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Safety of Direct Acting Antiviral treatment for hepatitis C in oncologic setting: a clinical experience and a literature review.

Anna Maria Spera

Abstract

Introduction: With a globally estimated 58 million people affected by, chronic HCV infection still represents a hard challenge for scientific community. A chronic course can occur among patients with a weak innate ad adaptive response with cirrhosis and malignancies as main consequences.

Oncologic patients undergoing chemotherapy represent a special immunocompromised population predisposed to HCV reactivation (HCVr) with undesirable changes in cancer treatment and outcome.

Aim of the study: highlight the possibility of HCVr in oncologic population eligible to chemotherapy and its threatening consequences on cancer treatment; underline the importance of HCV screening before oncologic therapy and the utility of direct aging antivirals (DAAs).

Material and methods: A comprehensive overview of scientific literature has been made. Terms searched in PubMed were: “HCV reactivation in oncologic setting” “HCV screening”, “second generation DAAs”.

Results: Pharmacokinetic and Pharmacodynamics characteristics of DAAs are reported, along with drug - drug interactions among chemotherapeutic drug classes regimens

and DAAs. Clinical trials conducted among oncologic adults with HCV infection eligible to both chemotherapy and DAAs were analyzed.

Conclusion: Viral eradication with DAAs in oncologic patients affected by HCV infection is safe and helps liver recovery, allowing the initiation of cancer treatment no compromising its course and success.

INTRODUCTION

Hepatitis C is a viral infection due to a single-stranded RNA enveloped virus, with a mainly hepatic trophism. Eight genotypes of HCV along with several different subtypes have been identified [1, 2]. Since its discovery, in 1989, 184 million patients with hepatitis C have been reported worldwide [3], and 40% of hepatic transplantations performed until 2009 were due to HCV-based liver cirrhosis [1]. According to the WHO, an estimated 58 million people worldwide live with chronic hepatitis C virus infection in 2021, with approximately 1.5 million new infections occurring per year, and approximately 400000 people died from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma, in 2019 [3].

Biological course of HCV infection: The interplay between viral replication and a patient's immune response determines the biological course of HCV infection [4], considering that viral immune tropism secondary to hepatocyteinfection activates the innate and adaptive immune systems.

The typical outcome of primary infection in immunocompetent subjects is a self-limited illness with spontaneous resolution after an acute phase, characterized by host-protective antibody production. Otherwise, a chronic course of hepatitis has been often described in exposed patients, with weak innate and adaptive immune responses determining an insufficient reduction in viral load, despite concomitant liver function recovery[4]. Consequences of chronicity are cirrhosis and hepatocarcinogenesis [5, 6], along with haematologic malignancies, including B cell non-Hodgkin's lymphoma (B-

NHL) [7], intrahepatic cholangiocarcinoma and other solid tumours, such as head and neck, colorectal, renal, and pancreatic cancers [7, 8, 9]. Any kind of immune central reconstitution after immunosuppressive medication can trigger viral reactivation in this chronic setting of hepatitis C virus, with diversified clinical manifestations ranging from asymptomatic flares of transaminases to severe liver damage [4].

Approximately two weeks before hepatitis flares, an increase in viral RNA often occurs [4]. Hepatitis C reactivation is therefore defined by an increase in HCV-RNA > 1 Log IU/mL over baseline, while the detection of anti-HCV antibodies cannot help in distinguishing between acute and chronic infection but can determine only the occurrence of an infection [10]. Early identification of HCV infection and/or its reactivation can be merely ensured only by liver function testing and anti-HCV and viral load level surveillance.

HCV reactivation in an oncologic setting: According to Rung Li *et al* [11], HCV reactivation (HCVr) in an oncologic setting is promoted by immunosuppression due to chemotherapy, often resulting in deleterious changes in the cancer treatment plan and its outcomes. HCVr prevalence rates in cancer patients receiving chemotherapy range from 1.5 to 32% worldwide [12]. Although less fearful than HBV reactivation, HCVr is challenging for oncologists and HCV treating physicians, who often avoid administering antiviral treatment to patients under chemotherapy because of a lack of data about the safety of this treatment combination [12, 10]. The multicentre, prospective cohort study performed by Ramsey and colleagues [13] among more than 5000 new oncologic patients found an observed infection rate of 2.4% (95%, CI 1.9% to 3.0%) for HCV, with a substantial proportion of patients being unaware of their viral status at the time of cancer diagnosis (31%) and having no identifiable related risk factors (32.4%). Finally, according to this cohort study, therapeutic decisions were changed in 8% of patients because of their viral status [4, 13]. In an observational study conducted at MD Anderson Cancer Center, an HCVr rate of 23% was estimated among patients with cancer (36% in haematologic and 10% in solid tumour settings), with a more frequent recurrence in patients with prolonged lymphopenia (median 95 vs. 22 days, p < 0.001)

and in patients receiving rituximab (44% vs. 9%), bendamustine (22% vs. 0%), high-dose steroids (57% vs. 21%) and purine analogues (22% vs. 5%). The study also showed an unanticipated discontinuation or dose reduction of chemotherapy for 26% (6 of 23) of oncologic patients with HCVr [4]. In both studies, it was concluded that the early identification and treatment of chronic HCV hepatitis prevent HCVr after iatrogenic immunodepression and the remodulation of chemotherapy itself. Thus, screening for HCV infection before cancer treatment appears to be useful and advisable. Figure 1 shows an HCV screening recommendation flowchart for oncologic patients eligible for chemotherapy.

Hepatitis C virus infection therapeutic strategies: Hepatitis C virus infection therapeutic strategies have changed over time [2]. The first therapeutic combination employed against HCV infection in 1990 was based on interferon (IFN) plus ribavirin, which was associated with suboptimal response rates and short- and long-term toxicity even related to drug-to-drug interactions with other medications taken [14]. Moreover, because of intrinsic contraindications for each element of the compound, patients with unbalanced mood unbalanced or anaemia were excluded from the treatment[14]. The first direct-acting antivirals (DAAs), boceprevir and telaprevir, were approved in 2011; since then, the HCV cure rates have markedly improved, and they have been added to the classic dual therapy represented by IFN + ribavirin [15]. After the introduction of the combined regimens based on glecaprevir/pibrentasvir (GLE/PIB), sofosbuvir/velpatasvir (SOF/VEL) with, or without voxilaprevir (VOX), and elbasvir/grazoprevir (EBR/GZR), summarized in **Table 1**, the majority of chronic HCV-infected patients have been treated since 2015, achieving sustained virologic response (SVR) [16-20].

Pharmacokinetic characteristics of currently used DAAs:

In relation to the pharmacokinetic characteristics of currently used DAAs, the time to maximal plasma concentration (tmax), maximal plasma concentration (cmax), area under the concentration time curve (AUC) and minimal plasma concentration (cmin) are

considered with regard to absorption, while the apparent volume of distribution (Vd/L) and percentage of protein binding are considered in relation to distribution. Metabolism is described in terms of the type of substrate elicited by DAAs and excretion as the elimination half-life (T ½) [1].

The pharmacokinetic characteristics of currently used DAAs are summarized in **Table 2**.

Elbasvir (EBR)/Grazoprevir (GZR)

Absorption: EBR is a substrate of P-gp, with a median tmax of 3 h and a range of 3–6 h. The bioavailability is estimated ~ 32%. Absorption (AUC 11% and Cmax 15%) can be decreased by a high-fat meal (900 kcal; 500 kcal fat). GZR acts as a substrate for P-gp and has a median tmax of 2 h with a range of 0.5–3 h. The absolute bioavailability varies from 15 to 27% after a single dose and from 20 to 40% after multiple doses. Absorption (AUC 50% and Cmax 108%) can be increased by a high-fat meal (900 kcal; 500 kcal fat). HCV-infected patients have increased exposure (~ 2-fold) compared with healthy individuals. Steady state is reached at approximately the sixth day of administration [21, 22].

Distribution: EBR and GZR are highly bound to albumin for > 99.9% and to α1-acid glycoprotein for > 98.8% [23, 24]. The estimated Vd/L values for EBR and GZR are 680 and 1250 L, respectively. The hepatic transporter OATP1B1/3 actively transports GZR [25]. EBR inhibits P-gp. EBR and GZR inhibit BCRP [21, 22].

Metabolism: EBR and GZR are metabolized by CYP3A4, but no circulating metabolites can be found in plasma. CYP3A4 is weakly inhibited by GZR [21, 22].

Excretion: EBR and GZR are excreted mainly by liver; more than 99% of the excreted dose can be found in faeces. The apparent t1/2 of EBR and GZR is 24 and 31 h [21, 22].

SOF/Velpatasvir (VEL)

Absorption: The SOF Cmax after administration is 0.5–1 h. The AUC∞ of SOF can be increased by 60% and 78% by a moderate- and high-fat meal, respectively. However, the SOF Cmax is not affected by food [23, 24]. The VEL median tmax is estimated around 3 h, while the AUC and Cmax values are lower in healthy volunteers (41% and 37%),

when compared to those of HCV-infected subjects. The AUC of VEL can be increased after a moderate- (600 kcal; 30% fat) and high-fat (800 kcal; 50% fat) meals, while the Cmax increases by only 34% and 5%, respectively. The solubility of VEL is pH-dependent: in fact the increase of pH determines a reduction in solubility and absorption [23, 24].

Distribution: Circulation proteins highly protein bind VEL (> 99.5%), regardless of the concentration range 0.09–1.8 µg/mL of the drug. SOF acts as a substrate of BCRP and P-gp. VEL acts as a substrate of BCRP, P-gp and OATP1B [25, 26]. Plasma proteins that are not dose-dependent (1–20 µg/mL) bind SOF at 61–65% [23, 24].

Metabolism: VEL is metabolized by CYP2B6, CYP2C8, and CYP3A4, but > 98% of the parent drug can be found in the blood after a single dose. VEL inhibits P-gp, BCRP, and OATP1B1/3 [23, 24]. Refers to the SOF/VEL/VOX paragraph for SOF metabolism.

Excretion: The clearance of VEL is mainly hepatic, VEL is retrieved in faeces for > 94% and in urine for 0.4%. The t1/2 of VEL is approximately 15 h [25, 26]. SOF is mainly excreted by kidneys (80%) as GS-331007 (78%). The t1/2 of SOF is 0.5 h, while the t1/2 of GS-331007 is 25 h [23, 24].

Glecaprevir (GLE)/Pibrentasvir (PIB)

Absorption: The tmax of GLE/PIB is about 5 h. Fat meals (moderate and high) can increase the absorption of GLE/PIB: the exposure of GLE after a meal is increased 83–163% and the exposure of PIB is increased 40–53%. Both drugs are P-gp substrates [25, 26].

Distribution: Plasma proteins highly bind 97.5% to GLE and > 99.9% to PIB, both of drugs are actively transported by BCRP. GLE constitutes also a substrate of OATP1B1/3 [25, 26].

Metabolism: GLE is metabolized by CYP3A4, and PIB does not undergo biotransformation. [25, 26].

Excretion: GLE is primarily excreted by the liver; in fact, 92.1% of a radioactive dose is retrieved in faeces. The t1/2 is 6–9 h at steady state. PIB is also primarily found in stool (96.6%), with a t1/2 of 23–29 h [25, 26].

SOF/Velpatasvir (VEL)/Voxilaprevir (VOX)

Absorption: The Cmax of VOX, VEL, and a major metabolite of SOF, namely GS-331007 is reached after approximately 4 h; the Cmax of SOF is reached after 2 h. The AUC and Cmax of VEL are 41% and 39% decreased in patients, respectively, while the AUC and Cmax of VOX are both elevated by 260% when comparing HCV-infected individuals and healthy volunteers [30, 31]. The AUC∞ and Cmax of SOF increasefrom 64 to 114% and 9 to 76%, respectively, after a meal. The Cmax of GS-331007 after a meal decreases (19-35%). The AUC∞ and Cmax of VEL increase (40-166% and 37-187%, respectively). The AUC of VOX increases from 112 to 435%, while the Cmax of VOX increases from 147 to 680% [27, 28].

Distribution: Plasma proteins highly bind to SOF, VEL, and VOX (61–65%, > 99%, and > 99%, respectively), with a concentration independent pharmacokinetics (ranging from 1 to 20 and 0.09 to 1.8 µg/mL, respectively) for SOF and VEL. SOF acts as a substrate of P-gp and BCRP, while VEL acts as a substrate of P-gp, OATP1B1/3, and BCRP. Finally, VOX acts as a substrate of P-gp and BCRP [27, 28].

Metabolism: VOX is a substrate of CYP3A4. VOX is an inhibitor of P-gp, BCRP, and OATP1B1/3 [27, 28]. The metabolism of SOF and VEL is reported in the paragraph on SOF/VEL combination therapy above.

Excretion: SOF is excreted by the kidneys (80%), mainly in the form of GS-331007 (78%). The t1/2 of SOF is 0.5 h and the t1/2 of GS-331007 is 29 h [28, 29]. The clearance of VEL is mainly hepatic. The t1/2 of VEL is approximately 17 h (27). The excretion is mainly biliary. [27, 28].

Pharmacodynamics of currently used DAAs

Intended as the balance between the effect (reduction of HCV-RNA under therapy) and toxicity (adverse effects), the pharmacodynamics of currently used DAAs consist of the duration of therapy, safety profile and estimated adverse effects.

EBR/GZR is efficacious for subjects affected by genotypes 1 and 4 HCV infection treated for 12 wk. EBR/GZR is approved for patients with renal insufficiency and compensated cirrhosis. This combination is approved in the fixed dose combination of 50 mg/100 mg once daily. The favourable safety profile with low discontinuation rates (< 5%) makes

this compound suitable for HCV-infected patients with genotypes 1 and 4. The most frequent adverse effects are fatigue, headache, asthenia, nausea, rash, and an increase in ALT/AST and ALP [1, 21].

SOF/VEL combination for 12 wk is valid in HCV pangenotypic patients treatment-experienced and/or treatment-naïve. Mild described adverse events are headache, fatigue, nausea and insomnia. Combination therapy with ribavirin leads to anaemia in over 10% of patients [1, 24].

GLE/PIB is a pangenotypic regimen that is highly effective when administered for 8 to 12 wk once daily at doses of 100 mg/40 mg. Naïve and experienced patients with or without cirrhosis can be treated with this compound, whichhas a mild toxicity profile, in which headache, fatigue, nasopharyngitis and nausea can arise [1, 25].

Finally, the pangenotypic highly effective SOF/VEL/VOX combination is licenced for patients who fail to respond to IFN/riba and DAAs and those with or without compensated cirrhosis. The adverse effects described are headache, diarrhoea, fatigue, nausea and constipation [1, 27].

The pharmacodynamic properties of currently used DAAs are summarized in **Table 3**.

Drug to drug interactions Drug-drug interactions are challenging in the course of cotreatment with chemotherapy and DAAs because most of these compounds are substrates and inhibitors of drug transporters and CYP enzymes [7]. Consulting the HEP drug interaction website can be extremely useful for clinical decision-making [29]: a report listing the summaries of potential interactions (i.e., "red", "amber" and "yellow" classifications) for the drugs considered can be downloaded to guide the choice on a case-by-case basis. Potential interactions between currently used DAAs and the following drug classes of chemotherapy regimens are reported in this review:

platinum-containing agents (cisplatin, carboplatin, oxaliplatin),

folate antagonists (methotrexate, pemetrexed),

pyrimidine compounds (fluorouracil, capecitabine, cytarabine, gemcitabine, decitabine),

purine analogues (mercaptopurine, fludarabine, cladribine, clofarabine),

alkylating agents (cyclophosphamide, ifosfamide, melphalan, bendamustine, busulfan),

anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin, bleomycin), topoisomerases (topotecan, etoposide, irinotecan),

cytidine analogues (azacytidine, decitabine),

immunosuppressants (tacrolimus, cyclosporine),

immunomodulatory drugs (lenalidomide, thalidomide),

mitotic inhibitors (paclitaxel, docetaxel, vinblastine, vincristine),

hormonal therapies (tamoxifen),

targeted therapies other than rituximab (e.g., cetuximab, bortezomib, alemtuzumab).

Interactions between DAAs and the main oncologic therapeutic categories considered in this review are summarized in **Table 4**.

According to the Liverpool HEP chart, drugs that absolutely **should not be coadministered (RED interactions)** are as follows:

Elbasvir/grazoprevir + immunosuppressants (cyclosporine): Concomitant use of elbasvir/grazoprevir with OATP1B inhibitors, such as cyclosporine, is contraindicated. The coadministration of multiple doses of elbasvir/grazoprevir and a single dose of cyclosporin increases the grazoprevir AUC by 15-fold. The risk of ALT elevations may be increased due to the significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition. [29]

Sofosbuvir/velpatasvir/voxilaprevir + folate antagonists (methotrexate)

Coadministration has not been studied but would not be recommended due to increased exposure tomethotrexate due to BCRP inhibition by voxilaprevir. [29]

Sofosbuvir/velpatasvir/voxilaprevir + immunosuppressants (cyclosporine)

Coadministration has been studied with sofosbuvir, velpatasvir or voxilaprevir, and coadministration with sofosbuvir/velpatasvir/voxilaprevir is not recommended. Concentrations of voxilaprevir increased by 19.0-fold due to OATP1B1 inhibition by cyclosporine. The safety of this increase has not been established. [29]

According to the Liverpool HEP chart, **potential clinically significant** interactions—likely to require additional monitoring and an alteration of drug dosage or the timing of administration **(AMBER interactions)**–are described among the following:

Elbasvir/grazoprevir + folate antagonists (methotrexate): Coadministration has not been studied. Methotrexate is a substrate of BCRP, and concentrations could increase due to inhibition by elbasvir/grazoprevir. No a priori dose alteration is recommended, but patients should be closely monitored. [29]

Sofosbuvir/velpatasvir + folate antagonists (methotrexate): Coadministration has not been studied. Methotrexate is a substrate of BCRP, and concentrations may increase due to inhibition by sofosbuvir/velpatasvir. Although no a priori dose alteration is required, close monitoring is recommended. [29]

Glecaprevir/pibrentasvir + immunosuppressants (cyclosporine): Concomitant use of glecaprevir/pibrentasvir with cyclosporine requires close monitoring of doses, as concentrations of glecaprevir/pibrentasvir may increase due to the inhibition of OATP1B. The coadministration of glecaprevir/pibrentasvir and cyclosporine (100 mg) increased glecaprevir/pibrentasvir concentrations within acceptable parameters (glecaprevir Cmax, AUC and Cmin by 30%, 37% and 34%, respectively; no change in pibrentasvir Cmax and AUC, but Cmin increased by 26%). However, at higher doses of cyclosporine (400 mg), glecaprevir concentrations increased significantly (Cmax 4.51-fold, AUC 5.08-fold). Glecaprevir/pibrentasvir is not recommended for use in patients requiring stable cyclosporinedosesat 100 mg per day. [29]

Glecaprevir/pibrentasvir + anthracyclines (doxorubicin): Coadministration has not been studied. Doxorubicin is metabolized by CYP enzymes and is a substrate for P-gp. Since glecaprevir/pibrentasvir inhibits P-gp and is a mild inhibitor of CYP3A4, there is the potential for increased doxorubicin exposure,and a clinically significant interaction has to be considered. [29]

Glecaprevir/pibrentasvir + folate antagonists (methotrexate): Coadministration has not been studied. Methotrexate is a substrate of BCRP, and concentrations could increase due to the inhibition of BCRP by glecaprevir/pibrentasvir. Patients should be closely monitored for methotrexate-associated toxicities. [29]

Glecaprevir/pibrentasvir + immunosuppressants (tacrolimus): The coadministration of glecaprevir/pibrentasvir with systemic tacrolimus (1 mg single dose) increased

tacrolimus Cmax and AUC by 1.5-fold and 1.45-fold, respectively. There was no change in the Cmax, AUC or Cmin of glecaprevir or pibrentasvir. As tacrolimus is a narrow therapeutic index drug, it should be used with caution. Therapeutic blood monitoring should be performed. [29]

Sofosbuvir/velpatasvir/voxilaprevir + immunosuppressant (tacrolimus): Coadministration with sofosbuvir/velpatasvir/voxilaprevir has not been studied. No clinically significant drug interactions were observed with sofosbuvir and tacrolimus. The coadministration of tacrolimus (5 mg single dose) and sofosbuvir (400 mg single dose, *n* = 16) decreased tacrolimus Cmax by 27% and increased AUC by 9%; sofosbuvir Cmax decreased by 3% but AUC increased by 13%. No effect of velpatasvir or voxilaprevir is expected. However, in the absence of data, the monitoring of tacrolimus concentrations should be considered. [29]

Elbasvir/grazoprevir + mitotic inhibitors (paclitaxel): Coadministration has not been studied. Paclitaxel is primarily metabolized by CYP2C8 and to a lesser extent by CYP3A4. Grazoprevir is a weak inhibitor of CYP3A4 and could potentially increase paclitaxel exposure. Paclitaxel-induced toxicity should be monitored. [29]

Glecaprevir/pibrentasvir + mitotic inhibitors (paclitaxel): Coadministration has not been studied. Paclitaxel is primarily metabolized by CYP2C8 and to a lesser extent by CYP3A4. Glecaprevir is a weak inhibitor of CYP3A4 and could potentially increase paclitaxel exposure. Paclitaxel-induced toxicity should be monitored. [29]

Elbasvir/grazoprevir + immunosuppressants (tacrolimus): The coadministration of elbasvir/grazoprevir with systemic tacrolimus increased tacrolimus AUC by 43% (due to weak inhibition of CYP3A4 by grazoprevir) but had no effect on the concentrations of grazoprevir and elbasvir. Frequent monitoring of tacrolimus whole-blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of coadministration is recommended. [29]

According to the Liverpool HEP chart, **potentially weak interactions**—for which additional action/monitoring or dosage adjustment is unlikely to be required **(YELLOW interactions)**—are described among the following:

Sofosbuvir/velpatasvir + hormonal therapies (tamoxifen): Coadministration has not been studied. Tamoxifen is mainly metabolized by CYP3A4 and CYP3A5, which are not affected by sofosbuvir/velpatasvir. However, tamoxifen induces CYP3A4 and could potentially decrease the concentrations of velpatasvir, although to a moderate extent. Coadministration with food is suggested if tamoxifen is coadministered with sofosbuvir/velpatasvir as this increases exposure to velpatasvir. [29]

Sofosbuvir/velpatasvir/voxilaprevir + hormonal therapies (tamoxifen): Coadministration has not been studied. Tamoxifen is mainly metabolized by CYP3A4 and CYP3A5, which are not affected by sofosbuvir/velpatasvir/voxilaprevir. However, tamoxifen induces CYP3A4 and could potentially decrease theconcentrations of velpatasvir and voxilaprevir, although to a moderate extent. Coadministration with food is suggested if tamoxifen is coadministered with sofosbuvir/velpatasvir/voxilaprevir as this increases exposure tovelpatasvir and voxilaprevir. [29]

DAA-chemotherapy drug-drug interactions (green) according to the Liverpool Drug Interactions Group are summarized in Table 5b. [29]

Some comedications with a green classification may require dose adjustment due to hepatic impairment.

Management of chronic HCV infection in patients with cancer

HCV-infected oncologic patients represent a special population needing guided treatment [12]: the updated guidelines provided by the AASL and IDSA [4] for the first time address treatment in this setting, supporting that the virologic and hepatic benefits of DAA treatment in oncologic patients with hepatitis C virus infection overcome the risk of no treatment [7, 30, 31]. In fact, the quick eradication of chronic HCV infection prior to cancer therapy helps liver recovery, normalizes liver enzymes and avoids potentially decompensating hepatitis flares; in other words, it allows the initiation of cancer treatment that could be hampered by persistent elevated ALT levels due to HCV virus

infection [12]. The eradication of HCV in oncologic patients can also diminish the risk of HCVr, allow patients to participate in experimental oncologic clinical trials based on new drug strategies against cancer, reduce the risk of the development of HCV-associated cancers [4], minimize drug-induced hepatotoxicity and avoid detrimental dose reduction.

DAA-based therapy can also promote liver disease progression [12]. In clinical practice, the temporary suspension of cancer treatment during DAA-based therapy has often been observed to avoid overlapping toxicities and DDIs. However, the present review proves that when cancer treatment cannot be interrupted, currently used DAAs can be simultaneously administered under close comonitoring by oncologists and hepatologists, especially during the first month of this dual therapy, since serious observed adverse events most usually appear within the first 2-4 wk of concomitant treatment.

CONCLUSION

Economides *et al* stated that DAA therapy in cancer patients was efficacious and durable in terms of SVR, and few drug-drug interactions were observed. Otherwise, prospective data on HCV in oncologic patients remain limited [12].

This review, in the absence of current specific available guidelines for the use of DAA therapy in HCV-infected cancer patients, tried to clarify that treatment with DAAs for oncologic patients undergoing chemotherapy affected by HCV infection is safe and favourably impacts oncologic outcomes.

Finally, given that cancer treatment can negatively impact untreated chronic HCV-related liver disease, it appears clear that pre-emptive antiviral therapy in the oncologic setting is necessary to pursue chemotherapy without risking the progression of viral liver disease.

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