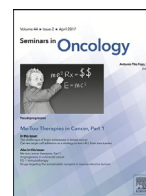




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# Management of hepatitis C positive patients undergoing active treatment for malignancies: A position paper from the Associazione Italiana di Oncologia Medica (AIOM) and the Società Italiana di Malattie Infettive e Tropicali (SIMIT)

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## ABSTRACT

**Purpose:** To develop, on behalf of Associazione Italiana di Oncologia Medica and Società Italiana di Malattie Infettive e Tropicali, evidence-based and practical recommendations for the management of cancer patients who are Hepatitis C virus (HCV)-positive and are undergoing antitumor treatment.

**Methods:** Recommendations were generated by panel of experts selected by the boards of the Societies Associazione Italiana di Oncologia Medica and Società Italiana di Malattie Infettive e Tropicali (4 oncologists and 6 infectious disease and hepatology specialist). The level of evidence and grade or recommendation was assessed according to the Grading of Recommendations Assessment, Development and Evaluation for practice guidelines [5]: A (high), B (moderate), and C (low), together with 2 recommendation levels: 1 (strong), and 2 (weak). Experts provided additional information, which helped greatly in clarifying some issues in the absence of clear-cut information from the literature. The final draft was then submitted to the evaluation of experts and the text modified according to their suggestion and comments.

**Results:** HCV screening rates are low in patients with malignancies. The risk of reactivation or exacerbation of hepatitis C is higher in patients receiving immunosuppressive agents. It may be difficult to discriminate naturally occurring cancer-related complications from true reactivation or exacerbation of hepatitis C and hepatotoxicity due to cancer treatment. No conclusive data are available concerning the appropriate monitoring of liver function and when an antiviral regimen should be proposed.

**Conclusions:** Patients at risk of any flare of HCV-related liver disease during active therapy for cancer should be managed with a multidisciplinary approach where all relevant diagnostic techniques and therapeutic resources are available. Prospective studies are needed to identify optimal strategies for the management of HCV infected cancer patients.

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## Introduction

Hepatitis C virus (HCV) is the leading cause of chronic liver disease and hepatocellular carcinoma (HCC) all over the world; approximately 130–150 million people globally have chronic HCV

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infection [1]. The prevalence of HCV infection increases steadily with age and, at the same time, advancing age is associated with an increased risk of developing solid tumors, other than HCC [2]. Viral hepatitis reactivation or exacerbation during or following chemotherapy for solid tumors has previously been reported: strong evidence has been reported in literature concerning hepatitis B virus reactivation during immunosuppression, whereas HCV reactivation or exacerbation is unusual and little knowledge is available [3].

HCV screening before chemotherapy is uncommon, even among groups at risk.

The spectrum of clinical manifestations during HCV reactivation or exacerbation can range from asymptomatic hepatitis flares to hepatic decompensation, fulminant hepatic failure, and death. Therefore, the identification of patients at risk and the early diagnosis are required to decrease significantly morbidity and mortality.

Since HCV is a hepatotropic and noncytopathogenic virus, viral replication control and liver injury are mainly related to several immune-mediated mechanisms, following a type 1 helper cell response [4]. During active treatment for cancer, the immune response might be suppressed favoring viral replication and the occurrence of potentially fatal complications.

For these reasons, the Associazione Italiana di Oncologia Medica and the Società italiana di Malattie Infettive e Tropicali undertook the present work with the aim to provide practical tools for diagnosis and management of HCV infection in patients undergoing active treatment for malignancies.

## Materials and methods

A web-based search of MEDLINE (PubMed) was performed from 2010 until March 2018 in order to identify pertinent articles. We structured our term search using the following keywords: “hepatitis C reactivation, hepatitis C exacerbation, chemotherapy, solid tumor.”

A total of 48 papers, including recommendations and expert opinions regarding HCV positive patients undergoing antitumor therapy, were evaluated by the authors.

A panel of experts of 4 oncologists and 6 infectious diseases and hepatology specialists was selected by Associazione Italiana di Oncologia Medica and the Società italiana di Malattie Infettive e Tropicali societies. The group was established in order to define the purpose of the consensus. Recommendations were generated according to the Grading of Recommendations Assessment, Development and Evaluation for practice guidelines [5]: A (high), B (moderate), and C (low), together with 2 recommendation levels: 1 (strong), and 2 (weak).

Experts provided additional information suitable to clarify issues in absence of clear-cut evidence from the literature. The final draft was then submitted to the evaluation of experts and modified according to their suggestion and comments.

## Results

### *Who is at risk for reactivation or exacerbation of HCV hepatitis?*

An appropriate HCV screening includes the detection of HCV antibodies and if positive followed by sensitive HCV RNA real-time Polymerase Chain Reaction (PCR) [6]. The rate of HCV screening is usually low; as shown by Hwang et al in their retrospective single-center study of 141,877 patients with cancer, HCV screening was performed in 13.9% patients before chemotherapy [7]. The 1945–1965 birth cohort has the highest incidence of HCV infection and HCV-related disease. Based on this information, the Centers for Disease Control and Prevention recommends HCV testing

for all individuals born between 1945 and 1965 (birth cohort-based screening). Centers for Disease Control and Prevention also recommends HCV screening for all patients presenting risk factors, including intravenous or intranasal drugs users, human immunodeficiency virus infection, patients with hemophilia who received clotting factor concentrates prior to 1987, hemodialysis patients, prisoners, and people who have received tattoos in unregulated settings (risk-based screening) [8]. However, HCV screening should also be considered when a liver disease is suspected.

Identification of HCV genotype is fundamental in order to guide antiviral treatment choice. While we still lack clear algorithms regarding the use of antiviral agents in patients with malignancies, one must consider that new antiviral therapies (direct-acting agents, DAA's) are characterized by low risk of side effects, low drug–drug interactions and treatment regimens that are generally short in duration [9]. For this reason, if a good outcome with prolonged life is anticipated from the planned anticancer treatment DAA's should be considered in patients in whom HCV eradication might offer a tangible advantage.

## Statements

- In patients with malignancies, we recommend risk-based and birth cohort-based HCV screening before anticancer treatment. These patients should be tested for HCV antibodies and, if positive, the infection should be confirmed by sensitive HCV RNA detection (A1).
- HCV screening should be considered also in patients with biochemical or instrumental signs of liver injury (C2).
- Where antiviral treatment is feasible, HCV genotype determination is recommended to select the most appropriate antiviral regimen (C2).

### *How to assess liver disease and the risk of HCC*

A correct diagnosis of chronic hepatitis C consists of detection of both HCV antibodies and HCV RNA in an individual with direct and indirect signs of chronic liver disease or assessment of fibrosis by liver stiffness measurement. The minimal diagnostic work up to detect liver damage or disease includes Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline phosphatase (ALP), Bilirubin, Albumin, total protein, GGT, prothrombin time, and blood cell counts [9]. In patients with liver disorders, current guidelines recommend performing abdominal ultrasound every 6 months, so as to monitor for the development of HCC and to identify indirect signs of portal hypertension including splenomegaly, portal vein enlargement, and the presence of collateral shunts [9]. Alpha fetoprotein testing is not recommended as part of the diagnostic work up. Elevated values have been observed more frequently in patients with chronic Hepatitis B Virus (HBV) than HCV and are rarely found in early HCC. Alpha fetoprotein may have utility for enhancing detection of HCC when used in combination with ultrasound scan in the screening setting of at-risk individuals; however, its role as a single biomarker is limited because of its low sensitivity (25%–30%) [10]. The risk of developing HCC varies widely according to geographic location and most HCCs occur in patients with chronic liver disease or cirrhosis. Patients with compensated cirrhosis are thought to have a 1%–8% annual incidence of HCC [11] and the risk of developing HCC is reduced but not eliminated after HCV eradication [12–13]. Torres et al have shown that among 1,291 cancer patients who had positive test results for HCV, 7% developed HCC as a second primary malignancy [14]. This issue should not be underestimated especially when antitumor treatment is given with a curative intent:

## Statements

- In HCV+ patients with cancer assessment of liver disease severity by performing abdominal ultrasound scan, liver stiffness measurement, and liver function tests (LFTs) should be performed (**A1**).
- Abdominal ultrasound scan should be performed regularly according to guidelines in order to identify the early appearance of HCC (**A1**).

## How to define reactivation or exacerbation of HCV hepatitis

In HCV+ patients, immune suppression might lead to 2 different scenarios: reactivation and exacerbation. While it is established that HCV does not undergo latency, HCV reactivation is defined as the reappearance of disease after a clinically silent period in patients with negative HCV RNA. Typically, reactivation can start from HCV RNA included in cryoglobulin complexes, even in patients who had achieved sustained virological response after antiviral therapy [15]. The pathophysiology of HCV hepatitis reactivation occurs in 3 stages: In the initial stage, chemotherapy suppresses the immune system and allows enhanced HCV replication to occur in hepatic cells. Immune restoration, after the discontinuation of chemotherapy, represents the second stage. In the third stage, liver function recovers (recovery phases) [3,4] whether high levels of HCV RNA and ALT co-exist, depends on the stage [16]. Acute exacerbation is defined as a greater than 3-fold increase in serum level of alanine aminotransferase, and “viral reactivation” as  $\geq 1$  log [10] IU/ml increase of HCV viral load following chemotherapy [17,18]. Clinicians should also discriminate between exacerbation and hepatotoxicity. In chronically infected patients, LFTs can fluctuate while HCV RNA levels may be altered by no more than 0.5 log. On this basis, clinicians usually check LFT at 6-month intervals among patients with stable chronic hepatitis C [18]. Hepatotoxicity is defined by an ALT increase  $> 5.1$  times the value seen in patients with normal baseline transaminases. For patients with elevated baseline aminotransferases, hepatic flare is defined as an ALT increase  $> 3.6$  times the patient’s baseline value [19]. Differentiating between chemotherapy-related hepatotoxicity and liver injury due to HCV exacerbation can be difficult. In the absence of accepted criteria, exacerbation of HCV hepatitis in patients with cancer should be defined by elevation of HCV RNA of more than 1 Log<sub>10</sub> IU/mL with an associated 3-fold increase of ALT, in the absence of tumor infiltration in the liver, recent blood transfusions or the intake of known hepatotoxic drugs [3,4].

## Statements

- Testing LFTs and HCV RNA is recommended before starting active treatment (**A1**).
- In course of anticancer therapy, ALT should be monitored every 4 weeks. If ALT levels rise more than 3 times the normal value, HCV RNA should be closely monitored (every 4 weeks) until 3 months after treatment discontinuation (**B2**).
- Advice from an infectious disease specialist or a hepatologist is mandatory when attempting to differentiate between chemotherapy-related hepatotoxicity and liver injury due to HCV exacerbation (**B1**).

## How to assess the risk

The risk of reactivation or exacerbation also depends upon the anticancer treatment used. Oncologists treating HCV-infected patients should be aware of the immune suppressive properties of each agent used and correlate it with reactivation or exacerbation

of viral hepatitis. Rituximab-containing regimens may cause reactivation of many viral diseases; with data from some studies showing that during and after chemotherapy with rituximab, HCV RNA viral load gradually increases with or without a clearly measurable increase in LFTs [3]. Thus, anti-HCV treatment should be considered before rituximab therapy. In small studies, HCV genotype 2 is found to be a risk factor for acute exacerbation in patients with B-cell lymphoma who received rituximab-containing regimens [20]. Acute exacerbation of liver diseases occurred in 11% (33 of 308 patients) with proven HCV infection and risk factors for this occurrence were the presence of hematological malignancies and cumulative dose of rituximab [20]. In a recent study, rituximab (odds ratio 9.52), and high-dose steroids (odds ratio 5.05) were independent predictors of reactivation in patients with hematologic malignancies or solid tumors [21].

Alemtuzumab therapy causes deep B and T immunosuppression and, even if the data are insufficient to make statements about the association of therapy and flare of HCV-related liver disease, clinicians should closely monitor LFTs and HCV RNA levels. Brentuximab has effects on antibody dependent cellular toxicity and may decrease humoral immunity. Thus, during brentuximab treatment of HCV infected patients, flare of HCV-related liver disease may occur [3].

Tyrosine kinase inhibitors do not seem to cause reactivation or exacerbation of hepatitis C [3]. However, as in the case of HBV reactivation in infected patients undergoing imatinib therapy, clinicians should be alert and carefully follow liver function alterations.

Anti-HER2 and anti-EGFR therapies can be given safely in HCV infected patients. Cetuximab and panitumumab have not been associated with reactivation or exacerbation of HCV hepatitis [3].

Given the risk of triggering exacerbations of chronic viral infections, clinical trials (including regulatory studies) evaluating checkpoint-blocking antibodies have excluded patients with chronic hepatitis B/C virus. However, recent reports have shown that ipilimumab or pembrolizumab did not cause any flare of HCV-related liver disease in melanoma patients [3,22]. Furthermore, nivolumab proved to be effective in reducing viral load in chronic HCV infection [23].

Corticosteroids have been strongly associated with flare of HCV-related liver disease caused by hepatitis C [21]; often corticosteroids are administered in combination with chemotherapeutic agents having immunosuppressive properties, such as alkylating agents and antimetabolites [24,25].

Although, few data are available and mainly derive from case reports or small case series, patients treated with chemotherapy, especially when combined with corticosteroids, appear to have a higher risk of flare of HCV-related liver disease due to hepatitis C [9]. Doses and specific combinations of chemotherapeutic agents may well be crucial issues in defining the risk of reactivation or exacerbation of HCV hepatitis.

Miura et al performed a retrospective survey of 1,110 patients screened for HCV serology at diagnosis of breast cancer. HCV-infected patients, who received conventional doses of anthracyclines and taxane with or without trastuzumab, did not experience elevation of transaminases or significant change in HCV viral load [2].

## Statements

- The risk of flare of HCV-related liver disease is very high in cancer patients treated with targeted immunosuppressive therapy and/or receiving chronic corticosteroids (**B2**).
- The risk of flare of HCV-related liver disease is high in patients treated with chemotherapeutic agents with immunosuppressive potential alone or in combination, especially when steroids are included in treatment schedules (**C1**).

**Table 1**

This table summarizes what, at present, can be reasonably recommended in this setting.

Risk-based and birth cohort-based HCV screening, followed by HCV RNA tests in positive subjects, has to be performed before initiating active cancer treatment.  
 Occurrence of HCC as secondary neoplasm has to be taken into consideration when treating HCV+ cancer patients with good prognosis.  
 Monitoring of ALT (every 3–4 weeks) is necessary. If ALT levels raise more than 3 times the normal value, HCV RNA should be closely monitored for 3 months following treatment discontinuation.  
 The risk of reactivation of hepatitis C is higher in patients receiving immunosuppressive drugs including rituximab, alemtuzumab, steroids, and certain chemotherapeutic agents. In course of targeted therapies, including check point inhibitors, clinicians should be conscious of the potential, in the absence of clear cut data, for immunosuppressive properties of these agents.  
 In patients at high risk of reactivation of hepatitis C, treatment with direct-acting antiviral agents for HCV is recommended, especially when anticancer therapy is administered with a curative intent.  
 When reactivation of hepatitis C is diagnosed, the decision to proceed with active anticancer therapy and/or initiating antiviral agents should be based on a discussion of prognosis and therapy options for both conditions.  
 Collaboration with a hepatologist or an infectious disease specialist is recommended in the management of HCV+ cancer patients.

- Tyrosine kinase inhibitors, anti-EGFR and anti-HER2 monoclonal antibodies, the latter also given in combination with conventional chemotherapy for breast cancer, do not increase the risk of reactivation or exacerbation of hepatitis C (**B1**).
- Thus far checkpoint inhibitors have not seemed to impact or lead to a flare of HCV-related liver disease (**B2**).

#### *How to manage patients with reactivation or exacerbation of HCV hepatitis*

Upon diagnosing any kind of flare of HCV-related liver disease, the decision to proceed with active anticancer therapy should be based on a discussion of prognosis and therapy options for both conditions. Frailty scores should be compiled to optimally adapt cancer treatments in these patients. Patients should be informed about the risk of any treatment, which may impact liver function [26]. Antiviral treatment for HCV infection is rapidly evolving; a number of DAAs have been approved by the Food and Drug Administration [8]. Current guidelines regarding antiviral treatment for HCV infection prior to or during chemotherapy or targeted therapies are lacking. Therefore, studies designed to define which patients are most likely to benefit from simultaneous antiviral therapy are needed [16]. It should be emphasized that drug interactions are possible with HCV DAAs; the mechanisms of these drug interaction may include alterations in the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion of a co-administrated drug. As data accumulate, guidance for contra-indications and dose adjustments can be found at [www.hep-druginteractions.org](http://www.hep-druginteractions.org) where they are regularly updated [9].

#### *Statements*

- Patients at risk of reactivation or exacerbation of HCV hepatitis, who require full doses of antitumor drugs, should be considered for concomitant therapy with DAA. Since this approach requires caution due to the potential interactions between drugs, it should be conducted in close collaboration with an infectious disease specialist or a hepatologist (**C2**).
- Where drug interaction is observed, the interacting co-medication (antiviral v antitumor agent) should be switched to an alternative drug regimen, if this is possible (**B1**).
- Another reasonable strategy could be the use of lower doses of immunosuppressive anticancer agents when the patient is treated without curative intent (**C2**).

#### **Discussion**

Although cancer patients are infrequently screened for hepatitis C such screening should be implemented to avoid potential complications during the course of treatment. The potential risk of HCC

as a secondary neoplasm should be regularly monitored, especially when antitumor treatment is given with curative intent (Table 1). Our analysis of the data has shown that we need to develop a consensus on a standardized definition of reactivation and exacerbation of HCV hepatitis and its severity, as many studies have used arbitrary criteria for defining it. This is important also in view of the difficulties in separating naturally occurring disease exacerbations from true reactivation of hepatitis C and hepatotoxicity due to anticancer therapy. Another pressing issue in this field is how to best manage cancer patients with reactivation of hepatitis C in the era of DAA, taking into account the cost-benefits of such extremely expensive drugs. In conclusion, we need prospective studies to identify optimal algorithms for screening, diagnosis, and treatment of patients who are HCV+ and who require active therapy for cancer.

#### **Conflicts of interest**

Raffaele Bruno: Honoraria for speaking or consultation: Gilead Sciences, MSD, Abbvie, BMS.

Carmine Pinto: Honoraria for speaking or Advisory Board: BMS, Bayer, Astra-Zeneca, Lilly, Servier.

Giovanni Battista Gaeta : Speaker and Advisor: Abbvie; BMS; Gilead; Merck; BioTest. Research grant: Abbvie; Gilead.

Massimo Puoti: Receipt of grants/research supports: ViiV, Gilead Sciences Receipt of honoraria or consultation fees: ViiV, Gilead Sciences, MSD, Abbvie, BMS, Roche, Beckman Coulter.

Gloria Taliani: Honoraria for speaking or consultation: Gilead Sciences, MSD, Abbvie, BMS. Travel grant: MSD, Gilead Sciences, Abbvie.

Paolo Pedrazzoli: Honoraria for speaking or Advisory Board: Baxter, Lilly.

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#### **Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:[10.1053/j.seminoncol.2018.07.004](https://doi.org/10.1053/j.seminoncol.2018.07.004).

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