer with advanced liver disease has not been demonstrated yet.

HCV treatment may halt, delay, or prevent progression to cirrhosis and end-stage liver disease in patients with cancer and in HCT recipients. In the DAA era, studies of
fibrosis regression versus progression after SVR are limited, but similar outcomes are anticipated in HCV-infected patients with cancer as long as HCV-associated comorbidities are controlled.

Viral eradication with anti-HCV therapy may improve liver function and normalize the ALT level, allowing patients access to multiple cancer chemotherapies, including agents with hepatic metabolism, and prevent HCV reactivation.\textsuperscript{5,10,125,159} HCV eradication might also open access to cancer clinical trials to patients who originally were excluded because of HCV-associated chronic liver disease.\textsuperscript{11}

HCV-infected patients with selected subtypes of B-cell NHL should be treated with DAAs first and then with chemotherapy. Antiviral treatment of HCV infection in patients with certain cancers, such as indolent B-cell NHL, has induced tumor regression and improved hematologic outcomes with the use of interferon-containing\textsuperscript{95} and interferon-free regimens.\textsuperscript{98,99} Our group and others have demonstrated that antiviral therapy, including DAA-based therapy, can improve oncologic outcomes, including survival, of patients who have developed HCV-associated NHL,\textsuperscript{13,98,99,160} including those with HCV-associated B-cell NHL undergoing HCT.\textsuperscript{5,13} In fact, the National Comprehensive Cancer Network guidelines on splenic marginal zone lymphoma recommend treatment of HCV without chemotherapy as first-line therapy for HCV-infected patients.\textsuperscript{161} Furthermore, anti-HCV therapy may reduce the risk of HCC or NHL as second primary cancers\textsuperscript{8,10} and improve the oncologic outcomes of patients with selected HCV-related cancers, such as NHL.\textsuperscript{13}

Nonrandomized studies of the effect of HCV eradication with DAAs on HCC progression or recurrence have yielded

| MEDICATION         | SOFOSBUVIR-LEDIPASVIR | SOFOSBUVIR-VELPATASVIR | RITONAVIR-BOOSTED PARITAPRECVIR-OMBITASVIR-DASABUVIR | GRAZOPRECVIR-ELBASVIR | DACLATASVIR | SIMEPRECVIR | RIBAVIRIN |
|--------------------|-----------------------|------------------------|-----------------------------------------------------|-----------------------|-------------|-------------|-----------|
| Acid-reducing agents |                       |                        |                                                     |                       |             |             |           |
| H2 antagonist      |                       |                        |                                                     |                       |             |             |           |
| Proton pump inhibitor |                   |                        |                                                     |                       |             |             |           |
| Anticoagulant      |                       |                        |                                                     |                       |             |             |           |
| Apixaban           |                       |                        |                                                     |                       |             |             |           |
| Dabigatran         |                       |                        |                                                     |                       |             |             |           |
| Edoxaban           |                       |                        |                                                     |                       |             |             |           |
| Rivaroxaban        |                       |                        |                                                     |                       |             |             |           |
| Warfarin           |                       |                        |                                                     |                       |             |             |           |
| Antiemetic         |                       |                        |                                                     |                       |             |             |           |
| Aprepitant         |                       |                        |                                                     |                       |             |             |           |
| Antiinfects        |                       |                        |                                                     |                       |             |             |           |
| Flucconazole       |                       |                        |                                                     |                       |             |             |           |
| Isavuconazole      |                       |                        |                                                     |                       |             |             |           |
| Posaconazole       |                       |                        |                                                     |                       |             |             |           |
| Voriconazole       |                       |                        |                                                     |                       |             |             |           |
| Bisphosphonate     |                       |                        |                                                     |                       |             |             |           |
| Pamidronate        |                       |                        |                                                     |                       |             |             |           |
| Immunosuppressants |                       |                        |                                                     |                       |             |             |           |
| Cyclosporine       |                       |                        |                                                     |                       |             |             |           |
| Mycophenolate      |                       |                        |                                                     |                       |             |             |           |
| Sirolimus          |                       |                        |                                                     |                       |             |             |           |
| Tacrolimus         |                       |                        |                                                     |                       |             |             |           |
| Growth factor      |                       |                        |                                                     |                       |             |             |           |
| Eltrombopag        |                       |                        |                                                     |                       |             |             |           |
| Filgrastim         |                       |                        |                                                     |                       |             |             |           |
| Steroids           |                       |                        |                                                     |                       |             |             |           |
| Dexamethasone      |                       |                        |                                                     |                       |             |             |           |
| Methylprednisolone |                       |                        |                                                     |                       |             |             |           |
| Prednisone         |                       |                        |                                                     |                       |             |             |           |

Abbreviation: H2, histamine 2 receptor. \textsuperscript{9} The table does not include all supportive care medications in oncology. Drug interactions are based on metabolism and clearance data rather than on direct study of coadministration, except where otherwise indicated. Symbols used to rank clinical significance of drug interactions are based on HEP Drug Interactions (hep-druginteractions.org; University of Liverpool), Lexicomp Online (Lexi-Comp, Inc, Hudson, OH; November 2016), and medication package inserts. For additional drug-drug interactions and more extensive range of drugs, detailed pharmacokinetic interaction data, and dosage adjustments, refer to the above-mentioned Web sites, medication package inserts, and specific references (Britnell et al,\textsuperscript{117} DeCarolis et al,\textsuperscript{174} Schulman,\textsuperscript{177} and Puglisi et al\textsuperscript{186}). \textsuperscript{*Legend: \textbullet, no clear data; \textbullet, no clinically significant interaction expected; \textbullet, potential interaction that may require a dosage adjustment, altered timing of administration, or additional monitoring; \textbullet, these drugs should not be co-administered; \textbullet, not included in HEP Drug Interactions; however, metabolism and clearance data suggest that an interaction is unlikely; \textbullet, not included in HEP Drug Interactions; however, metabolism and clearance data suggest that an interaction may occur. Ribavirin is often used in combination with direct-acting antivirals; therefore, it is included to provide a comprehensive drug-drug interaction overview. \textsuperscript{*Coadministration was studied directly.}
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TABLE 7. Unmet Clinical and Research Needs and Knowledge Gaps on Hepatitis C Virus Infection in Patients With Cancer

| Optimal screening strategy in patients with cancer and HCT recipients |
|-----------------|
| Value of routine HCV screening in cancer centers |
| Need for systematic cancer screening of HCV-infected patients with cancer to identify HCV-related second primary cancers |
| Optimal strategy for monitoring HCV infection during cancer treatment |
| Impact of DAA-based therapy in cancer prevention |
| Most favorable strategy for early detection and treatment of coinfections caused by carcinogenic viruses (eg, HBV, HIV, and HPV) in HCV-infected patients with cancer |
| Studies on HBV reactivation in patients who have cancer with HBV and HCV coinfection and are receiving DAs |
| Optimal timing of antiviral therapy in relation to chemotherapy and HCT |
| Efficacy and safety of various DAA regimens in patients with cancer and HCT recipients |
| Predictors of liver disease progression, even if an SVR is achieved |
| Reliability of serologic markers of fibrosis and FibroScan VCTE in predicting the presence of advanced fibrosis and cirrhosis in patients with cancer and HCT candidates |
| Inclusion of HCV-infected patients with cancer in clinical trials of both cancer treatment and DAs |
| Virologic, hepatic, and oncologic impact of treating HCV in patients with various cancers |
| Large, well designed, prospective studies focused on patients with cancer from distinct geographic areas analyzing the impact of geographic variations of HCV genotypes |
| Characterization of interactions between DAs and chemotherapeutic agents |

Abbreviations: DAA, direct-acting antiviral; HBV, hepatitis B virus; HCT, hematopoietic cell transplantation; HCV, hepatitis C virus; HPV, human papillomavirus; SVR, sustained virologic response; VCTE, vibration-controlled transient elastography.

Disparate results.162 One early report summarizing the outcomes of 58 Spanish patients with radiologically negative HCC who had completed DAA therapy revealed a surprisingly high rate of tumor recurrence (28%).37 However, the retrospective nature of the study, the lack of consistency in obtaining imaging at baseline and follow-up, and the lack of consistency in the timing of DAA therapy, as detailed by our group,163 preclude drawing firm conclusions from this study. In another large study from Spain, rates of HCC recurrence were high and were similar to those in previous reports,164 but the authors acknowledged that their results must be interpreted with caution given the lack of a routine surveillance monitoring protocol. Larger retrospective analyses from a French population and a meta-analysis did not reveal an increased risk of HCC recurrence or a negative impact on overall and recurrence-free survival.44,165

Whether the risk of HCC recurrence is increased with DAA therapy is therefore controversial.37,163 HCC recurrence is closely related to other risk factors, including age at infection, sex, and HCV-associated comorbidities, including HIV and HBV coinfections, alcohol use disorders, and diabetes.30 Loss of cancer immune monitoring and progression of HCC favored by interferon-free treatments could be another mechanism underlying HCC recurrence.166–169

Regardless of whether it is ultimately demonstrated that antiviral therapy increases the risk of cancer recurrence among HCV-infected patients with cancer, the main message is that surveillance for cancer occurrence or recurrence is important among patients with an SVR who are at risk for liver disease progression. The field awaits prospective trials to determine the merits of DAA therapy in HCV-infected patients with cancer as well as the characteristics of patients who will likely experience cancer progression after DAA therapy, including those who have undergone resection or received locoregional therapy for HCC.165

Potential Interactions Between DAs and Chemotherapy, Targeted Therapy, and Supportive Care Medications

DAs are highly effective and well tolerated in HCV-infected patients with cancer. However, the potential for interactions between DAs and other drugs used in the treatment of cancer poses a challenge.

To our knowledge, there is only a single published prospective study of interactions between DAs and chemotherapy.145 That study found no significant interactions when DAs and various chemotherapy agents were administered concomitantly to treat various malignancies. No toxic effects were observed that required discontinuation of either agent. In addition, there was a trend toward normalization of ALT levels during and after combination therapy. Until further research establishes a better understanding of clinically significant interactions between DAs and chemotherapy, clinicians should use pharmacodynamic and pharmacokinetic data to guide treatment decisions.

Pharmacodynamic drug interactions result from physiologic activities of 2 interacting drugs, whereas pharmacokinetic drug interactions may lead to altered concentrations of drugs or metabolites due to changes in absorption, distribution, metabolism, or elimination. The most common sites for drug-drug interactions are hepatocytes and intestinal enterocytes via the cytochrome P450 enzyme system as well as the P-glycoprotein (P-gp) membrane transporter. Furthermore, additional drug transporters, such as breast cancer resistance protein and organic anion transporting polypeptide,170 have known metabolic pathways that may contribute to interactions with DAs.

DAs used to treat HCV infection and their metabolism, transporter effects, and potential for interactions with chemotherapy, targeted agents, and supportive care medications commonly used to treat cancer are outlined in

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The oncologic burden of HCV infection is 2-fold. First, HCV infection is associated with the development of several cancers, an effect often intertwined with the consequences of HCV-associated comorbidities. Second, chronic HCV infection causes significant morbidity and mortality in patients with cancer. Anti-HCV therapy is associated with viral clearance, improved liver function, and, in many cases, favorable oncologic outcomes for patients who have already developed HCV-associated malignancies (e.g., B-cell NHL). Chronic HCV infection can affect the cancer treatment plan (e.g., necessitating chemotherapy dose reduction), but this infection is manageable and, in most cases, can be virologically cured. HCV-infected patients should not be systematically deprived of effective treatment for their cancer, including HCT if indicated, because only a very small proportion of HCV-infected patients with cancer have a contraindication to cancer treatment or HCT. The optimal timing of DAA therapy for HCV-infected patients with cancer and HCT recipients remains to be determined. At the same time that HCV infection is treated with antiviral therapy, HCV-associated comorbidities should be addressed. Patients with cirrhosis (or even advanced fibrosis) and those with HCV-associated comorbidities, including alcohol use disorder, should be maintained in the health care system even if viral eradication is achieved. HCV-infected patients with cancer will require specialized care delivered by a multidisciplinary team of HCV-treating physicians, oncologists, and pharmacists who work together toward optimizing patient care and outcomes. However, the management of HCV infection in patients with cancer should not be limited to tertiary cancer centers. Unmet needs and knowledge gaps with respect to HCV infection in patients with cancer are listed in Table 7.

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