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The oncologic burden of hepatitis C virus infection: A clinical perspective

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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 management of HCV infection in patients with cancer. The substantial burden of HCV infection in patients with cancer and the inconclusive evidence regarding detection and management of HCV infection in patients with cancer prompted us to review the literature and formulate recommendations. Patients for whom HCV screening is recommended included all patients with hematological malignancies, hematopoietic cell transplant candidates or patients with hepatocellular carcinoma (HCC). There is lack of consensus-based recommendations for the

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identification of other cancer patients but physicians may consider screening patients belonging to groups at heightened risk of HCV infection including persons born during 1945–1965 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 cancer patients with 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 HCC. HCV infection and its treatment should not be considered contraindications to cancer treatment and should not delay the initiation of an urgent cancer therapy.

Keywords

HCV; cancer; primary liver cancer; hepatocellular carcinoma; non-Hodgkin lymphoma; direct-acting antiviral

Introduction

Chronic hepatitis C virus (HCV) infection affects millions of people worldwide.[1] The oncologic burden of HCV infection is substantial. First, HCV infection is associated with the development of several different types of cancer.[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.[4] Second, chronic HCV infection in cancer patients causes significant additional morbidity and mortality and can interfere with cancer treatment.[5–10]

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

The burden of HCV in patients with cancer and the inconclusive evidence regarding detection and management of HCV infection in patients with cancer 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 treatment of HCV infection, including with the use of new DAAs.

We searched PubMed and Web of Science 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.[16]

Global epidemiology of HCV infection

The main mode of transmission of HCV 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 transmission of HCV infection before July 1992. Intravenous drug use has been and is still a leading contributor to the epidemic of HCV infection worldwide. [17,18] In low-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%[19] to 2.8%.[20] The highest prevalences are reported in low-income countries, including Egypt (15%), Pakistan (4.7%), and Taiwan (4.4%)[21]; prevalences are lower in North America (1.1%–1.3%), Australia (1.7%), and Eastern and Western Europe (0.5%–4.5%).[19] The latest epidemiologic reports suggest that there are currently 80 million HCV-RNA-positive individuals around the globe.[19,22]

In the United States, it is estimated that at least 3.5 million people (range, 2.5 million to 4.7 million) live with HCV infection[23] and that about half of them are unaware they are infected.[24] Individuals born during 1945–1965 have a 3% prevalence of HCV antibodies, which is five times the prevalence in adults born in other years.[25]

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.[26] Once cirrhosis develops in a patient with chronic HCV infection, the risk of hepatocellular carcinoma (HCC) is estimated to be 1% to 4% annually, similar to the risk of end-stage liver disease.[27,28] A small proportion of HCC cases, fewer than 10%, develop in patients with HCV infection without cirrhosis.[29] 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.[22]

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 HIV and HBV co-infections, alcohol use disorders, and diabetes.[30] Given the many factors affecting the natural progression of HCV infection, it is very difficult to determine exactly which factors have the biggest impact.[31,32] For example, in historical, community-based studies, liver disease progression in patients with HCV infection remained rare over decades after diagnosis with HCV infection, and liver disease progression was associated with obesity and alcohol use. In cohorts in which intravenous

drug use was the main mode of transmission of HCV, 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.[33]

Comorbidities associated with HCV infection probably underlie the unexpected observations of early HCC occurrence and recurrence among patients at risk for liver disease progression following HCV eradication with DAAs.[34–37] These observations from uncontrolled studies contrast with previous models of liver disease progression that support widespread use of DAAs to reduce the burden of HCV infection.[38] 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 cure of HCV-associated comorbidities, in observational cohorts.[39–42]

Some cancer patients with HCV infection will probably remain at risk for liver disease progression after a SVR, and the risk of progression is probably greatest in patients with HCV-associated comorbidities, including alcohol use disorders. Alcohol use has not been entered in most liver disease progression models, including those that support current cost-effectiveness strategies in industrialized countries, and therefore the benefits of treatment of HCV infection with DAAs could have been overestimated.[38,43] 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 have a SVR. [41]

Associations between HCV infection and cancer

Among adults with cancer who were newly registered at The University of Texas MD Anderson Cancer Center from January 2004 through April 2011, the prevalence of HCV antibodies was 1.5% overall,[44] and much higher in certain subtypes – e.g. 10.6% in selected solid tumors other than HCC.[45] In some regions of Europe and Asia, HCV antibodies have been reported in up to 2.8% of patients with solid tumors and 30% of those with hematological malignancies.[46,47]

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 reporting associations between HCV infection and hepatic and extrahepatic malignancies are summarized in Supplementary Table 1. The strength of the evidence supporting associations between HCV infection and cancer is presented in Table 2 and in previous meta-analyses.[48–59]

HCV and primary liver cancer

The strongest reported association between HCV infection and cancer is the association between HCV and primary liver cancer, including HCC and intrahepatic cholangiocarcinoma.

The association between HCV and HCC was first reported in 1989, in reports of 2 European case-control studies.[60,61] Both studies demonstrated the synergistic carcinogenic effects of HCV infection and HCV-associated comorbidities, including alcohol use and HBV infection.[60,61] 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.[62] 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.[63]

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.[64,65] Two meta-analyses[54,66] and a cohort study[67] showed that the odds ratio (OR) for intrahepatic cholangiocarcinoma in patients with HCV infection compared to patients without HCV infection ranged from 3.42 (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 extrahepatic solid tumors

The literature on the relationship between HCV infection and extrahepatic solid tumors is inconclusive. In a large non-veteran 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; 1.3–1.9)[2]; however, this study was unadjusted for major confounders, including alcohol and tobacco uses. In fact, alcohol-related and tobacco-related cancers were overrepresented in this cohort, suggesting that HCV could be a lifestyle marker. A prospective community-based cohort study from Taiwan[68] showed that chronic HCV infection was associated with increased risks of esophagus, prostate, and thyroid cancer. In another case-control study,[45] HCV infection was associated with non-oropharyngeal (except nasopharyngeal) and human-papillomavirus-positive oropharyngeal head and neck cancers (OR, 2.97; 95% CI, 1.31–6.76).

HCV and hematological malignancies

The second most robust association between HCV infection and cancer is the association 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. [69] In a large European multicenter case-control-study,[70] 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 lymphoplasmacytic lymphoma (OR, 2.57; 95% CI, 1.14–5.79). In a large population-based study in the United States,[71] HCV infection was associated with increased risks of Burkitt 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 hematological malignancies have been reported (Table 2, Supplementary Table 1).

Mechanisms by which HCV contributes to 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.[72,73] In a cellular model of HCV, NS3/4A (HCV viral protease) and NS5B (RNA-dependent RNA polymerase) impeded DNA repair via interaction with the ATM-driven response pathway.[74] Selected genotypes of HCV also might be associated with risk of development of HCC: greater carcinogenic potential has been reported for some variants, mostly genotypes 1 [1b] and 3,[75,76] although definitive studies are lacking.[77]

The main mechanism by which HCV contributes to development of HCC seems related to chronic inflammation, which mediates cycles of death and regeneration and eventually can lead to cirrhosis and to HCC.[78,79] 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.[70,80,81] 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. [82,83] A small proportion of HCC cases develop in patients with HCV infection without cirrhosis; in almost all such cases, the patients also had or have HBV infection.[29]

Genetic studies suggest that mutations accumulate in the premalignant stage of HCC and that mutation of the *TERT* promoter is an early genetic event.[84] The other genes most commonly mutated in HCC are *TP53* and *CTNNB1*.[81,85] Recurrent mutations in epigenetic modifier genes *ARID1A* and *ARID2* are also often present.[80] These and other genetic defects impact telomere maintenance and oxidative stress. Other pathways dysregulated in HCC include the PI3K-AKT-mTOR, RAS/RAF/MAPK, and JAK/STAT pathways. [81,85]

Confounders hinder determination of the precise impact of HCV infection on the development of HCC. Common risk factors for development of HCC include environmental exposures to hepatotoxins (e.g., alcohol and aflatoxins), misdirected host immune and DNA damage responses, co-infections (e.g., with HBV and HIV), advanced age, male sex, and metabolic factors (nonalcoholic fatty liver disease, obesity, metabolic syndrome, and type 2 diabetes). Diabetes[77,86] and the metabolic syndrome with steatosis are important risk factors for HCC, associated with alcohol use disorders but also with the worldwide obesity epidemic.[87] Furthermore, evidence is accumulating that even past heavy alcoholism in people who have since stopped drinking can contribute to liver disease progression to cirrhosis and liver cancer in HCV-infected patients, including those with a SVR.[41,88]

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.[89]

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, most epidemiologic studies showing 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, as HCV is found in precancerous lesions.[90] Potential synergism between HCV and human papillomavirus has also been suggested in the development of oral and head and neck cancers.[45] To date, potentiation of human papillomavirus by HCV has not been reported in other cancers.

HCV infection and hematological malignancies

Evidence for a mechanistic contribution of HCV to cancer is strongest for B-cell HNL. A subset of HCV-associated lymphomas produce immunoglobulins against E2 (HCV envelope glycoprotein), suggesting that these malignancies originate from B cells activated by HCV recognition.[91] 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.[92] Mechanisms that have been postulated to explain the HCV-induced transformation process include cryoglobulinemia, t(14;18), chronic lymphocyte proliferation stimulated by viral antigens, HCV replication in B cells mediated by viral proteins, and virus-induced B-cell damage.[93,94] Treatment of HCV is thought to reduce the risk of development of NHL and may aid in the treatment of some HCV-associated NHLs.[94] The best evidence of a direct relationship between HCV and B-cell NHL is the demonstration of regression of B-cell NHL with anti-HCV therapy with interferon, which has antiproliferative properties.[95] Early reports of the use of interferon-free regimens also suggest benefit.[96–98]

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, after HCC treatment.[8,99] Hepatitis flare occurs in 26% to 45% of HCV-infected cancer patients and can lead to liver dysfunction that necessitates discontinuation or dose reduction of potentially life-saving chemotherapy.[5,100]

Hepatitis flare is defined as an increase in alanine aminotransferase (ALT) level to at least 3 times the upper limit of normal in the absence of liver infiltration by tumor, use of hepatotoxic drugs other than chemotherapeutics,[101] 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[5,100]. 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 confirmatory test for patients with positive anti–HCV antibody testing during screening. Among patients with proven infection (detectable HCV RNA), HCV specialists monitor for hepatitis flare checking ALT level before the initiation of chemotherapy (baseline) and every 2 to 8 weeks during chemotherapy. HCV RNA level is also checked before the initiation of 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 for chemotherapy regimens incorporating rituximab.[5,100] Therefore, because chemotherapy and hematopoietic cell transplant (HCT) are potentially life-saving, 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 hematological malignancies

The highest risks of HCV reactivation, hepatitis flare, and increased rate of liver disease progression have been reported among patients with hematological malignancies. Among HCV-infected patients with hematological 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),[102] hepatitis flare,[102,103] liver decompensation,[104] and fatal fibrosing cholestatic hepatitis C (rare) than patients without HCV.[105] Use of mycophenolate mofetil has been linked to development of fibrosing cholestatic hepatitis C in patients undergoing HCT.[105,106]

HCV reactivation is more common in patients with lymphoma and in patients treated with rituximab than in patients with other types of cancer. HCV reactivation is defined as an increase in HCV RNA level of at least 1 $\log_{10}$ IU/mL over baseline following administration of chemotherapy[5] as chronically infected patients generally have stable HCV RNA levels that vary within 0.5 $\log_{10}$ IU/mL.[107] HCV reactivation due to chemotherapy is less common than HBV reactivation.[108] HCV reactivation is rarely fatal[109]; most patients have an indolent course.[100] HCV reactivation mainly occurs during the weeks of chemotherapy treatment and frequently regresses at cessation of it.[5,100]

Patients with solid tumors

Evidence concerning the potential for HCV reactivation and hepatitis flare in HCV-infected patients receiving chemotherapy is weaker for patients with solid tumors than for patients with hematological malignancies, and is based on only limited published data.[100,110]

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 time 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 the median survival time for HBV-infected patients who developed HCC, 22.3 months.[63] Similar results were found in a nationwide study from France.[111]

To date, there have been no randomized clinical studies directly comparing the impact of cancer therapy in HCV-related and HBV-related HCC. However, subanalyses of the pivotal trials of systemic therapy with sorafenib and local therapy with transarterial chemoembolization have been reported that address the question. The key results, summarized in Supplementary 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.[112]

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 cancer patients is a neglected topic.[6] The objective of HCV screening in cancer patients is to ensure that patients with HCV infection are identified to help prevent the spread of this infection, while also increasing opportunities for preventive care and potentially reducing HCV associated morbidity and mortality in infected patients. They can receive proper care for this infection which could slow liver disease progression,[12,99,113] and give patients access to a maximum of cancer drugs.[11]

In the United States, the Centers for Disease Control and Prevention (CDC) 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 persons with past behaviors, exposures, and conditions associated with an increased risk of HCV infection (e.g., injection-drug use, long-term hemodialysis, prior recipients of transfusions or organ transplants before July 1992, HIV infection, etc.).[15,114,115] Periodic testing is also recommended for persons with ongoing risk factors for exposure to HCV.

The importance of screening the 1945–1965 birth cohort is illustrated in the *Annual Report to the Nation on the Status of Cancer (1975–2012)*, which showed that HCV-associated and liver cancer–associated death rates were highest among persons born during 1945–1965.[116] NCI Surveillance, Epidemiology, and End Results 1975–2013 data show that 50.6% of all new cancers in the United States are diagnosed among people aged 55 to 74 years.[117] In 2017, the baby boomers, who have a high rate of HCV infection, will be in approximately

that age range (aged 52 to 72 years) (gray box, Figure 1), meaning that the number of HCV-infected cancer patients in the United States may peak around this time. Certainly, birth cohort–based HCV screening of new cancer patients would allow the identification of a substantial number of patients but still leave many patients unknowingly infected (Figure 1).

Unfortunately, the large majority of cancer centers in the United States do not even adhere to the birth cohort–based HCV screening recommendation for the general population. Only 14% of patients receiving chemotherapy were screened for HCV at MD Anderson Cancer Center from January 2004 to April 2011.[118] Predictors of HCV screening included not only birth after 1965 and traditional HCV risk factors but also Asian race and rituximab therapy,[118] indicating that decisions about screening for HCV were extrapolated from HBV screening recommendations.[119]

Of interest, a more recent community-based study demonstrated that screening only patients in the 1945–1965 birth cohort would mean missing HCV infection in approximately one-quarter of HCV-infected patients.[120] The risk of such selective screening in a cancer center was illustrated in a 2008–2011 retrospective cohort of adult patients with hematological malignancies. Of the HCV-infected patients, only three-fourths had at least 1 HCV risk factor identified by the oncologists or were born during 1945–1965, meaning that one-quarter of the seropositive cancer patients would have been missed without universal screening.[121] A prospective study from France also found that selective screening using a questionnaire on HCV risk factors had low sensitivity in the identification of HCV-infected patients receiving chemotherapy for solid tumors.[122] As a result of the findings from this study, authors recommended that HCV screening be conducted routinely and systematically in every cancer patient.

For over a decade, universal HCV screening has been standard practice among the hematological services at MD Anderson Cancer Center. Professional societies such as the American Society for Blood and Marrow Transplantation,[7] the European Conference on Infection in Leukemia (ECIL-5), a joint initiative of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT), European Organization for Research and Treatment of Cancer (EORTC), Immunocompromised Host Society (ICHS), and European Leukemia Net (ELN)[9] have generated guidance documents for diagnosis and treatment of HCV infection in patients with hematological malignancies and HCT recipients; universal screening is recommended in this population. In terms of those with solid tumors, all patients with HCC should undergo screening for HCV but the optimal screening strategy for patients with other solid tumors is less clear. One-time HCV screening in cancer patients belonging 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 CDC and the US Preventive Services Task Force (USPSTF) in non-cancer patients.[25,123] A possible approach also to identify such infected cancer patients is combining risk-based and birth cohort–based strategies with education for oncologists.[44] Since 2016, the standard practice at MD Anderson of universal HCV screening in the hematologic patient populations has been expanded to all other cancer patients. 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

those with hematologic malignancies,[106] but also with solid tumors. For instance, viral eradication may normalize transaminases, allowing access to chemotherapeutic agents that would otherwise be contraindicated,[11,106,124] eliminate the risk of developing HCV reactivation that can lead to discontinuation of chemotherapy,[5] prevent liver disease progression,[6] or the development of HCC or NHL as a secondary cancer,[8,10] and allow access to multiple clinical trials of cancer chemotherapies[11,106] (see more details in section *Potential benefits of antiviral therapy*). Exceptions to screening could be patients with contraindications for DAAs (e.g., 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 U.S. Food and Drug Administration has approved 2 methods of diagnosing HCV: serologic assays that detect antibodies are used for screening, and molecular assays that detect HCV RNA (e.g., nucleic acid testing) are used to confirm HCV infection. The specificity of current serologic assays is greater than 99%. Guidelines from the U.S. Public Health Service, Infectious Diseases Society of America, Veterans Affairs Hepatitis C Resource Center Program, and National Hepatitis C Program Office recommend HCV antibody screening in immunocompromised patients, such as those with HIV infection.[125] However, little is known about the optimal approach to diagnosis of HCV infection in cancer patients, particularly those who are immunocompromised, such as patients with hematological 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 cancer patients. 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 antibody to HCV test results after transplant.[13] Therefore, molecular diagnostic methods (e.g., 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.[7,9]

Evaluation and treatment of HCV-infected cancer patients

HCV infection is a supplementary burden in patients with a new diagnosis cancer. HCV-infected cancer patients are at risk for serious adverse effects of cancer treatment, including sinusoidal obstruction syndrome and chemotherapy-associated steatohepatitis resulting from oxaliplatin or irinotecan.[126,127] Ischemic hepatitis, cholangiopathy, impaired liver regeneration, sinusoidal obstruction syndrome, and death during HCT and liver surgery have also been reported in HCV-infected cancer patients.[128,129] Moreover, patients with chronic viral hepatitis are often excluded from cancer trials: approximately 48% of early-phase cancer clinical trials at MD Anderson Cancer Center exclude HCV-infected patients.

New entry into the healthcare system with close follow-up and subsequent lifestyle modifications can improve outcomes of patients with HCV infection.[40] Treatment and eradication of HCV infection with subsequent normalization of liver function tests might also open access to cancer clinical trials to patients originally excluded because of HCV infection.[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.[130] Therefore, evaluation of liver fibrosis in HCV-infected cancer patients is mandatory, regardless of whether or not there is a 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 kPa rules out significant liver fibrosis, whereas a liver stiffness value above 12.5 kPa is very predictive of cirrhosis.[131] Between these thresholds, 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 with a SVR to treatment, and decisions regarding care should not be based on such measurements.[132] Therefore, liver biopsy should remain the standard for diagnosis of cirrhosis in HCV-RNA-negative patients.[133]

The simplest method for classification of patients with HCV infection and cirrhosis is to classify patients according to whether they have compensated or decompensated cirrhosis. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy, and/or jaundice.[134] Median survival is significantly longer in patients with compensated cirrhosis than in those with decompensated cirrhosis (>12 years vs. 2 years).[135] As the outcome of HCV-infected cancer patients with 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 classification of patients with HCV infection and cirrhosis is based on the Child-Pugh score. The score is based on bilirubin and albumin levels, prothrombin time, and the presence or absence of ascites and encephalopathy. Patients with Child-Pugh C disease are usually 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 and tumor and patient characteristics (e.g., 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 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.[136] 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

with compensated cirrhosis to avoid systematic dose reduction that could be associated with poor cancer outcome.

Patients with cirrhosis and portal hypertension are at risk for postoperative hepatic decompensation after liver resection or bleeding due to treatment with an antiangiogenic agent.[137,138] 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 per microliter) or the presence of large varices on preoperative imaging rules out patients with cirrhosis as candidates for major liver resection. Patients with a liver stiffness value of less than 20 kPa with a platelet count of greater than 150,000 per microliter have a very low risk of clinically significant portal hypertension, but whether this holds true among HCV-infected patients with a SVR to treatment has not been validated. [139] The future liver remnant volume after liver resection should always be assessed before surgery by experts in liver volume manipulations.[129]

Patient selection for treatment

Data on treatment of HCV infection in cancer patients are limited, largely because studies of anti-HCV therapy typically exclude patients with cancer. There is currently no standard of care antiviral therapy; however, data are becoming available, and SVR rates seem similar to those observed in HCV-infected patients without cancer.[11] Unlike interferon-based regimens, DAA therapy can be used in cancer patients with bone marrow compromise or cytopenias without dose adjustments or discontinuation. [11,13,103] Our algorithm for treatment of HCV-infected cancer patients is depicted in Figure 2.

Antiviral therapy should be offered to HCV-infected cancer patients except those with contraindications to antiviral therapy, including uncontrolled cancer, comorbidity associated with a life expectancy of less than 12 months, pregnancy or 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.[15,106]

Antiviral therapy could also be contraindicated in HCV-infected cancer patients with Child-Pugh class B or C cirrhosis because incurable extrahepatic malignancy is considered a contraindication to listing for liver transplant,[140] the only available treatment for decompensated cirrhosis.[15,141] In addition, decompensated cirrhosis is a contraindication to DAA therapy in oncologic patients because of an increased risk of lactic acidosis that could be even higher with cancer treatment.[142,143]

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 (details on interactions are provided later in this article). If a HCV-infected

cancer patient is deemed to be a candidate for treatment with DAAs, he or she should receive antiviral therapy according to the guidelines for patients without cancer. [15,115]

To avoid drug-drug interactions and overlapping toxic effects, we recommend starting anti-HCV therapy when the patient is not receiving chemotherapy. However, DAAs can be used concomitantly with selected antineoplastic agents if patients are closely monitored. In selected patients, the concomitant approach could be appropriate to achieve viral clearance and normalization of ALT levels just before initiation of chemotherapy. Simultaneous antiviral and oncologic therapy may also prevent delays in the administration of chemotherapy in HCV-infected cancer patients.[144] In some major cancer centers, HCV-treating physicians (infectious disease specialists and hepatologists), oncologists, and pharmacists work together in the diagnostic work-up, monitoring, and treatment of HCV-infected patients.[14]

In HCV-infected patients without cancer, SVR at 12 weeks has a positive predictive value for SVR at 24 weeks of greater than 97%. However, confirmation of SVR by repeat HCV RNA testing at 24 weeks is still appropriate as late relapses are reported following treatment with DAAs.[145] 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 as DAAs eradicate HCV in most infected patients within 2 to 3 months without viral relapse after cancer therapy.[146]

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.[9,147] 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.[148,149] Most of these reports were from patients with detectable HBV surface antigen (HBsAg), none of them on anti-HBV therapy.[149] Of interest, a few cases of reactivation of HBV infection in HCV-coinfected patients occurred in patients with isolated hepatitis B core antibody,[148,150] even in the absence of immunomodulatory medications.[151] However, on the basis of currently available data, the impact of HBV reactivation in HCV-coinfected patients receiving DAAs appears to be minor.[150,151] Cancer patients with HBV and HCV co-infection 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 HBV reactivation risk.[152] We recommend periodic monitoring of ALT, HBsAg, and HBV DNA according to the guidelines for HBV-monoinfected cancer patients[153] for early detection of hepatitis flare and HBV reactivation in cancer patients with HBV and HCV co-infection receiving DAAs. Recommendations are less clear for cancer patients with isolated hepatitis B core antibody, but close observation is still advised as most of those patients are not routinely given anti-HBV therapy.[152,153]

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, is demonstrated.[40]

Eradication of HCV with interferon-based treatment was associated with a 75% reduction in the risk of liver cancer.[116,154,155]

DAA therapy with close follow-up has been reported to improve liver function in patients with decompensated cirrhosis,[113,156] although there have also been cases of DAA-associated lactic acidosis and sudden hepatic decompensation.[142,143,157] Decompensated cirrhosis is the main cause of death among HCV-infected patients in complete remission of cancer.[99] The benefit of DAA therapy in infected cancer patients 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 cancer patients, 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.[5,100,124,158] HCV eradication might also open access to cancer clinical trials to patients originally excluded because of HCV-associated chronic liver disease.[11]

HCV-infected patients with selected subtypes 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 hematological outcomes with the use of interferon-containing[94] and interferon-free regimens.[97,98] 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,[13,97,98,159] including patients with HCV-associated B-cell NHL undergoing HCT.[6,13] 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.[160]

Furthermore, anti-HCV therapy may reduce the risk of HCC or NHL as second primary cancers[8,10] and improve the oncologic outcomes of patients with selected HCV-related cancers, such as NHL.[13]

Nonrandomized studies of the effect of HCV eradication with DAAs on HCC progression or recurrence have yielded disparate results.[161] 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%).[35] 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,[162] preclude drawing firm conclusions from this study. In another large study from Spain, rates of recurrence of HCC were high and similar to those in previous reports,[163] 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 negative impact on overall survival and recurrence-free survival.[42,164]

Whether the risk of HCC recurrence is increased with DAA therapy is controversial.[35,162] HCC recurrence is closely related to other risk factors, including age at infection, sex, and HCV-associated comorbidities, including HIV and HBV co-infections, alcohol abuse 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.[165–168] Regardless of whether antiviral therapy is ultimately shown to increase the risk of cancer recurrence among HCV-infected cancer patients, the main message is that surveillance for cancer occurrence or recurrence is important among patients with a SVR at risk for liver disease progression. The field awaits prospective trials to determine the merits of DAA therapy in HCV-infected cancer patients as well as the characteristics of patients who will likely to experience cancer progression after DAA therapy, including those who have undergone resection or locoregional therapy for HCC.[164]

Potential interactions between DAAs and chemotherapy, targeted therapy, and supportive care medications

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

To our knowledge, there is only 1 published prospective study of interactions between DAAs and chemotherapy.[144] This study found no significant interactions when DAAs and various chemotherapy agents were administered concomitantly to treat various malignancies. No toxic effects were observed that required discontinuation of either agent. Additionally, 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 DAAs and chemotherapy, clinicians should utilize pharmacodynamic and pharmacokinetic data to guide treatment decisions.

Pharmacodynamic drug interactions result from physiological 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 polypeptides,[169] have known metabolic pathways that may contribute to interactions with DAAs.

DAAs 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 Tables 3 to 6.[170–187] For more detailed information, please refer to www.hep-druginteractions.org, Lexicomp Online (Hudson, Ohio: Lexicomp, Inc.; November 2016) and medication package labeling.

Conclusions

The oncologic burden of HCV infection is twofold. 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 cancer patients. Anti-HCV therapy is associated with viral clearance, improved liver function, and in many cases favorable oncologic outcomes of 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 virologically cured. HCV-infected patients should not be systematically deprived of effective treatment of their cancer, including HCT if indicated, as only a very small proportion of HCV-infected cancer patients have a contraindication to cancer treatment or HCT. The optimal timing of DAA therapy for HCV-infected cancer patients 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)[188] and those with HCV-associated comorbidities, including alcohol use disorder, should be maintained in the healthcare system even if viral eradication is achieved. HCV-infected cancer patients will require specialized care delivered by a multidisciplinary team of HCV-treating physicians, oncologists, and pharmacists who work together towards optimizing patient care and outcomes. However, management of HCV infection in cancer patients should not be limited to tertiary cancer centers. Unmet needs and knowledge gaps with respect to HCV infection in patients with cancer are shown in Table 7.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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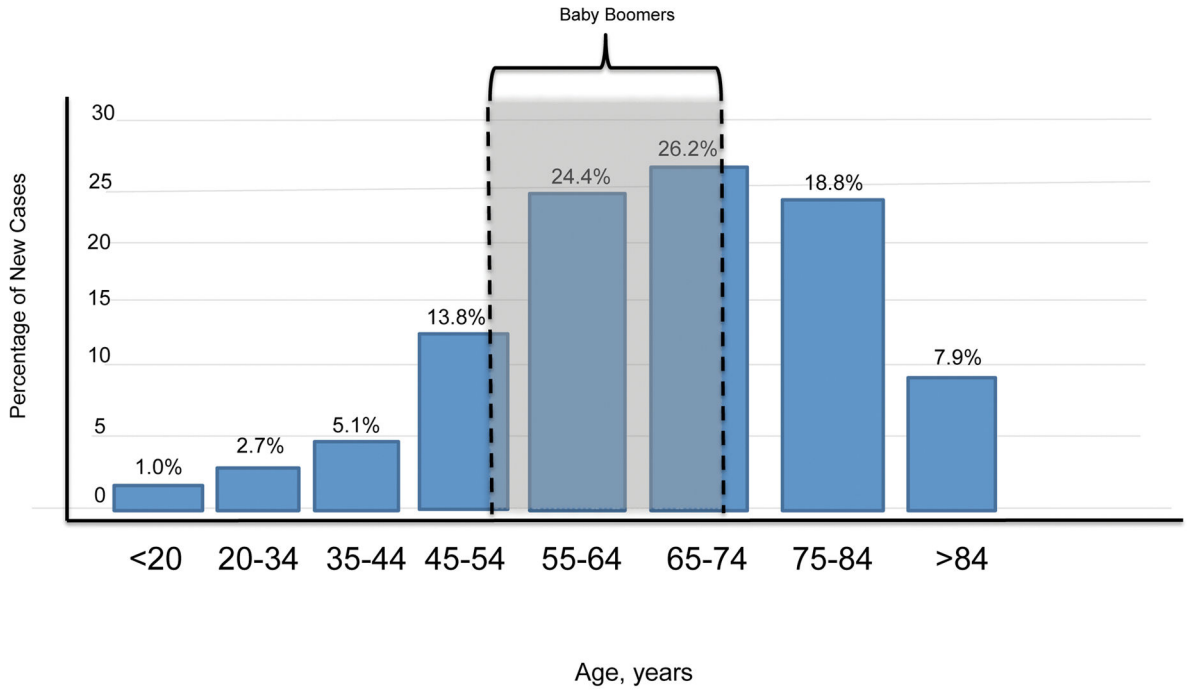

FIGURE 1. Relationship between ages of baby boomers in 2017 and ages at which cancer is most commonly diagnosed

Bar graph shows the percentage of new cancer cases by age at diagnosis (SEER 18 2009–2013, any site, all races, both sexes). In 2017, baby boomers (individuals born in 1945–1965), the targets of birth-cohort-based HCV screening, will be 52 to 72 years old. Birth-cohort-based HCV screening of new cancer patients would identify a substantial proportion of HCV-infected patients but leave many patients with undiagnosed HCV infection.

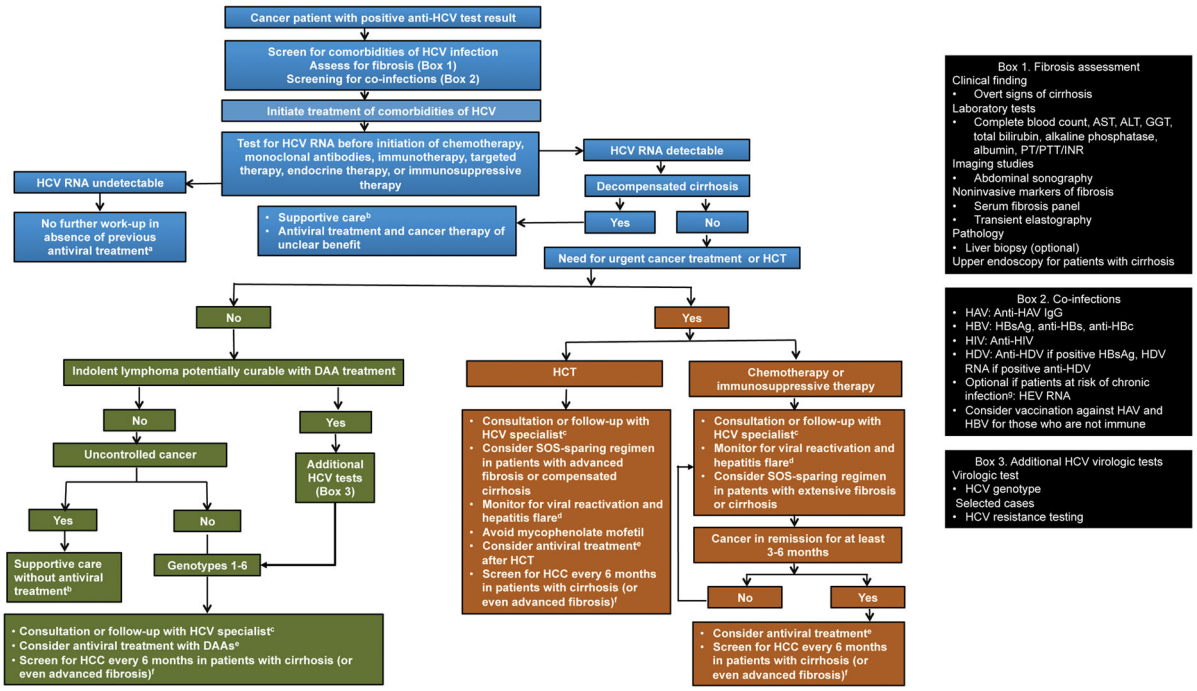

FIGURE 2.

Management algorithm for patients with cancer and HCV infection

TABLE 1

Characteristics of HCV 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 development of 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

DAA, direct-acting antiviral; HCT, hematopoietic cell transplant; HCV, hepatitis C virus

TABLE 2

Summary of evidence on the association between HCV and cancer

Type of cancer	Type(s) of studies[a]	Number of studies analyzed	No. of patients with HCV infection/ total no. of patients[a]	Quality of evidence[b]
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
Waldenström 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	11,613/1,091,516	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

[a] All studies are detailed in Supplementary Table 1.

[b] The quality of evidence was assessed using the GRADE approach.[16] Using 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.

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[a]	Slow oxidative metabolism via unknown mechanism	P-gp and BCRP substrate Inhibits P-gp, BCRP, OATP1B1, OATP1B3, and bile salt export pump
Sofosbuvir-velpatasvir[a]	Hepatic via CYP2B6, CYP2C8, and CYP3A4	P-gp and BCRP substrate Inhibits P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1
Ritonavir-boosted paritaprevir-omibitasvir-dasabuvir[b]	*Ritonavir-boosted paritaprevir* Hepatic via CYP3A4 (primary) and CYP3A5 *Ombitasvir* Hydrolysis *Dasabuvir* Hepatic- via CY2C8 (primary) and CYP2C8	*Ritonavir-boosted paritaprevir* P-gp, BCRP, OATP1B1, and OATP1B3 substrate Inhibits P-gp, BCRP, UGT1A1, OATP1B1, and OATP1B3 *Ombitasvir* P-gp and BCRP substrate Inhibits P-gp, BCRP, and UGT1A1 *Dasabuvir* P-gp and BCRP substrate Inhibits P-gp, BCRP, and UGT1A1
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[c]	Hepatic and intracellular	Inhibits CYP1A2 and IMDH

BCRP, breast cancer resistance protein; CYP, cytochrome P450 enzymatic system; IMDH, inosine monophosphate dehydrogenase; OATP, organic anion transporting polypeptide; P-gp, p-glycoprotein.

[a]Metabolism and transporter effects do not include sofosbuvir; refer to sofosbuvir for information.

[b]Ritonavir has no activity against HCV but is given as a low-dose CYP3A inhibitor to boost paritaprevir concentration.

[c]Ribavirin is often used in combination with DAAs; therefore, it is included to provide a comprehensive overview.

TABLE 4

Major interactions between HCV direct-acting antivirals and standard chemotherapy drugs[a]

Chemotherapy drug	Sofosbuvir	Sofosbuvir-ledipasvir	Sofosbuvir-velpatasvir	Ritonavir-boosted paritaprevir-ombitasvir-dasabuvir	Grazoprevir-elbasvir	Daclatasvir	Simeprevir	Ribavirin[b]
Alkylating agents								
Chlorambucil	◆	◆	◆	◆	◆	◆	◆	◆
Cyclophosphamide	▲	▲	▲	▼	▲	▲	▲	▲
Antifolate								
Methotrexate	◆	◆	■	◆	■	■	◆	■
Antitumor antibiotics								
Doxorubicin	◆	■	■	■	■	■	■	◆
Idarubicin	◆	◆	◆	◆	◆	◆	◆	◆[c]
Cytidine analog								
Gemcitabine	◆	◆	◆	◆	◆	◆	◆	■
5-Fluoropyrimidine								
Capecitabine	◆	◆	◆	◆	◆	◆	◆	■
Microtubule agents								
Docetaxel	▲	▼	▼	▼	▼	▼	▼	▲
Paclitaxel	▲	▼	▼	▼	▼	▼	▼	▲
Platinum analogs								
Carboplatin	◆	◆	◆	◆	◆	◆	◆	◆
Cisplatin	◆	◆	◆	■	◆	◆	◆	◆
Oxaliplatin	◆	◆	◆	■	◆	◆	◆	◆
Purine antimetabolites								
Fludarabine	◆	◆	◆	◆	◆	◆	◆	◆
Mercaptopurine	◆	◆	◆	◆	◆	◆	◆	●[c]
Topoisomerase I/II inhibitors								
Etoposide	◆	◆	◆	■	◆	◆	■	◆
Irinotecan	◆	■	■	■	■	■	■	◆
Topotecan	▲	▲	▼[c]	▲	▼	▼	▲	▲
Vinca alkaloids								
Vinblastine	◆	◆	◆	■	◆	◆	■	◆
Vincristine	◆	◆	◆	■	◆	◆	■	◆
Vinorelbine	◆	■	■	■	■	■	■	◆

[a] Table does not include all chemotherapeutic agents. Drug interactions are based on metabolism and clearance data rather than direct study of co-administration except where otherwise indicated. Symbols used to indicate clinical significance of drug interactions are based on HEP Drug Interactions (www.hep-druginteractions.org; University of Liverpool), Lexicomp Online (Hudson, Ohio: Lexi-Comp, Inc.; 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 websites, medication package inserts, and specific references.[172,173,179]

[b] Ribavirin is often used in combination with DAAs; therefore, it is included to provide a comprehensive drug-drug interaction overview.

[c] Co-administration studied directly.

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 co-administered
▲	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

TABLE 5

Major interactions between HCV direct-acting antivirals and monoclonal antibodies, targeted chemotherapy, and endocrine therapy[a]

Drug	Sofosbuvir	Sofosbuvir-ledipasvir	Sofosbuvir-velpatasvir	Ritonavir-boosted paritaprevir-ombitasvir-dasabuvir	Grazoprevir-elbasvir	Daclatasvir	Simeprevir	Ribavirin[b]
Endocrine agents								
Anastrozole	◆	◆	◆	◆	◆	◆	◆	◆
Exemestane	◆	◆	◆	◆	◆	◆	◆	◆
Letrozole	◆	◆	◆	■	◆	◆	■	◆
Tamoxifen	◆	◆	◆	■	◆	◆	■	◆
HDAC inhibitors								
Vorinostat	▲	▲	▲	▲	▲	▲	▲	▲
Romidepsin	▲	▼	▼	▼	▼	▼	▼	▲
Immunotherapy								
Ipilimumab	◆	◆	◆	◆	◆	◆	◆	◆
Nivolumab	▲	▲	▲	▲	▲	▲	▲	▲
Tocilizumab	▲	▲	▲	▲	▲	▼	▼	▲
Immunomodulators								
Lenalidomide	▲	▼	▼	▼	▼	▼	▼	▲
Thalidomide	◆	◆	◆	◆	◆	◆	◆	❖ *c*
Monoclonal antibodies								
Rituximab	◆	◆	◆	◆	◆	◆	◆	◆
Brentuximab	▲	▲	▲	▲	▲	▲	▲	▲
mTOR kinase inhibitor								
Everolimus	◆	■	■	■	■	■	■	◆
Proteasome inhibitor								
Bortezomib	◆	◆	◆	■	◆	◆	■	◆
TKIs								
Dasatinib	◆	◆	◆	■	◆	■	■	◆
Erlotinib	◆	■	■	●	■	■	■	◆
Gefitinib	◆	◆	◆	■	◆	◆	■	◆
Imatinib	◆	◆	■	■	■	◆	■	❖ *c*
Lapatinib	◆	■	■	■	■	■	■	◆
Nilotinib	◆	◆	■	■	■	■	■	◆
Ponatinib	▲	▲	▼	▼	▼	▲	▼	▲

Drug	Sofosbuvir	Sofosbuvir-ledipasvir	Sofosbuvir-velpatasvir	Ritonavir-boosted paritaprevir-ombitasvir-dasabuvir	Grazoprevir-elbasvir	Daclatasvir	Simeprevir	Ribavirin[b]
Sorafenib	◆	◆	◆	■	◆	◆	■	❖ [c]
Sunitinib	◆	◆	◆	■	◆	◆	■	◆

HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

[a] Drug interactions are based on metabolism and clearance data rather than direct study of co-administration except where otherwise indicated. Symbols used to indicate clinical significance of drug interactions are based on HEP Drug Interactions (www.hep-druginteractions.org; University of Liverpool), Lexicomp Online (Hudson, Ohio: Lexi-Comp, Inc.; 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 websites, medication package inserts, and specific references[170,171,173–175].

[b] Ribavirin is often used in combination with DAAs; therefore, it is included to provide a comprehensive drug-drug interaction overview.

[c] Co-administration studied directly.

Legend

❖	No clear data
◆	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 co-administered
▲	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

TABLE 6

Major interactions between HCV direct-acting antivirals and common supportive care medications in oncology[a]

Medication	Sofosbuvir	Sofosbuvir-ledipasvir	Sofosbuvir-velpatasvir	Ritonavir-boosted paritaprevir-ombitasvir-dasabuvir	Grazoprevir-elbasvir	Daclatasvir	Simeprevir	Ribavirin[b]
Acid-reducing agents								
H2 antagonist	◆	■	■	◆	◆ [c]	◆	◆	◆
Proton pump inhibitor	◆	■	●	■ [c]	◆ [c]	◆	◆ [c]	❖
Anticoagulant								
Apixaban	◆	■	■	●	■	■	■	◆
Dabigatran	◆	■	■	■	■	■	■	◆
Edoxaban	◆	■	◆	■	■	■	■	◆
Rivaroxaban	◆	■	■	●	■	■	■	◆
Warfarin	■ [c]	■ [c]	■ [c]	■ [c]	◆	◆	■ [c]	■ [c]
Antiemetic								
Aprepitant	◆	◆	◆	■	◆	■	■	◆
Antifungals								
Fluconazole	◆	◆	◆	◆	◆	◆	●	❖
Isavuconazole	▲	▲	▲	▼	▲	▲	▼	▲
Posaconazole	◆	◆	◆	●	◆	■	●	❖
Voriconazole	◆	◆	◆	●	◆	■	●	❖
Bisphosphonate								
Pamidronate	◆	◆	◆	◆	◆	◆	◆	◆
Immunosuppressants								
Cyclosporine	◆ [c]	◆	◆	■ [c]	● [c]	◆ [c]	● [c]	❖
Mycophenolate	◆	◆	◆	■	◆ [c]	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	◆	■	❖
Tacrolimus	◆ [c]	◆	◆	■ [c]	■ [c]	◆ [c]	■ [c]	❖
Growth factor								
Eltrombopag	◆	◆	◆	◆	●	■	■	❖
Filgrastim	◆	◆	◆	◆	◆	◆	◆	❖
Steroids								
Dexamethasone	◆	■	◆	■	■	●	●	❖
Methylprednisolone	◆	◆	◆	■	◆	◆	■	❖

Medication	Sofosbuvir	Sofosbuvir-ledipasvir	Sofosbuvir-velpatasvir	Ritonavir-boosted paritaprevir-ombitasvir-dasabuvir	Grazoprevir-elbasvir	Daclatasvir	Simeprevir	Ribavirin[b]
Prednisone	◆	◆	◆	■	◆ [c]	◆	◆	❖

H2, histamine 2 receptor.

[a] Table does not include all supportive care medications in oncology. Drug interactions are based on metabolism and clearance data rather than direct study of co-administration except where otherwise indicated. Symbols used to rank clinical significance of drug interactions are based on HEP Drug Interactions (www.hep-druginteractions.org; University of Liverpool), Lexicomp Online (Hudson, Ohio: Lexi-Comp, Inc.; 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 websites, medication package inserts, and specific references.[176–178,187]

[b] Ribavirin is often used in combination with DAAs; therefore, it is included to provide a comprehensive drug-drug interaction overview.

[c] Co-administration studied directly.

Legend

❖	No clear data
◆	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 co-administered
▲	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

TABLE 7

Unmet clinical and research needs and knowledge gaps on HCV infection in patients with cancer

Optimal screening strategy in cancer patients and HCT recipients
Value of routine HCV screening in cancer centers
Need for systematic cancer screening of HCV-infected cancer patients 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 (e.g., hepatitis B virus, HIV, and human papillomavirus) in HCV-infected cancer patients
Studies on HBV reactivation in cancer patients with HBV and HCV co-infection receiving DAAs
Optimal timing of antiviral therapy in relation to chemotherapy and HCT
Efficacy and safety of various DAA regimens in cancer patients and HCT recipients
Predictors of liver disease progression, even if a SVR is achieved
Reliability of serologic markers of fibrosis and FibroScan VCTE in predicting the presence of advanced fibrosis and cirrhosis in cancer patients and HCT candidates
Inclusion of HCV-infected cancer patients in clinical trials of both cancer treatment and DAAs
Virologic, hepatic and oncologic impact of treating HCV in people with various cancers
Large well-designed prospective studies focused on cancer patients from distinct geographic areas analyzing the impact of geographic variations of HCV genotypes
Characterization of interactions between DAAs and chemotherapeutic agents

DAA, direct-acting antiviral; HBV, hepatitis B virus ; HCT, hematopoietic cell transplant; HCV, hepatitis C virus ; SVR, sustained virologic response; VCTE, vibration-controlled transient elastography