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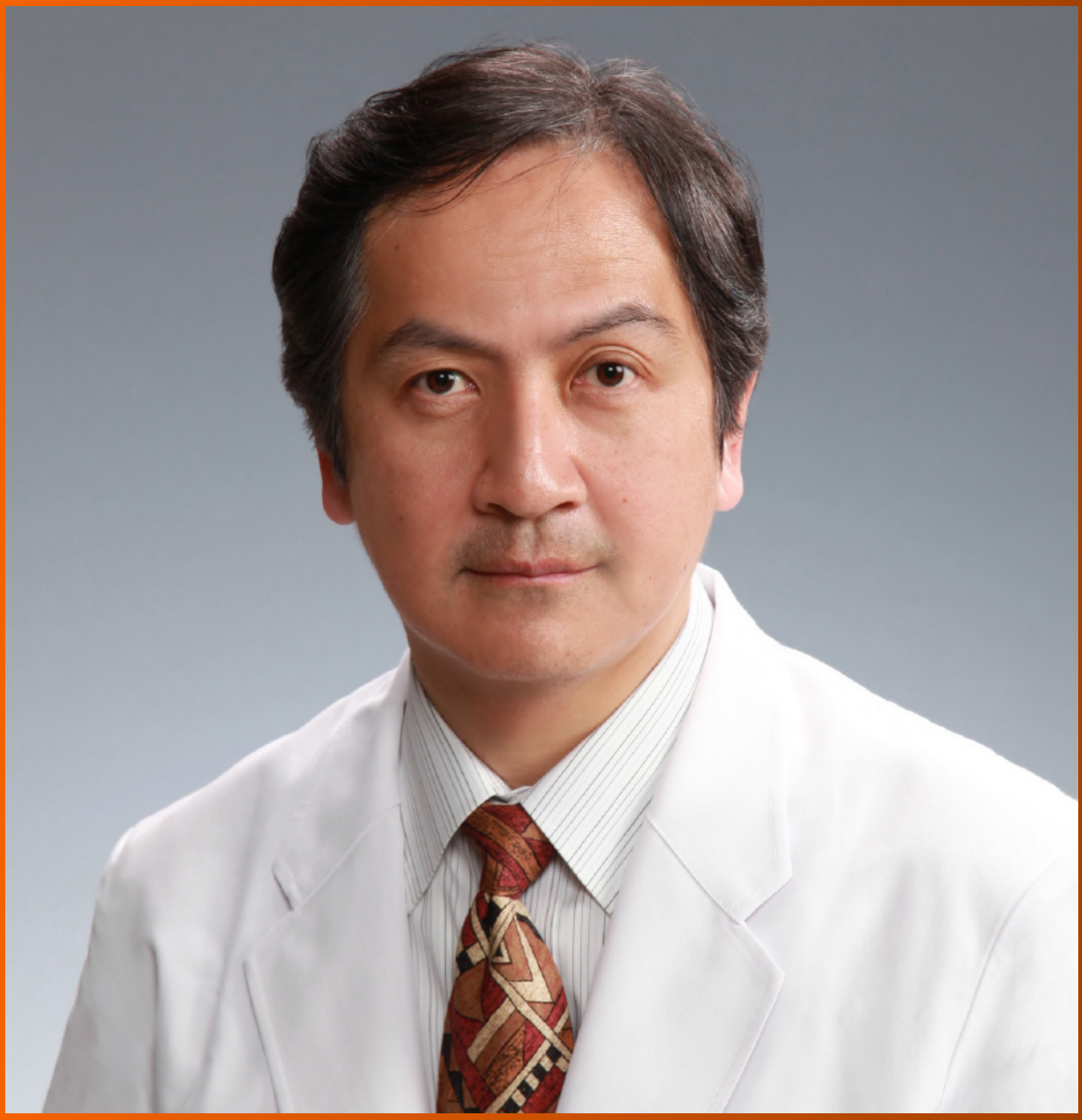

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MINIREVIEWS

Screening and prevention of hepatitis C virus reactivation during chemotherapy

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Abstract

Hepatitis C virus (HCV) reactivation occurs in 23% of HCV-infected cancer patients receiving chemotherapy. Forty-three percent of the patients with reactivation of HCV during chemotherapy develop a hepatitis flare. Most of the cancer patients with HCV reactivation have an unremarkable clinical course following an HCV-related hepatitis flare during chemotherapy. However, 26%–57% of the cancer patients developing an acute flare of chronic hepatitis C during chemotherapy require unanticipated discontinuation or dose reduction of chemotherapy, which results in deleterious changes in the cancer treatment plan. Although an optimal strategy for HCV screening in cancer patients receiving chemotherapy has not been established, universal pre-chemotherapy HCV testing for patients with hematological malignancies is recommended by current guidelines. All the currently approved direct-acting antivirals (DAAs) can be used in cancer patients, but the use of DAAs during chemotherapy should avoid drug–drug interactions between chemotherapy and antiviral agents. If there are no contraindications or anticipated drug–drug interactions, DAAs treatment can be administered before, during, or after chemotherapy. In conclusion, HCV reactivation occurs in approximately one-fourth of HCV-infected cancer patients receiving chemotherapy. An HCV-related hepatitis flare during chemotherapy may lead to the discontinuation of potentially life-saving chemotherapy.

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Currently, universal HCV screening is recommended in hematological malignancy patients before chemotherapy, but there is no evidence-based guideline for other cancer patients. DAAs treatment can cure HCV infection and prevent HCV reactivation during chemotherapy.

Key Words: Hepatitis C virus; Chemotherapy; Screening; Reactivation; Hepatitis flare

Core Tip: Hepatitis C virus (HCV) reactivation occurs in approximately one-fourth of HCV-infected cancer patients receiving chemotherapy. An HCV-related hepatitis flare during chemotherapy may lead to the discontinuation of potentially life-saving chemotherapy. Currently, universal HCV screening is recommended in hematological malignancy patients before chemotherapy, but there is no evidence-based guideline for other cancer patients. direct-acting antivirals treatment can cure HCV infection and prevent HCV reactivation during chemotherapy.

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INTRODUCTION

Hepatitis C virus (HCV) infection affects millions of people worldwide and is a significant burden for cancer patients[1,2]. The prevalence of chronic HCV infection among cancer patients in the United States ranges from 1.5% to 10.6%[3]. A recent study with universal pre-chemotherapy screening of HCV infection by testing for anti-HCV antibody showed that the prevalence of HCV infection in cancer patients receiving chemotherapy was 6.0% (337/5601) in Taiwan[4]. Chemotherapy can lead to immunosuppression and reactivate quiescent HCV infection in cancer patients[5-13]. The acute flare of HCV infection may result in deleterious changes in the cancer treatment plan and has a negative impact on the treatment outcome of cancer patients. Currently, evidence-based guidelines for HCV screening and treatment in cancer patients undergoing chemotherapy have not been established because data on the efficacy of pre-chemotherapy HCV testing and treatment are very limited. In this article, we review the incidence of HCV reactivation during chemotherapy and the outcome of HCV-related hepatitis flare in cancer patients receiving chemotherapy. Additionally, the recommendations for the pre-chemotherapy HCV screening and the prevention of HCV reactivation during chemotherapy are also reviewed.

DEFINITION OF QUIESCENT HCV INFECTION, HCV REACTIVATION AND HCV-RELATED HEPATITIS FLARE IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

This article summarizes current evidences dealing with HCV reactivation and HCV-related hepatitis flare in cancer patients receiving chemotherapy. It is worthy to note that the definitions of HCV reactivation and hepatitis flare during chemotherapy varied in previous studies[4,14-22]. In this review article, we list the definitions of HCV reactivation and HCV-related hepatitis flare in each study quoted in the Tables. The definitions of HCV reactivation and HCV-related hepatitis flare recommended by authors are summarized in Table 1. Recommended HCV reactivation during chemotherapy is increase in HCV-RNA level of ≥ 1 Log_{10} IU/mL over baseline[17], and recommended definition of HCV-related hepatitis flare is unexplained increase in alanine aminotransferase (ALT) to 3 times the upper limit of normal during chemotherapy and increase in HCV-RNA level of ≥ 1 Log_{10} IU/mL over baseline[18]. Most retrospective works lacked the data of HCV viral load before chemotherapy. The

Table 1 Recommended definitions of quiescent hepatitis C virus infection, hepatitis C virus reactivation and hepatitis C virus-related hepatitis flare in cancer patients receiving chemotherapy

Term	Definition	Ref.
Quiescent HCV infection	An HCV infection with a positive serum HCV-RNA and normal serum levels of liver enzymes	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 59[30]
HCV reactivation	Increase in HCV-RNA level during chemotherapy of ≥ 1 $\log_{10}$ IU/mL over baseline	Talima *et al*[17]
HCV-related hepatitis flare	Unexplained increase in ALT to 3 times the upper limit of normal during chemotherapy and increase in HCV-RNA level of ≥ 1 $\log_{10}$ IU/mL over baseline	Torres *et al*[18]

IARC: International Agency for Research on Cancer; HCV: Hepatitis C virus.

scientific strengths of these retrospective evidences were therefore not robust.

INCIDENCE OF HCV REACTIVATION IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

In a retrospective observation study by Lee *et al*[16], enhanced replication of HCV (increase in HCV-RNA level of ≥ 1 Log_{10} IU/mL over baseline) was noted in 9 (27%) of 33 HCV-infected cancer patients who underwent chemotherapy. Another retrospective study by Talima *et al*[17] demonstrated that the incidence of HCV reactivation (increase in HCV-RNA level of ≥ 1 Log_{10} IU/mL over baseline) in 34 HCV-infected breast cancer patients receiving chemotherapy was 6% (2/34). In a prospective observation study by Torres *et al*[18], reactivation of HCV infection (increase in HCV-RNA level of ≥ 1 Log_{10} IU/mL over baseline) occurred in 23 (23%) of 100 cancer patients undergoing chemotherapy. Among these cancer patients, those with hematological malignancies had a higher incidence of HCV reactivation than those with solid tumors (36% *vs* 10%).

INCIDENCE OF HCV-RELATED HEPATITIS FLARE IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

HCV-related hepatitis flare is a significant burden for cancer patients undergoing chemotherapy[6,19-20]. Table 2 displays the incidence of HCV-related hepatitis flare in cancer patients receiving chemotherapy. In a retrospective observation study by Li *et al*[4], universal pre-chemotherapy screening of HCV infection by testing for anti-HCV antibody was conducted in 5601 cancer patients undergoing chemotherapy. HCV-infected cancer patients had a higher incidence of severe acute liver injury (serum ALT increases beyond 10 times the upper limit of normal during chemotherapy or 6 mo following chemotherapy) than those without HCV infection (2.3% *vs* 0.7%). Among the HCV-infected patients who did not have chronic HBV infection, the incidences of severe liver injury in those with hematological malignancy, hepatocellular carcinoma (HCC) and non-HCC solid tumors were 9.4% (3/32), 1.9% (2/105), and 1.2% (2/169), respectively. In this study, the incidence of severe acute liver injury in HCV-infected hematological cancer patients was higher than that in those with HCC patients and non-HCC solid tumor patients (9.4% *vs* 1.9 % and 1.1%, respectively). Rituximab-containing chemotherapy and hematological malignancy were identified risk factors related to severe acute exacerbation of HCV infection in cancer patients undergoing chemotherapy. In another retrospective study by Mahale *et al*[5], the incidence of acute exacerbation of HCV infection (3-fold or greater increase in serum ALT level) during chemotherapy was 23% in 104 patients with hematological malignancy and 4% in 204 patients with solid tumors. The former also had a higher incidence of HCV-related acute exacerbation than the latter. In a prospective observation study at MD Anderson Cancer Center[18], reactivation of HCV infection occurred in 23% of 100 cancer patients receiving chemotherapy. Among those with HCV reactivation, 10 patients (43%) developed a hepatitis flare (unexplained increase in ALT to 3 times the upper limit of normal). Overall, the incidence of HCV-related hepatitis flare in cancer patients receiving chemotherapy was 10% in this prospective study.

Table 2 Incidence of hepatitis C virus-related hepatitis flare in cancer patients receiving chemotherapy

Ref.	Study type	Cancer type	Results
Torres *et al* [18]	Prospective observation study	Hematological tumor (n = 50)	A hepatitis flare occurred in 10% of HCV-infected cancer patients receiving chemotherapy
		Non-HCC solid tumor (n = 50)	Definition of HCV-related hepatitis flare: unexplained increase in ALT to 3 times the upper limit of normal and increase in HCV-RNA level of ≥ 1 $\log_{10}$ IU/mL over baseline
Li *et al*[4]	Retrospective observation study	Hematological tumor (n = 569); HCC (n = 256); Non-HCC solid tumor (n = 3900)	The incidence of severe acute liver injury in HCV-infected hematological cancer patients was higher than that in those with HCC patients and non-HCC solid tumor patients (9.4% *vs* 1.9 % and 1.1%, respectively). Definition of severe acute liver injury: ALT increased beyond 10 times the upper limit of normal during chemotherapy or 6 months following chemotherapy
Tomizawa *et al*[28]	Retrospective observation study	Colorectal cancer (n = 24)	The incidence of severe acute exacerbation rate in HCV-infected patients was 8%. Definition of severe acute exacerbation: ALT increased beyond 5 times the upper limit of normal
Hsu *et al* [22]	Retrospective observation study	Hematological tumor (n = 104); Solid tumor (n = 204)	The incidence of HCV acute exacerbation was 11% (hematological tumor: 23%; solid tumor: 4.4%). Definition of HCV acute exacerbation: 3-fold or greater increase in serum ALT level

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; ALT: Alanine aminotransferase.

CLINICAL OUTCOME OF HCV-RELATED HEPATITIS FLARE DURING CHEMOTHERAPY

Most of the cancer patients with HCV reactivation have an unremarkable clinical course following HCV flare during chemotherapy. In a prospective observation study by Fujii *et al*[6], 6 (28.6%) of 21 Leukemia patients with HCV-related hepatitis flare during chemotherapy developed hepatic decompensation (Table 3). Another prospective observation study by Torres *et al*[18] showed that none of 23 cancer patients (hematological malignancy: n = 18; solid tumor: n = 5) with HCV-related hepatitis flare during chemotherapy developed liver decompensation or mortality. In a retrospective study including 33 hematological cancer patients with HCV-related hepatitis flare, the incidence of hepatic decompensation was also 0%[7]. Although most of the cancer patients with HCV reactivation or hepatitis flare during chemotherapy have a benign clinical course, a significant number of patients with severe flare of HCV infection have to discontinue potentially life-saving chemotherapy. Currently, there are no randomized controlled trials comparing the outcomes of the patients with chemotherapy-related HCV reactivation who stop chemotherapy and who go on cancer treatment. Therefore, whether chemotherapy should be stopped in cancer patients with HCV reactivation remains unclear. Nonetheless, physicians often discontinue chemotherapy in HCV-infected cancer patients who develop severe liver dysfunction during cancer treatment because it is a life-threatening condition and can be induced by either chemotherapeutic drugs or viral reactivation.

In a retrospective study by Li *et al*[4], four of seven patients (57.1%) with HCV-related severe acute liver injury discontinued chemotherapy due to hepatitis flare. In a prospective study by Torress *et al*[18], 6 of 23 HCV-infected patients (26%) with hepatitis flare required unanticipated discontinuation or dose reduction of chemotherapy. Since interruption of chemotherapy in cancer patients would result in deleterious changes in the cancer treatment plan and has a negative impact on patient outcome, the aforementioned findings support the identification and treatment of chronic HCV infection to prevent HCV reactivation and hepatitis flare.

PRE-CHEMOTHERAPY HCV SCREENING IN CANCER PATIENTS

A standard strategy for HCV screening in cancer patients before chemotherapy has not been established. However, a retrospective study by Hosry *et al*[21] demonstrated that early diagnosis of HCV infection with virological cure improved the outcomes of cancer and survival of HCV-infected patients who developed non-Hodgkin lymphoma. To improve pre-chemotherapy HBV and HCV testing, Hsu *et al*[22] developed a computerized order entry-based therapeutic control system (e-CONTROL) to notify healthcare providers in a medical center in Taiwan for pre-

Table 3 Clinical outcomes of hepatitis C virus-related hepatitis flare during chemotherapy

Ref.	Study type	Cancer type	Liver decompensation	Interruption of chemotherapy	Mortality due to HCV reactivation
Torres *et al*[18]	Prospective observation study	Hematological tumor (n = 18) Solid tumor (n = 5)	Total: 0%	Total: 26%	Total: 0%
Fujii *et al*[6]	Prospective study	Leukemia (n = 21)	Total: 28.6%	–	–
Li *et al*[4]	Retrospective observation study	Hematological tumor (n = 3) HCC (n = 2) Non-HCC solid tumor (n = 2)	Total: 0% (Hematological tumor: 0%; HCC: 0%; Non-HCC solid tumor: 0%)	Total: 57% (Hematological tumor: 67%; HCC: 50%; solid tumor: 50%)	Total: 0% (Hematological tumor: 0%; HCC: 0%; Non-HCC solid tumor: 0%)
Lee *et al*[16]	Retrospective study	Hematological tumor (n = 14) Solid tumor (n = 11)	Total: 0%	Total: 32%	Total: 0%
Mahale *et al*[5]	Retrospective study	Hematological tumor (n = 24) Solid tumor (n = 9)	Total: 0%	Total: 45%	Total: 0%
Zuckerman *et al*[7]	Retrospective study	Hematological tumor (n = 33)	Total: 0%	–	Total: 0%

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

chemotherapy HBV and HCV testing. The e-CONTROL system achieved a pre-chemotherapy HCV screening rate of 97.7% (5601/5735). The HCV screening rate in cancer patients receiving chemotherapy is low in the United States. According to an observation study at MD Anderson Cancer Center, the HCV screening rate in cancer patients receiving chemotherapy was only 13.9%[23]. Currently, an optimal strategy for HCV screening in cancer patients receiving chemotherapy has not been established. Figure 1 illustrates current recommendations for testing and treating HCV infection in cancer patients receiving chemotherapy[24,25,29]. The 5th European Conference on Infections in Leukemia recommended that all patients with hematological malignancy be screened for hepatotropic viruses (HBV and HCV) before cancer treatment[24]. The European Association for the Study of the Liver (ESAL) recommends that all patients with malignancy should be screened for HCV infection before cancer treatment due to HCV reactivation possibility after treatment[25].

Anti-HCV antibody is a recommended tool for initial screening of HCV infection in cancer patients receiving chemotherapy because of its cheap and cost-effective advantages. However, the disadvantage of screening HCV infection by serum anti-HCV antibody is a positive result indicating either current or past HCV infection. Therefore, cancer patients with a positive result of anti-HCV antibody should be further tested for serum HCV RNA to confirm current infection status of HCV (Figure 1). In clinical practice, serum HCV RNA is not recommended as a routine screening tool for HCV infection in cancer patients because it is an expensive diagnostic method.

TREATMENT OF HCV INFECTION IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

All the currently approved direct-acting antiviral (DAA) agents can be applied in cancer patients, but the use of DAA treatment during chemotherapy should avoid drug–drug interactions between chemotherapy agents and antivirals (Figure 1). The initiation of DAA treatment in HCV-infected cancer patients undergoing chemotherapy should be individualized and determined by the cancer treatment plan. Contraindications to DAA treatment in HCV-infected cancer patients include (1)

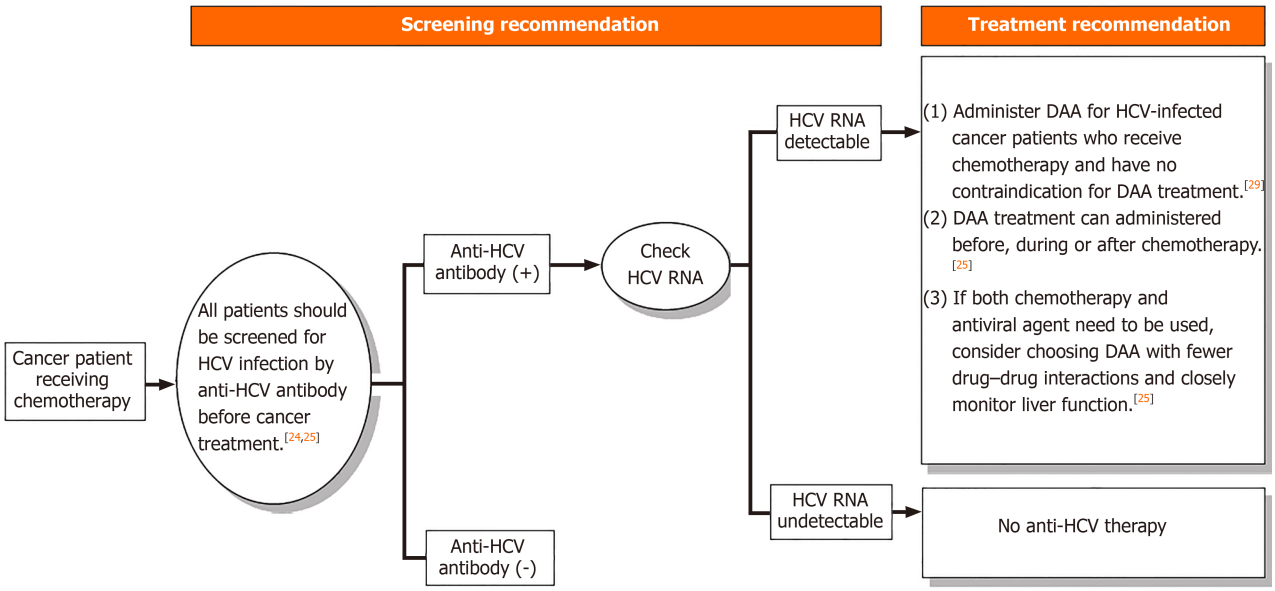

Figure 1 Current recommendations for testing and treating hepatitis C virus infection in cancer patients receiving chemotherapy. HCV: Hepatitis C virus; DAA: Direct-acting antiviral.

Pregnancy; (2) Uncontrolled cancer; (3) Patients with a life expectancy of < 12 mo that cannot be remediated by cancer treatment; (4) Hypersensitivity or intolerance to DAAs; and (5) Anticipated major drug–drug interactions with cancer treatment. If there are no contraindications or anticipated drug–drug interactions, DAA treatment can be administered before, during or after chemotherapy.

The use of DAAs for HCV infection in infected cancer patients receiving chemotherapy may increase the risk of drug–drug interactions. Physicians can identify potentially significant interactions between DAAs and chemotherapy agents based on information obtained from current databases (http://hepdruginteractions.org) and then choose adequate DAAs for HCV treatment or alter the regimen of chemotherapy to avoid drug-drug interactions. In general, treatment for HCV infection in cancer patients receiving chemotherapy by sofosbuvir/Ledipasvir or glecaprevir/pibrentasvir is safe and effective[26]. A prospective observation study from MD Anderson Cancer Center showed that the cure rate of HCV infection by sofosbuvir-based therapy in HCV-infected cancer patients was 91%[27].

CONCLUSION

In conclusion, chemotherapy can lead to immunosuppression and reactivate quiescent HCV infection. Most of the cancer patients with HCV reactivation have an unremarkable clinical course following HCV hepatitis flare during chemotherapy. However, 26%–57% of the cancer patients developing acute exacerbation of chronic hepatitis C during chemotherapy require unanticipated discontinuation or dose reduction of chemotherapy. Currently, the optimal strategy for HCV screening in cancer patients receiving chemotherapy has not been established. Nonetheless, the ESAL recommends that all patients with malignancy should be screened for HCV before cancer treatment due to HCV reactivation possibility after treatment. Currently, universal HCV screening is recommended in hematological malignancy patients before chemotherapy, but there is no evidence-based guideline for other cancer patients. Administration of DAAs can cure HCV infection and prevent HCV reactivation during chemotherapy.

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