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Expert opinion on managing chronic HCV in patients with non-Hodgkin lymphoma and other extrahepatic malignancies: scoping document

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Abstract

Hepatitis C virus (HCV) is a carcinogen that is well established as a major risk factor for hepatocellular carcinoma. Evidence that HCV plays a role in the development of extrahepatic malignancies is less robust; however, epidemiological studies have consistently demonstrated an association between HCV infection and B-cell non-Hodgkin lymphoma (NHL). The strongest evidence for a link between HCV and tumourigenesis is the clear association between viral eradication, as indicated by achievement of sustained virological response, and remission of B-cell NHL. All-oral direct-acting antiviral-based therapies are effective in patients with HCV-associated NHL and well tolerated. For this reason, it is important that clinicians assess HCV-infected patients for HCV-associated extrahepatic malignancies so patients can receive timely diagnosis and treatment.

Introduction

Hepatitis C virus (HCV) is a carcinogen that is associated with several types of malignancy [1]. It is well established that chronic infection with HCV is a major risk factor for hepatocellular carcinoma (HCC). Indeed, HCV infection is considered a causative factor in approximately 20.5% of HCC cases in the US [2,3]. A growing body of evidence shows that patients with chronic HCV infection are at increased risk for extrahepatic malignancies versus the general population [1]. The objective of this article is to describe associations between HCV infection and extrahepatic malignancies, the impact of antiviral treatment on HCV-associated extrahepatic malignancies, and recommendations for management of patients with HCV-associated extrahepatic malignancies.

Epidemiological evidence for HCV-associated malignancies

Non-Hodgkin lymphoma

Following the first reports of a high prevalence of HCV infection in patients with 'idiopathic' B-cell non-Hodgkin lymphomas (NHLs) [4,5], the association between HCV infection and B-cell NHL has been clearly established during the past 20 years by an increasing number of clinico-epidemiological investigations [6-26]. The association between HCV infection and B-cell malignancies was suggested by analyses of patients with mixed cryoglobulinaemia, a common extrahepatic manifestation of chronic HCV infection that may be complicated by malignant B-cell neoplasias [6-8]. Several meta-analyses of epidemiological studies provide estimates of the increased risk of B-cell NHL in HCV-infected patients [19-23]. An early meta-analysis of 48

studies of patients with B-cell NHL estimated that the prevalence of HCV infection in patients with B-cell NHL was 15%, which was considerably higher than the estimated prevalence of HCV in the general population (1.5%) and in patients with other haematological malignancies (2.9%) [19]. This analysis also suggested that the prevalence of HCV-associated B-cell NHL varied geographically, with the highest rates in Italy (20%) and Japan (14%) [19]. In contrast, the prevalence of HCV-associated B-cell NHL was 6.4% in Europe (after excluding Italy) and 11% in the US [19]. Subsequently, a meta-analysis of 15 case-control studies and three prospective studies of patients with chronic HCV infection showed that the pooled relative risk (RR) of B-cell NHL was 2.5 (95% confidence interval [CI] 2.1–3.0) in HCV-positive patients [22]. Notably, Dal Maso, *et al.* [22] found that the RR was higher in countries with higher HCV prevalence. In countries with an HCV prevalence above 5%, the RR for NHL was 3.01, whereas in countries with an HCV prevalence below this threshold the RR was 1.9. As a consequence, the fraction of NHL attributable to HCV varies markedly by country, such that in high prevalence countries like Italy, HCV may account for ~10% of NHL cases whereas in the US, a low prevalence country, fewer than 1% of NHL cases are attributable to HCV.

A pooled analysis of data from seven case-control studies from the International Lymphoma Epidemiology Consortium that included 4,784 patients with B-cell NHL and 6,269 controls showed that HCV is significantly associated with NHL (odds ratio [OR] 1.78; 95% CI 1.40–2.25) [23].

HCV is associated with a number of different types of B-cell NHL. The strongest associations are with specific low-grade NHL sub-types such as marginal-zone lymphoma (MZL) and

lymphoplasmacytic lymphoma, particularly when arising in the spleen or liver. A large US study found that HCV was associated with Waldenström's macroglobulinemia (aRR 2.76) but not with multiple myeloma [14]. The association with other low-grade NHL like follicular NHL and chronic lymphocytic leukemia (CLL) is weaker, however HCV is also associated with high-grade NHL such as diffuse large B cell lymphoma (DLBCL) [23].

The higher incidence of NHL in HCV-infected individuals has been confirmed in a retrospective analysis of the Chronic Hepatitis Cohort Study database in the US [17]. When compared with the US general population, HCV-infected patients had a significantly higher incidence rate of B-cell NHL. Moreover, B-cell NHL was diagnosed a mean of 4.6 years earlier in HCV-infected patients than in those without HCV [17]. Mortality rates were also significantly higher for HCV-infected patients with B-cell NHL, and mortality occurred on average 12.6 years earlier in HCV-infected patients with NHL than in those without HCV.

Among individuals with HCV, the risk of NHL is increased in women, people from HCV-endemic countries and in those with a longer duration of infection. However, by far the strongest association between HCV and NHL is the presence of symptomatic mixed cryoglobulinaemia. A retrospective, multicentre study that included data from 1,255 patients with chronic HCV infection and mixed cryoglobulinaemia showed that the overall incidence of B-cell NHL was approximately 35.5 times that in the general population [24].

Clonal B lymphocytes are often detected in the blood and liver of patients with chronic HCV infection and are usually, but not always, associated with cryoglobulinaemia. A study in 166 HCV-positive patients showed that patients with B-cell clonality in both the blood and liver are more likely to be diagnosed with B-cell malignancies [27].

HCV-infected patients with DLBCL have unique characteristics that make their lymphoma more difficult to treat than HCV-negative patients [28]. DLBCL is an aggressive subtype of NHL that can develop *de novo* or evolve from a pre-existing indolent lymphoma. A case-control study showed that among patients with transformed DLBCL, HCV-infected patients are younger, have more advanced disease, and are more likely to have gastrointestinal involvement and bone marrow involvement when compared with HCV-negative patients [28]. In addition, HCV-infected patients were more likely to have CD5-positive B cells, CD10-negative B cells, activated B-cell phenotypes and worse 2-year survival than HCV-negative patients. The presence of CD5-positive B cells is a poor prognostic factor and was significantly associated with relapse in this analysis [28].

Importantly, the evolution of B-cell NHL in patients with chronic HCV infection occurs independently of the progression of hepatic fibrosis [25]. In an analysis of data from patients diagnosed with HCV-associated NHL at a large tertiary care cancer centre in the US, most patients (82%) had minimal hepatic fibrosis, defined as Metavir stage <3, at the time of diagnosis of NHL [25]. These results have implications for the selection and prioritisation of

patients for treatment of chronic HCV infection, as early treatment of HCV (i.e. before fibrosis progression) may also benefit patients by preventing B-cell NHL.

The spectrum of HCV-related extrahepatic disorders includes a number of organ- and non-organ-specific conditions and malignancies, with or without clinically overt hepatic manifestations [26]. Therefore, all HCV-infected individuals should be carefully investigated for both liver-related complications and HCV-related extrahepatic disorders at the patient's first assessment and during subsequent follow-up visits [29].

The diagnosis of HCV-related lymphoma requires histological examination of involved tissue (nodal and extranodal), and the specific histotype must be defined according to World Health Organization Classification of Tumours of Hematopoietic and Lymphoid Tissues [30]. Cytology and flow cytometry analyses are generally not sufficient to establish a definitive diagnosis of NHL; however, in the absence of nodal and extranodal disease, a diagnosis of monoclonal B-cell lymphocytosis in HCV-positive patients can be established on the basis of bone marrow histology coupled with flow cytometric findings [31,32]. Also, in specific situations such as splenic marginal zone lymphoma (SMZL), a reliable diagnosis can be established based on bone marrow histology and phenotype, as determined by immunohistochemistry and flow cytometry, without need of splenectomy [33]. Overlapping histological features have been reported in HCV-positive and HCV-negative patients [32], and differentiating between monoclonal B-cell lymphocytosis and SMZL can be difficult in patients with splenomegaly attributable to HCV infection [34].

Staging of HCV-associated NHL is done using the Lugano classification [35]. In contrast, MZL is generally not an ^{18}F -fluorodeoxyglucose-avid disease and must be staged by means of computed tomography alone, whereas ^{18}F -fluorodeoxyglucose-positron emission tomography is indicated in DLCL and in indolent NHL in case of suspected transformation [36].

Specific lymphomas have been reported in association with HCV infection. Among MZLs, SMZL is frequently associated with HCV infection, although there is a great geographical variability [37-39].

Other malignancies

Epidemiological data exist for an association between chronic HCV infection and many other extrahepatic malignancies [26] (**Table 1**). A retrospective analysis of the Chronic Hepatitis Cohort Study database in the US revealed significantly higher rates of extrahepatic malignancies and mortality in a cohort of 12,126 HCV RNA-positive patients compared with the general US population [17]. A total of 595 individuals aged ≥ 25 years were diagnosed with 612 incident malignancies between 2006 and 2010. Of these 612 malignancies, 565 met the inclusion criteria for the analysis. Only cancers detected after the first visit were included in the analysis. In addition, recurrences of pre-existing cancers were excluded. When compared with the US general population using data derived from the Surveillance, Epidemiology, and End Results database, HCV-infected patients had significantly higher incidence rates for four of eight smoking-related malignancies including pancreas, rectum, lung and kidney, as well as

borderline higher incidence rates for malignancy of the oral cavity (**Table 2**). Among alcohol-related malignancies (excluding HCC), rectal cancer had a significantly higher incidence in HCV-infected individuals [17]. For 10 out of 16 cancers, the mean age at diagnosis was 7.4 years younger among HCV-infected patients versus the general population. Mortality rates were significantly higher for NHL and for three of seven smoking-related malignancies (oral, rectum, pancreas) in HCV-infected patients than in the general population; conversely, mortality rates were significantly lower in HCV-infected patients with the remaining four smoking-related malignancies and for breast cancer than in the general population [17]. An important limitation of this analysis was the inability to control for smoking or alcohol use due to the absence of these data in the databases. Thus, the findings may be confounded by exposure to risk factors related to cancer incidence and mortality.

A significant positive association between HCV infection and a range of extrahepatic malignancies was observed in elderly (age ≥ 66 years) US adults included in a case-control study, in which Surveillance, Epidemiology, and End Results data were linked with Medicare data [40]. This registry-based study evaluated data from 1,623,538 patients with cancer and 200,000 cancer-free individuals. The prevalence of HCV was significantly higher among cases than controls (0.7% vs 0.5%; adjusted OR 1.32; 95% CI 1.22–1.42; $p < 0.0001$). Significant associations between HCV infection and a range of malignancies were observed (**Table 3**).

Significantly increased incidence of papillary thyroid cancer has also been observed in HCV-infected patients compared with the general population [41,42].

Mechanisms of HCV-associated malignancies

The precise manner by which HCV infection contributes to lymphomagenesis remains to be elucidated [1]. Proposed mechanisms include chronic antigenic stimulation and an influence of genetic, epigenetic and/or environmental factors (**Figure 1**) [43]. There may be both antigen-dependent and antigen-independent mechanisms as well as direct (virological) and indirect (proliferation) stimuli driving the development of lymphoma [44]. Specific HCV proteins may be particularly oncogenic. A role for the HCV non-structural protein 3 (NS3) and core proteins has been proposed because they have been directly identified in lymphoma cells. Proliferation is initially antigen-dependent but may become antigen independent if specific oncogenic mutations (e.g. P53, beta-catenin) occur in proliferating clonal lymphocyte populations. Another antigen-dependent mechanism may be related to the up-regulation of activation-induced deaminase (AID) by HCV proteins, leading to DNA breaks with a higher probability of oncogenic translocations (e.g. BCL-2, t14-18) ultimately leading to NHL. An Ag-independent mechanism involving B-cell-activating factor (also known as B-lymphocyte stimulator receptor ligand) has also been suggested [45]. Serum levels of this cytokine, which is essential for B-lymphocyte development and survival, are significantly higher in patients with HCV-induced mixed-cryoglobulinaemia-vasculitis, a common extrahepatic manifestation of chronic HCV infection, and in patients with HCV-associated B-cell NHL [45]. Exposure to a common antigenic epitope of viral origin may lead to selection and expansion of a B-cell clone, leading to B-cell NHL [46]. A genetic alteration, such as a point mutation or the B-cell lymphoma (BCL)

rearrangement associated with mixed cryoglobulinaemia [translocation t(14:18)], may also be involved in the pathogenesis of B-cell NHL [46,47].

In contrast, HCV-positive patients with *de novo* DLBCL lack BCL translocations [48]. A recent analysis suggests that there are differences in gene expression between HCV-positive and HCV-negative patients with *de novo* DLBCL including genes that regulate innate immune responses and those that modulate apoptotic pathways. HCV-infected patients included in the analysis had higher proliferative indices and lacked BCL2 translocations when compared with HCV-negative patients with DLBCL.

Additionally, HCV-derived proteins have also been implicated in the transformation of high-grade B-cell NHL. A pathology substudy of the French ANRS HC-13 LymphoC study demonstrated by immunostaining that NS3 was present in samples from 17 of 37 patients evaluated [49]. NS3 was detected in 12 of 14 patients with DLBCL with high-grade features, whereas only 4 of 14 patients with MZL were NS3-positive ($p=0.006$). These data suggest that HCV may have a direct oncogenic effect, although further study is required to confirm this hypothesis and to reveal the mechanism by which NS3 leads to malignant transformation.

The presence of a serum biomarker signature identifies HCV-infected patients with overt B-cell NHL [50]. A study of 155 HCV-infected patients with and without mixed cryoglobulinaemia and/or B-cell NHL showed that a signature involving sCD27, sIL-2R α , gammaglobulins and C4

levels was associated with the presence of overt B-cell NHL. The signature had a negative predictive value of 100% for distinguishing patients with versus without overt B-cell NHL.

Few data are available to indicate how HCV contributes to extrahepatic malignancies other than B-cell NHL. Presumably, HCV may act as either a direct or an indirect carcinogen [51,52]. HCV RNA and/or HCV antigens have been detected in a wide range of extrahepatic tissues, suggesting that HCV can infect a broad range of cell types [53-63]. For example, HCV can infect and replicate inside pluripotent haematopoietic stem cells *in vitro*, and HCV proteins and HCV RNA have been isolated *in situ* from these cells [55]. Evidence that HCV can replicate in oral lichen planus tissue was obtained in a study in which HCV RNA was detected in mucosal tissue in anti-HCV-positive patients with oral lichen planus [59]. In addition, HCV RNA has been detected in HCV-positive patients with oral cancer [59]. HCV RNA and HCV core protein have also been recovered from the glomeruli of HCV-positive patients with membranoproliferative glomerulonephritis, membranous glomerulonephritis, segmental glomerulosclerosis and immunoglobulin A-nephropathy [63]. It remains to be determined whether HCV RNA is present in tumour cells in patients with HCV-associated renal cancer, and whether such an association is carcinogenic. The mechanisms underlying the other associations (pancreas, rectum and lung) are unknown.

Therapeutic strategies for HCV-associated malignancies

The treatment of HCV-associated malignancies should be considered in the context of HCV-related hepatic and extrahepatic manifestations. The latter phenomena are generally

associated with HCV-related malignancies in the setting of HCV syndrome [26,29], even though a malignancy may seem to be a clinically discrete entity in a significant proportion of HCV-infected individuals. As shown in Figure 1, treatment of HCV-related diseases includes three interventions: direct-acting antiviral drugs (DAAs); immunomodulatory or antineoplastic treatments; and symptomatic treatment, such as corticosteroids and plasma exchange [26,29,64].

In clinical practice, treatment should be individualised, considering the activity/severity of clinical manifestations as well as the presence of adverse prognostic factors and possible comorbidities.

DAAs can achieve HCV eradication in most patients, represent the gold-standard therapy for chronic HCV infection and are preferred in all patients with HCV-related disorders, particularly those with B-cell lymphomas [64].

Impact of SVR on regression of HCV-associated malignancies

Perhaps the strongest evidence for a link between HCV and tumourigenesis is the observation that successful antiviral therapy may lead to regression of tumours and prevention of recurrence) [65-67]. This is consistent with resolution of a range of extrahepatic manifestations of chronic HCV infection following achievement of SVR [64,66,68].

In a seminal observation, Hermine, *et al.* [65] reported complete resolution of splenic lymphoma with villous lymphocytes, an indolent B-cell lymphoproliferative disorder, in HCV-infected patients after achievement of an SVR with interferon-based therapy. Disappearance of

villous lymphocytes from blood and regression of splenomegaly occurred concurrently with elimination of HCV RNA in serum. A complete haematological response was obtained in seven of nine patients who achieved an SVR, whereas one patient had a partial haematological response after achievement of an SVR. The remaining individual experienced a relapse of splenic lymphoma with the return of detectable HCV RNA at the end of antiviral therapy but subsequently experienced a complete haematological response following re-treatment with interferon plus ribavirin, and achievement of an SVR. Several patients in this series had not responded to prior chemotherapy for B-cell NHL. Of note, treatment with interferon-based therapy had no impact on haematological disease in six HCV-negative control patients with splenic lymphoma with villous lymphocytes [65]. This critical observation was one of the first demonstrations that treatment of a viral (or bacterial) infection could lead to cancer regression, something that has also been observed in other settings such as B-cell gastric lymphoma of mucosa-associated lymphoid tissue and *H. pylori* infection [69,70]. The observation that clinical symptoms of lymphoma resolved with interferon-based therapy for chronic HCV infection was consistent with a previous report of the disappearance of aberrant B-cell clones with the t(14:18) translocation from the blood of patients with chronic HCV infection after treatment with interferon [71].

Numerous studies have confirmed the association between lymphoma response and SVR. Indeed, a meta-analysis of 20 studies that reported outcomes in 254 patients with HCV-associated B-cell NHL showed that lymphoma response was significantly associated with achievement of SVR [72]. Overall, the lymphoma response rate was 73% (95% CI 67–78%) in

patients who received antiviral therapy. Among patients who achieved an SVR, the lymphoma response rate was 83% (95% CI 76–88%), whereas among patients without an SVR, the lymphoma response rate was 53% (95% CI 39–67%) ($p=0.0002$). The authors of this meta-analysis did not report how many patients received chemotherapy.

HCV clearance has been reported to improve progression-free survival (PFS) in HCV-positive patients with indolent B-cell NHL [73]. The 5-year PFS rate was 63% among 80 patients who experienced HCV RNA clearance compared with an overall 5-year PFS rate of 48% in a total of 704 consecutive HIV-negative patients with HCV-associated NHL who were diagnosed and treated between 1993 and 2009 in 39 Italian centres.

Similarly, in the French ANRS HC-13 Lympho-C study, antiviral therapy was associated with better survival in patients with HCV-associated B-cell NHL, including patients with high-grade disease [74]. Among 116 enrolled patients, 70 (60%) received interferon-based antiviral therapy. Patients who received antiviral therapy at the time of diagnosis or during follow-up had significantly better overall survival ($p=0.029$) and PFS ($p=0.049$) than those who did not receive antiviral therapy. The cohort included 45 patients with MZL, 45 patients with DLBCL and 26 patients with other B-cell NHL subtypes.

A subsequent analysis of the French ANRS HC-13 Lympho-C study confirmed that haematological response rates were higher in patients who achieved an SVR with antiviral

therapy compared with those who did not achieve an SVR (69% vs. 31%; $p=0.02$) [75]. This analysis showed that response rates were similar in patients with MZL and DLBCL. Of note, haematological response was observed in four of 19 patients who received antiviral therapy prior to chemotherapy for lymphoma.

Importantly, not only is the primary response improved with HCV eradication but viral clearance markedly reduces the risk of relapse after initial remission of NHL. La Mura and colleagues reported that after initially achieving remission with chemotherapy, the NHL relapse rate was 35% at 5 years in non-responders to interferon-based therapy compared with 0 of 8 patients who achieved an SVR ($p=0.038$) [76]. This study led to recommendations to treat patients for HCV upon establishment of NHL remission [77].

SVR with DAA therapy has also been associated with regression of lymphoma. Alric, *et al.* [75] reported results in 10 patients who received interferon-free, all-oral therapy. Nine of these patients received DAA therapy for HCV together with chemotherapy for B-cell NHL (one individual did not receive concurrent chemotherapy). The SVR rate in this small cohort was 90% (9/10), and all nine patients with an SVR had a haematological response 6 months post treatment. The patient who did not respond had cirrhosis, was infected with HCV genotype 6 and was HCV RNA negative after 4 weeks of treatment with sofosbuvir/ledipasvir (breakthrough occurred at Week 16). These preliminary results show that all-oral DAA-based therapies are effective in patients with HCV-associated NHL.

The results of a larger case-series provide further evidence for the association of viral clearance with DAA therapy and remission of B-cell NHL [78]. An SVR was obtained in 45 of 46 patients (98%) after a median duration of 12 weeks of treatment (range 6–24 weeks), and a lymphoproliferative disease response was obtained in 31 patients (67%), 12 of whom had a complete response. Ten patients (22%) had previously received chemotherapy. One-year PFS and overall survival rates were 75% and 98%, respectively. The one patient who did not achieve an SVR had decompensated cirrhosis with encephalopathy and a high tumour burden; they died 4 weeks after discontinuation of DAA therapy. Four patients experienced early disease progression during or within three months of completing DAA therapy, and two patients with splenic MZL experienced disease progression more than 3 months post-DAA therapy.

More recently, the results of an observational study suggest that all-oral DAA therapy may be administered concomitantly with chemotherapy in patients with B-cell NHL [79]. In this series, 20 HCV genotype 1b-infected patients received ledipasvir/sofosbuvir while undergoing standard chemotherapy for DLBCL. All patients achieved an SVR, and one patient died during follow-up (unrelated to DAA therapy). Disease-free survival after 52 weeks was significantly higher in this cohort of patients compared with an untreated historical control group.

All-oral therapy with ledipasvir/sofosbuvir has also been administered to patients who have developed acute HCV infection during chemotherapy or shortly after completing chemotherapy [80]. All six patients included in this series cleared HCV, and four of six achieved an SVR at 12

weeks post treatment (SVR12; two individuals died because of relapse of haematological cancer after 8 weeks of follow-up and, thus, did not achieve an SVR12).

On balance, these data demonstrate that achievement of an SVR with antiviral therapy may lead to regression of low-grade HCV-associated NHL and reduces the remission rate of both low and high-grade NHL after treatment with chemotherapy.

Impact of SVR on reducing risk for extrahepatic malignancies

Treatment of chronic HCV infection has been shown to reduce the risk of B-cell NHL [81]. In a retrospective Japanese study of 501 patients with chronic HCV infection who had never received interferon therapy and 2708 patients with chronic HCV infection who were treated with interferon-based therapy, patients who achieved an SVR had an approximately 7 times lower risk of NHL compared with those who did not achieve an SVR (hazard ratio 0.13; $p=0.049$). None of the patients who achieved an SVR developed B-cell NHL after 5, 10 or 15 years of follow-up, whereas an increasing number of patients who had never received treatment or who did not achieve an SVR developed lymphoma after 5, 10 and 15 years of follow-up. A total of 0.6%, 2.3% and 2.6% of patients who had never received treatment developed lymphoma after 5, 10 and 15 years of follow-up, respectively, and a total of 0.4%, 1.5% and 2.6% of patients who did not achieve an SVR developed lymphoma after 5, 10 and 15 years of follow-up, respectively, (**Figure 2**) [81].

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Additionally, a retrospective analysis of data collected over 10 years from 160, 875 HCV-infected individuals showed that achievement of an SVR was associated with a reduced incidence of several, but not all, extrahepatic manifestations of chronic HCV infection [66]. Risk of cryoglobulinaemia, glomerulonephritis, porphyria cutanea tarda, NHL, diabetes mellitus and stroke were all lower in patients who achieved an SVR versus untreated patients. A total of 31,143 (19.4%) patients in the cohort were treated with antiviral therapy among whom the SVR rate was 33.9% (10,575/31,143). Risk of B-cell NHL was significantly reduced among patients who achieved an SVR compared with those who did not (adjusted hazard ratio 0.64; 95% CI 0.43–0.95) [66]. A total of 731 cases of B-cell NHL were reported in the cohort.

Not all studies have shown that SVR is associated with a reduced risk of extrahepatic malignancies. For example, a prospective analysis of data from 1,671 patients with histologically proven cirrhosis and compensated liver disease (Child-Pugh A) showed that achievement of an SVR was associated with a significantly lower incidence of liver-related complications, including HCC and hepatic decompensation ($p < 0.001$ for patients with vs. without an SVR) [67]. However, achievement of an SVR had no apparent impact on the occurrence of extrahepatic malignancies after a median of 58.2 months of follow-up in this cohort. The risk of lymphoma and haemopathies was similar in patients with and without an SVR in this series (1.4% vs. 1.3% over 5 years; $p = 0.87$) [67].

Clinical care of patients with chronic HCV infection and malignant neoplasms

It is important that clinicians assess patients for HCV-associated extrahepatic malignancies and other extrahepatic manifestations of chronic HCV infection so that patients can receive timely diagnosis and treatment (**Figure 1**) [29,64]. Patients with malignancies known to be associated with HCV should be screened for HCV and other blood-borne viruses, including hepatitis B virus and HIV, during the diagnostic workup [82].

International guidelines on the treatment of chronic HCV infection prioritise treatment of patients with clinically significant extrahepatic manifestations of HCV infection, including B-cell NHL (**Figure 1**) [64,77,83,84].

Management of patients with chronic HCV infection and B-cell NHL depends on the aggressiveness of the lymphoma, which in turn depends on the histological subtype [52]. Indolent HCV-associated B-cell NHLs have been shown to respond well to treatment of HCV infection with IFN- and DAA-based therapies [52,72-74,78]; HCV treatment is recommended first line without chemotherapy for these patients [1,64].

Optimal management of patients with chronic HCV infection and aggressive lymphomas remains to be determined [52]. The 2013 National Comprehensive Cancer Network (NCCN) Guidelines recommend that patients with aggressive B-cell NHL are initially treated with chemotherapy regimens and that liver function tests and HCV RNA levels be monitored during and after chemotherapy to detect development of hepatotoxicity. Antiviral treatment should

be deferred and then considered on completion of lymphoma therapy and achievement of a complete remission [85]. However, at the time these guidelines were developed, only data on the impact of interferon-based therapies on lymphoma outcomes were available and few DAA-based regimens were available. Zignego, *et al.* have recommended that concurrent administration of DAAs and immunochemotherapy be tested in prospective trials [64].

More recently, it was recommended that antiviral therapy should be started prior to administration of chemotherapy in patients with aggressive B-cell NHL who require chemotherapy to avoid potential drug–drug interactions and to normalise alanine aminotransferase levels prior to chemotherapy [1]. It seems reasonable that this is a concern only where the potential for clinically significant drug–drug interactions is considerable and/or the patient has severely compromised hepatic function. The demonstration that DAA-based therapy can be safely administered concomitantly with standard chemotherapy regimens in patients with high-grade lymphomas is promising [79].

In summary, HCV is a known carcinogen that is associated with certain B-cell lymphomas and may be associated with other malignancies. Viral eradication with antiviral agents is associated with resolution of lymphoproliferative disease in a substantial proportion of patients with HCV-associated B-cell lymphomas, and early antiviral treatment may decrease the risk for B-cell NHL in HCV-infected patients. Screening for HCV is recommended in patients diagnosed with malignancies that are potentially associated with HCV (Table 1). Conversely, careful clinical assessment is recommended for HCV-related comorbidities, including cancer, in all HCV-

infected individuals (27). Recommendations regarding the timing of antiviral therapy vary in patients with B-cell lymphomas, although recent preliminary data suggest that early treatment may be preferred in all patients, including those with indolent and aggressive disease.

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Table 1: Hepatitis C virus-related hepatic and extrahepatic malignancies. Associations with HCV infection is based on solid pathogenic evidence for some cancers and on epidemiological data for others. Cancers are presented in alphabetical order regardless of prevalence or strength of evidence of an association with HCV infection

Malignancies
Anus
Appendageal skin cancer
B-cell lymphoma
Extrahepatic bile duct
Intrahepatic bile duct
Liver
Merkel cell carcinoma
Myelodysplastic syndrome
Nonmelanoma nonepithelial skin cancer
Pancreas
Papillary thyroid cancer
Prostate cancer
Uterine cancer

Table 2: Incidence and age-adjusted mortality for extrahepatic malignancies in patients with chronic HCV infection versus the general US population. Data are from 12,126 chronic HCV-infected persons in the Chronic Hepatitis Cohort Study who contributed 39,984 person years of follow-up from 2006 to 2010 and 133,795,010 records from 13 Surveillance, Epidemiology and End Results Program cancer registries, and approximately 12 million U.S. death certificates from Multiple Cause of Death data [17]

Malignancy	Incidence, SSR (95% CI)	Age-adjusted mortality, RR (95% CI)
Pancreas	2.5 (1.7–3.2)	1.6 (1.6–1.7)
Oral	–	5.2 (5.1–5.4)
Rectum	2.1 (1.3–2.8)	2.6 (2.5–2.7)
Kidney	1.7 (1.1–2.2)	–
Colon	0.4 (0.3–0.6)	–
NHL	1.6 (1.2–2.1)	2.3 (2.2–2.3)
Lung	1.6 (1.3–1.9)	–

CI, confidence interval; HCV, hepatitis C virus; NHL, non-Hodgkin lymphoma; RR, relative risk; SSR, standardised rate ratio; US, United States.

Table 3: Incidence and age-adjusted mortality for extrahepatic malignancies in patients aged ≥66 years with chronic HCV infection versus the general US population. Data are from a registry-based case-control study that used Surveillance, Epidemiology, and End Results (SEER)-Medicare data in US adults aged ≥66 years. Cases (n=1,623,538) were patients who had first cancers identified in SEER registries (1993-2011), whilst controls (n=200,000) were randomly selected, cancer-free individuals who were frequency matched to cases on age, sex, race, and calendar year [40]

Malignancy	Adjusted odds ratio (95% CI)
Liver	31.6 (29.0–34.3)
Intrahepatic bile duct	3.38 (2.51–4.56)
Extrahepatic bile duct	1.91 (1.41–2.58)
Pancreas	1.23 (1.09–1.40)
Anus	1.97 (1.42–2.73)
Nonmelanoma nonepithelial skin cancer	1.54 (1.15–2.04)
Myelodysplastic syndrome	1.56 (1.33–1.83)
Diffuse large B-cell lymphoma	1.57 (1.34–1.84)
Merkel cell carcinoma	1.92 (1.30–2.85)
Appendageal skin cancer	2.02 (1.29–3.16)
Uterine cancer	0.64 (0.51–0.80)
Prostate cancer	0.73 (0.66–0.82)

CI, confidence interval; HCV, hepatitis C virus; US, United States.

Figure 1: Therapeutic strategies for HCV-related disease

Left: Schematic representation of aetiopathogenesis of different manifestations of HCV syndrome; it is a multifactorial and multistep process triggered by HCV infection along with predisposing genetic factors and other unknown environmental/toxic triggers. HCV infection may represent a chronic stimulus for the immune system, leading to 'benign' lymphoproliferation and/or oncogenetic alterations, two different pathogenetic mechanisms that are not mutually exclusive. Potential virus-related factors include: HCV antigens (core, envelope E2, NS3, NS4, NS5A proteins), high-affinity binding between HCV-E2 and CD81 with consequent t(14;18) translocation and Bcl-2 proto-oncogene activation, cross-reactions between particular HCV antigens and host autoantigens (molecular mimicry mechanism), and/or direct infection of B-lymphocytes by HCV. Potential host factors include specific HLA alleles and/or metabolic and hormonal conditions. The consequent 'benign' B-cell proliferation with multiple autoimmune alterations may be responsible for different organ- and non-organ-specific autoimmune disorders, including mixed cryoglobulinaemia syndrome (cryoglobulinaemic vasculitis). On the other hand, Bcl2 proto-oncogene activation is responsible for prolonged B-cell survival. This latter condition may predispose to other genetic aberrations (c-myc, Bcl6 and p53 activation) that could lead to frank B-cell lymphomas (B-cell NHL) and other malignancies, i.e. HCC and papillary thyroid cancer. There is often a clinico-serological and pathological overlap among immunological and neoplastic disorders; namely, autoimmune organ-specific manifestations may evolve to systemic diseases such as mixed cryoglobulinaemia and, less frequently, to malignant neoplasia and vice versa. In this context, mixed cryoglobulinaemia syndrome represents a crossroads between autoimmune diseases and malignancies.

Right: Therapeutic strategies for HCV-related disease should include three interventions:

1. Direct-acting antiviral drugs to achieve HCV eradication;
2. Pathogenetic therapies with immunomodulatory/antineoplastic treatments;
3. Pathogenetic/symptomatic therapies, such as corticosteroids and plasma exchange.

Treatment should be individualised and should consider the activity/severity of clinical manifestations, as well as the presence of adverse prognostic factors and possible comorbidities.

Ab, antibody; B-NHL, B-cell non-Hodgkin lymphoma; CPX, cyclophosphamide; Cryo, cryoglobulinaemia; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; inv, HLA, human leukocyte antigen; IC, immune complexes; IgG, immunoglobulin G; PCT, porphyria cutanea tarda; RF, rheumatoid factor RTX, rituximab.

Figure 2: Lymphoma risk in patients with persistent chronic HCV infection versus patients with a sustained virologic response following interferon treatment [81]

HCV, hepatitis C virus; HR, hazard ratio.