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Recommendations of Polish HCV Expert Group and Polish Society of Haematologists and Transfusiologists on diagnosis and treatment of HCV-infected hemato-oncology patients

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Abstract

Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease. About 70% of infections lead to chronic hepatitis, which is associated with a risk of cirrhosis within 20 years in 15–30% of patients. A vaccine against hepatitis C is still not available, but directly-acting antiviral drugs allow eradication of the virus in more than 95% of those infected. HCV infection is particularly dangerous in patients with cancer, including proliferative hematological diseases. This is because patients chronically infected with HCV can develop exacerbations of hepatitis during oncological treatment, making therapy much more difficult to manage and thus adversely affecting prognosis. In addition, HCV infection plays an important role in the development of certain subtypes of B-cell non-Hodgkin lymphoma (NHL), such as marginal zone lymphoma, diffuse large cell lymphoma, and Waldenström macroglobulinemia. Antiviral treatment leads to a hematological response in 60–75% of patients with HCV-associated indolent NHL. This article presents epidemio-

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logical data on HCV infection in hematooncological patients, as well as recommendations on methods of diagnosis and principles of treatment of the infection in hematooncological patients, including patients with lymphomas associated with HCV infection.

Keywords: hematooncological patients, hepatitis C virus, HCV, prevention, treatment

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Introduction

Hepatitis C virus (HCV) can cause both acute and chronic hepatitis, ranging from mild to severe, and lead to cirrhosis and liver cancer. HCV infections are one of the leading causes of chronic liver disease. According to a 2020 estimate by the World Health Organization (WHO), 58 million people worldwide are chronically infected with the virus, with about 1.5 million new infections occurring annually [1]. Since HCV is a blood-borne virus, most infections occur through contact with the blood of an infected individual, which usually occurs while in a healthcare facility or during procedures which break the continuity of skin and mucous membranes, including cosmetic procedures, tattooing, and the use of intravenous and intranasal drugs. According to WHO estimates, about 290,000 people died from hepatitis C in 2019, mainly from cirrhosis and hepatocellular carcinoma [1]. About 30% of those infected spontaneously, i.e. without treatment, eliminate the virus within six months of infection. In the remaining 70%, HCV remains in the body, leading to chronic hepatitis. In this group of patients, the risk of cirrhosis within 20 years ranges from 15% to 30%. Currently, there is no vaccine available against hepatitis C (HCV). However, the availability of highly effective directly-acting antivirals (DAAs) allows the virus to be eradicated in more than 95% of infected individuals.

Of particular importance are HCV infections in patients with cancer, including proliferative hematological diseases. Exposure to HCV infection in this group is primarily due to frequent healthcare-related physical contacts. Recognizing and eliminating HCV infection in these patients reduces the burden of the underlying disease.

The prevalence of HCV infection among cancer patients generally exceeds that of the general population. In the United States, it ranges from 1.5–10.6%, while in Taiwan, it affects 6.0% of cancer patients undergoing chemotherapy [1, 2]. Chemotherapy can lead to immunosuppression and reactivation of chronic infections, including HCV. The recurrence of infection with this virus, on the one hand creates hepatological problems, and on the other hand can result in the need to discontinue chemotherapy, which negatively affects the results of oncological treatment.

The advent of highly effective DAAs several years ago gave hope that HCV infections could be rapidly eliminated as a global health problem [3, 4]. However, since most of these infections are asymptomatic for a long time, mass screening is needed in addition to effective treatment. Unfortunately, the will to implement this is lacking in the vast majority of countries despite an unquestionably favorable cost-effectiveness analysis. In addition, any screening campaign in 2020–2022 was hampered by the coronavirus disease pandemic (COVID-19). Therefore, achieving the goal set by the WHO i.e. to eliminate HCV infections from the list of humanity's most important social threats by 2030, seems unrealistic. Observing the results of large screening surveys carried out in recent years in Poland, it can be assumed that about 140,000 people infected with HCV are living in ignorance of their ongoing disease process of varying degrees [5, 6].

At the same time, an association between successful treatment of HCV infection with DAAs and regression of B-cell non-Hodgkin lymphoma (B-NHL) has been demonstrated [7, 8]. This indicates a particular rationale for HCV screening in this group of patients. Analysis of data from the EpiTer-2 database, collecting information on more than 13,000 patients treated for chronic hepatitis C, showed that two-thirds of HCV-infected patients with hematooncological disease were lymphoma patients, half of whom had non-Hodgkin lymphoma (NHL). Hematooncological patients were characterized by older age and more advanced liver disease. Despite this, the efficacy of DAA therapy in this group reached 100%.

Diagnosis of hemato-oncology patients for HCV infection

Chronic HCV-infected patients may develop reactivation or exacerbation of hepatitis associated with HCV infection during oncology treatment. Hepatological diagnosis should also consider the possibility of a *de novo* HCV infection.

HCV reactivation during chemotherapy is defined as an increase in HCV RNA levels of at least 1 $\log_{10}$ IU/mL from baseline. Recurrence of HCV-related hepatitis is defined as an increase in alanine aminotransferase (ALT) activity to three times the upper limit of normal during chemotherapy, and an increase in HCV RNA levels of at least 1 $\log_{10}$ IU/mL from baseline [3, 9] (Table I). It is estimated that 26–57% of cancer patients who develop an exacerbation of chronic hepatitis C during chemotherapy require discontinuation or modification of chemotherapy [9].

Table I. Definitions of hepatitis C virus (HCV) reactivation and HCV-related hepatitis exacerbation in cancer patients undergoing chemotherapy

Term	Definition
HCV reactivation	Increase in HCV RNA levels during chemotherapy by ≥1 $\log_{10}$ IU/mL from baseline
Exacerbation of HCV-related hepatitis	Unexplained increase in ALT activity to three times the upper limit of normal during chemotherapy and an increase in HCV RNA by ≥ 1 $\log_{10}$ IU/mL from baseline values

ALT — alanine aminotransferase

In a prospective observational study by Torres et al. [10], reactivation of HCV infection occurred in 23% of oncology patients undergoing chemotherapy and was significantly more common in patients with hematological malignancies than in those with solid tumors (36% vs. 10%).

In a retrospective study by Li et al. [11], the incidence of severe acute liver injury in HCV-infected patients with hematological malignancies was higher than in patients with hepatocellular carcinoma (HCC) and in patients with solid organ tumors (9.4% vs. 1.9% and 1.1%, respectively). The use of rituximab and the presence of hematological malignancy have been identified as risk factors for severe exacerbation of chronic HCV infection [11]. At the same time, early diagnosis of HCV infection and its cure have been proven to improve treatment outcomes and survival time for patients with NHL [12].

Following the example of other scientific societies [the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)], it is recommended that all patients with hematological malignancies be screened for hepatitis B virus (HBV, hepatitis B virus) and HCV infections before starting chemotherapy or immunochemotherapy [3, 13, 14].

The standard for diagnosis of HCV infection includes two tests:

- determination of the presence of anti-HCV antibodies in serum, and
- identification of HCV RNA in serum.

In some countries, a test to detect the presence of the virus core antigen (HCV core antigen) is also used, which can replace HCV RNA testing in the process of diagnosing HCV infection. However, this is yet to gain widespread recognition in Poland.

The genetic material of the virus (HCV RNA) is detected in the blood 1–3 weeks after infection and remains present until self-elimination — by force of nature or by cure with antiviral drugs. Anti-HCV antibodies are detectable in the blood 4–10 weeks after infection and will remain present in the serum for life, even in patients after pharmacological eradication of the virus [15, 16].

The method of determination of the presence of anti-HCV antibodies is a screening test. For this purpose, an enzyme immunoassay (EIA) or rapid diagnostic test (RDT) is used. The test material for RDT can be serum or plasma, as well as whole blood from the capillaries of a fingertip or saliva. RDT rapid anti-HCV antibody diagnostic tests are easy to perform at room temperature — they do not require specialized equipment or intensive training. They have been shown to have high sensitivity and specificity. If anti-HCV antibodies are found, HCV RNA should be tested by polymerase chain reaction (PCR) or, alternatively, HCV core antigen testing to identify patients with active infection. Confirmation of viral load by HCV core antigen testing from whole blood by the dried blood spot (DBS) method is not recommended, as DBS is insufficiently sensitive at identifying HCV core antigen [16].

In 40–70% of people in whom anti-HCV antibodies are present, HCV RNA is detected. Testing for the presence of HCV RNA in a sample obtained for anti-HCV antibody testing has been shown to significantly increase the percentage of positive patients. Sensitive molecular methods are recommended for the diagnosis of HCV RNA. Recently, the possibility of performing rapid molecular tests, the results of which are available in as little as 45 minutes, has emerged.

HCV RNA testing is required in detecting reinfection after prior spontaneous or treatment-related viral clearance, as anti-HCV antibodies are likely to persist for life. In patients with secondary immunodeficiency and those with possible exposure to HCV in the past six months, HCV antibody testing may be negative because of delayed or failed seroconversion or testing performed during the serological window [16].

It is recommended that serum HCV RNA be determined as the first/single test, without evaluating the presence of anti-HCV antibodies, in cases of:

- suspected repeat HCV infection in persons who have eliminated the virus spontaneously or as a result of therapy;
- persons after exposure to HCV infection who are in the serological window period;
- persons with secondary immunodeficiency, **including those receiving immunosuppressive therapy**;
- **individuals prior to hematopoietic cell transplantation;**
- children born to HCV-infected mothers, up to 18 months of age.

The rules for interpreting the results of laboratory tests used in the diagnosis of HCV are presented in Table II [16]. Persons with anti-HCV antibodies present and an undetectable HCV viral load (HCV RNA–) should be informed that there is no evidence of HCV infection in them. HCV RNA testing can be repeated if there is an increased risk of HCV infection or if a recent infection is suspected. If the clinician or the patient wishes to determine whether

Table II. Interpretation of test results for hepatitis C virus (HCV) infection (compiled from [16])

Anti-HCV antibodies	HCV RNA determined by PCR	Clinical interpretation
Present	Present	Acute or chronic hepatitis (depending on clinical picture and liver lesions)
Present	Absent	Past HCV infection signifying status after: • spontaneous elimination or • cure of infection or a false serologic test result
Absent	Present	Early phase of HCV infection or HCV infection in immunocompromised individuals
Absent	Absent	No HCV infection

PCR — polymerase chain reaction

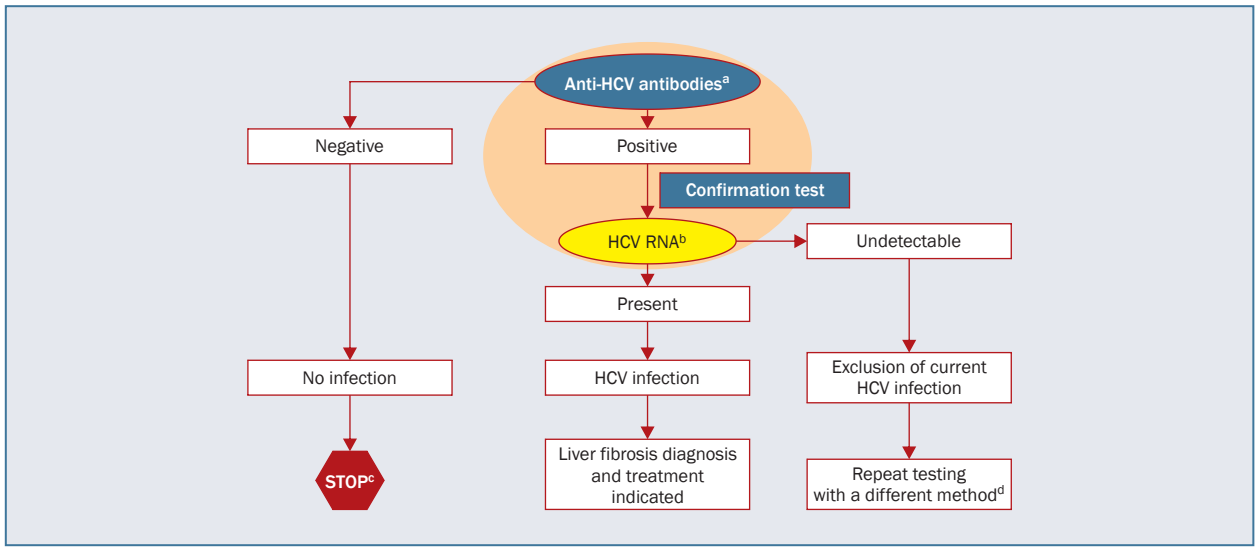

Figure 1. Schematic for diagnosis of hepatitis C virus (HCV) infection — recommended tests for diagnosis of current HCV infection or reinfection (compiled from [14]); [a]for diagnosis of current initial HCV infection, start with HCV antibody (anti-HCV) testing; [b]for recurrent HCV infection, start with HCV RNA testing; [c]for individuals who may have been exposed to HCV in the past six months, HCV RNA testing or further anti-HCV testing should be performed. For immunocompromised individuals, HCV RNA testing should be performed; [d]by distinguishing past HCV infection from false positives for anti-HCV, another anti-HCV test may be considered

a positive anti-HCV antibody test result in the absence of HCV viremia indicates a history of HCV infection, or a false positive, a repeat test can be performed using a different test to evaluate the presence of anti-HCV antibodies. A false-positive result is usually not obtained in two different tests (Figures 1, 2).

Universal screening for HCV in hematological cancer patients before chemotherapy is now recommended.

Prior to antiviral treatment, quantitative HCV RNA testing is recommended to determine baseline viral load. With the advent of pan-genotypic DAA regimens, HCV genotyping is not commonly required before starting treatment, especially in previously untreated patients without cirrhosis if a pan-genotypic regimen is used. Pre-treatment genotyping is recommended in patients after previous HCV treatment failure, or in a situation of planned genotype-specific therapy. In addition, whenever there is an increase in aminotransferase activity during hematooncological treatment, the diagnosis of HCV infection should be repeated, as it is possible for a patient to become infected *de novo* during medical procedures.

Treatment of HCV infection in patients with HCV-associated lymphomas

Epidemiology

The results of many epidemiological analyses have shown that HCV infection plays an important role in the development of certain subtypes of B-NHL. These are among the most important extrahepatic manifestations of HCV infection. At the same time, it has been suggested that genetic and environmental factors may account for geographical differences in lymphoma incidence [17–19]. The results of a meta-analysis by Pozzato et al. [20], including 19 cohort

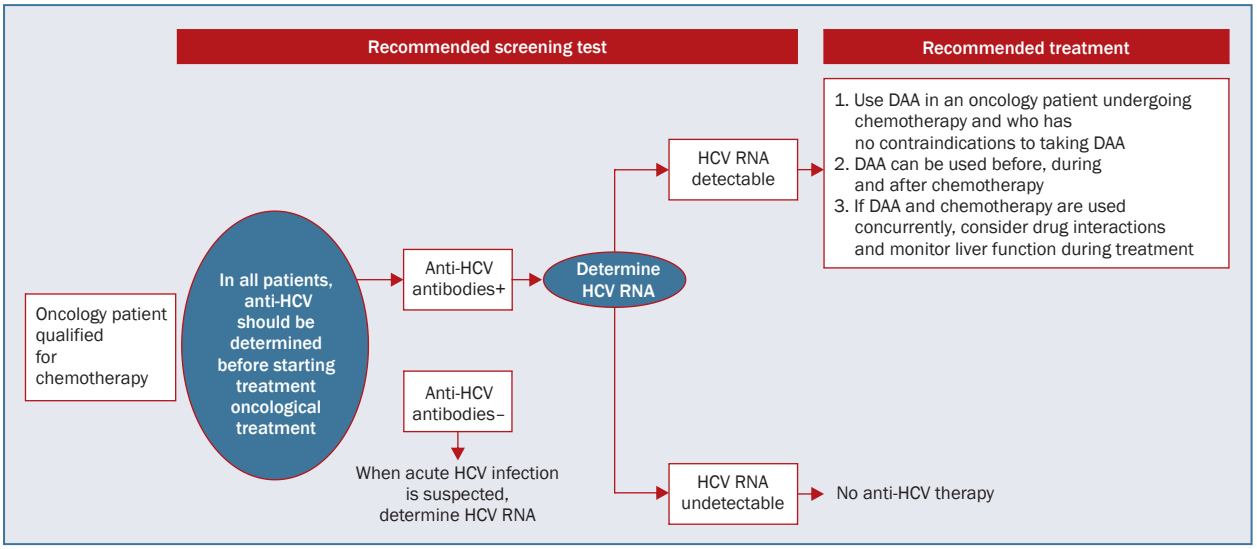

Figure 2. Recommendations for testing and treatment of hepatitis C virus (HCV) infection in cancer patients undergoing chemotherapy (compiled from [13]); DAAs — directly-acting antivirals

and four case-control studies, found that HCV infection is associated with a 2.5-fold increased risk of developing lymphoma. The incidence of HCV-associated lymphoma depends on the geographical zone, reaching as high as 20% in endemic areas such as Egypt or some areas of Italy, and being much lower in non-endemic areas such as Northern Europe [20]. On average, about 10% of NHL cases are thought to be associated with HCV infection. A meta-analysis by the InterLymph Epidemiology Consortium showed the presence of HCV infection in 172 of 4,784 NHL patients. HCV infection has been found most frequently in three types of lymphoma: marginal zone lymphoma (MZL), diffuse large B-cell lymphoma (DLBCL), and Waldenström macroglobulinemia (WM). The risk of developing DLBCL in HCV-infected patients was 2.4, of developing MZL was 2.47, and of developing WM was 2.57 [21]. In a group of 116 HCV-associated B-NHL patients described by Michot et al. [22], the two most common lymphoma subtypes were MZL and DLBCL (39% each). Among MZLs, splenic marginal zone lymphoma (SMZL) was found to be particularly associated with HCV infection. In an Italian analysis involving 255 patients with SMZL, HCV infection was found in 49 (19%) [23]. An association with HCV infection has also been described in patients with extranodal and nodal MZL [24]. An Italian case-control study involving 400 NHL patients showed that a significantly higher risk was associated with the development of DLBCL [odds ratio (OR) 3.5] compared to indolent NHL (iNHL), suggesting that 1/20 of DLBCL cases in the Italian population were potentially associated with HCV [25]. A study by a French group found that one in three patients with HCV-associated DLBCL developed aggressive lymphoma from iNHL, usually MZL [26]. This confirms that MZL is the most common type of HCV-associated lymphoma, at which time it seems to be characterized by an increased risk of transformation into DLBCL. In contrast, follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL) have rarely been associated with HCV infection.

Pathogenesis

Hepatitis C virus is a single-stranded RNA virus that does not integrate into the host genome due to the lack of reverse transcriptase. Thus, it can perform its oncogenic role indirectly through modulation of the host's immune system. The process of HCV transformation can be explained by three possible theories, according to which: 1) the external receptors of lymphocytes are continuously stimulated by viral antigen, resulting in their proliferation; 2) HCV replication occurs inside B cells and then mediates its oncogenic effects through intracellular HCV proteins; or 3) there is permanent B cell damage caused by intracellular virus (e.g. mutation of tumor suppressor genes) — the so-called 'hit and run' theory [2]. HCV can protect B lymphocytes from apoptosis, possibly through suppression of caspase 1 (CASP1) and caspase 4 (CASP4) and overexpression of the anti-apoptotic protein BCL2. In addition, HCV has been linked to reduced expression of major histocompatibility complex (MHC) class II molecules in B lymphocytes and thus may result in inhibition of antigen processing and presentation [8]. The classic manifestation of extrahepatic manifestations of HCV is mixed cryoglobulinemia, which is essentially a lymphoproliferative disease of B-cell clones with low-grade malignancy that is initially limited to the bone marrow and then in 10–20% of patients transforms into an aggressive malignant lymphoma several years after diagnosis [19].

Clinical characteristics

HCV-associated non-Hodgkin lymphomas are characterized by distinct clinical presentation and prognosis. An analysis of 13,368 NHL patients, including 3,063 HCV-infected patients, was published in 2021, showing that HCV-infected patients had significantly shorter progression-free survival (PFS) and overall survival (OS), as well as lower response rates than uninfected patients. In addition, they had a more advanced stage of lymphoma and more frequent liver and spleen involvement. Antiviral treatment was associated with prolonged OS, better response rates, and lower rates of NHL progression [27]. HCV-associated marginal zone lymphomas develop after a very long (15–25 years) period of infection. Splenic involvement has been described in 44% of patients, and marrow/blood involvement in 45%. Extranodal forms of HCV-associated lymphoma are also common [28]. Autoimmune complications, monoclonal gammopathy, and mixed cryoglobulinemia are more common in patients with HCV-associated iNHL than in patients with HCV-positive aggressive lymphomas. Compared to DLBCL, MZL patients were more likely to have cryoglobulinemia (75% vs. 44%) and rheumatoid factor (68% vs. 35%). Data from a retrospective analysis by Tsai et al. [29] showed that patients with HCV-associated DLBCL tended to be older, with frequent splenic and extranodal organ involvement, high lactate dehydrogenase (LDH) activity, and a high International Prognostic Index (IPI), compared to patients without HCV infection. In the era of rituximab in the treatment of DLBCL, the prognosis of patients with HCV-associated DLBCL does not differ from that of patients with DLBCL unrelated to HCV infection when treated appropriately [29].

The most convincing evidence of the role of HCV in the development of lymphomas concerns observations of hematological response in the form of lymphoma regression in iNHL patients after antiviral treatment, and the beneficial effect of antiviral treatment on anticancer outcomes. In iB-NHL patients, a beneficial effect and the possibility of achieving lymphoma regression after antiviral treatment, both based on interferon alpha (IFN-alpha-2) and via non-interferon (DAA) therapies, have been described. The use of antiviral therapy leads to a hematological response in 60–75% of patients with HCV-related iNHL [12, 30, 31]. A meta-analysis of 20 clinical trials found that the use of IFN-alpha-2-based therapies resulted in lymphoma regression in 73% of patients with HCV-associated lymphomas, with a significant correlation described between sustained viral response (SVR) and hematological response. The efficacy of IFN-based antiviral therapy seems to confirm a link between HCV infection and lymphoma development, but the antiproliferative effect of IFN-alpha-2 on tumor cells alone cannot be ruled out. Therefore, only the results of non-interferon therapies have definitively confirmed the etiological role of HCV in lymphoma transformation. The use of DAA therapy induces SVR in almost 100% of HCV-infected patients, regardless of genotype or degree of fibrosis, and has better tolerability than IFN-alpha-2-based therapies. Directly-acting antiviral drugs are now the standard of care for HCV infection. In 2016, the results of an international study were published, in which 46 patients with iNHL or small lymphocytic lymphoma (SLL)/CLL with concomitant HCV infection received DAA treatment. A sustained virological response was achieved in 98% of patients and a hematological response in 67%, with a better response in SLL patients (73%) than in patients with lymphomas of other subtypes (44%). Interestingly, despite the virological response, none of the SLL/CLL patients achieved a hematological response. After a median follow-up of eight months from the start of DAA therapy, one-year PFS and OS rates were 75% and 98%, respectively [32]. Similar data was obtained in a larger group of 100 patients with HCV-associated NHL. The percentage of SVR was higher in patients treated with DAA compared to those treated with IFN-alpha-2 (98% vs. 80%). Response rates were similar, being 69% among DAA-treated and 80% among IFN-treated patients, while complete remission (CR) rates were higher in IFN-alpha-2-treated patients (21% vs. 48%). After a median follow-up of 17 months, the estimated 3-year time to PFS and OS were similar in the DAA- and IFN-alpha-2-treated populations [33]. DAA therapy thus achieved both HCV eradication and hematological response in the majority of patients, confirming both the pathogenetic role of HCV and the sensitivity of certain types of lymphoma to antiviral therapy. A growing body of data indicates that HCV eradication is also important for optimal response in the form of disease-free survival (DFS) in DLBCL patients. Antiviral treatment alone did not provide a benefit over standard immunochemotherapy in patients with HCV-associated DLBCL lymphoma, probably due to loss of antigenic dependence and the emergence of additional mutations affecting a more aggressive clinical course. Concomitant antiviral treatment based on IFN-alpha-2 with or without ribavirin was shown not to be feasible due to hematological toxicity [34]. In 2018, Occhipinti et al. [35] described the results of DAA treatment used concurrently with immunochemotherapy in seven HCV+ DLBCL patients. The treatment was well tolerated, and, according to the authors, could probably also prevent chemotherapy-induced liver damage [35]. In an observational study, Persico et al. [7] evaluated the safety and efficacy of DAA (sofosbuvir/ledipasvir) used concomitantly with immunochemotherapy in 20 DLBCL HCV+ patients. No differences were observed regarding OS or the incidence of side effects, while DFS was significantly longer in patients receiving antiviral treatment [7]. Similar findings were described in a retrospective international analysis in which DAA was used concurrently or sequentially with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). The sustained virological response

was 96% for both treatments. Hepatic toxicity was more common with sequential treatment. After a median follow-up of 2.8 years, the 2-year PFS and OS were 97% and 93%, respectively. Merli et al. [36] also used DAA concurrently with salvage therapy in patients with refractory or relapsed DLBCL, achieving SVR with good treatment tolerance. Based on the above data, the following recommendations were made:

1) HCV screening should be performed in all lymphoma patients, especially MZL, DLBCL and WM;
2) in MZL patients with coexisting HCV infection not requiring immediate anticancer treatment, DAA treatment should be used;
3) in DLBCL patients with coexisting HCV infection, DAA should be administered concurrently with or sequentially after immunochemotherapy, with concurrent treatment likely to be preferable due to the prevention of hepatic toxicity of anticancer treatment.

Treatment of HCV infection in hemato-oncology patients with HCV-independent diseases

On the one hand, the varied course of cancers of the hematopoietic and lymphatic systems makes it possible, in some cases, to defer anticancer therapy and, if necessary, to use anti-HCV treatment in advance. In each case, the risk of progression and deterioration of the patient's clinical condition resulting from tumor progression must be taken into account. On the other hand, anticancer treatment can result in profound immune deficits and hepatotoxicity, worsening the course of hepatitis C. This accompanies transplantation procedures to the greatest extent because they are associated with the need for high doses of cytostatics. With allo-HCT, cell-specific immunity is temporarily eliminated. It is rebuilt from donor cells, a process that takes months or years, and the immune deficit is further aggravated by the use of immunosuppressive drugs, usually for at least six months [13].

However, it should be noted that elevated ALT activity, or other features of liver damage resulting from HCV infection, can sometimes be mistaken for hepatotoxicity of anticancer drugs, leading to decisions to reduce their doses or discontinue them. Another potential adverse impact is the possible influence of systemic inflammation associated with HCV infection on the course of hematooncological diseases, even if it is not directly related to HCV proteins.

An additional argument for deferring anticancer treatment in hepatitis C patients is the possibility of interaction between cytostatics and antiviral drugs (Table III) [37]. It should be noted that such a deferral will rarely be for longer than 8–12 weeks. On the other hand, in the absence of interaction, it is possible to carry out anti-HCV and hematological treatment simultaneously, provided that the hematologist and the infectious disease physician work closely together. Most hematological drugs and biologics have a very low potential for drug interactions and can usually be used concurrently with anti-HCV drugs. Unfortunately, for 'classic' hematological drugs, interactions with DAAs are often poorly understood.

Summary

The recommendations of the Polish HCV Expert Group and the Polish Society of Hematology and Transfusion Medicine on the diagnosis and treatment of HCV-infected hematological patients were prepared on the basis of etiopathogenetic data on the co-occurrence of HCV infection and certain cancers of the lymphatic system, as well as on current knowledge of the principles of diagnosis and treatment of HCV infection in patients diagnosed with cancer. The above recommendations unequivocally indicate the need for changes in the hitherto functioning principles of management of HCV-infected hematological patients, both in the process of diagnosis and treatment. According to previous clinical practice, all patients with blood cancers were recommended to determine anti-HCV antibodies before starting treatment, and in a case of a positive result — HCV RNA testing. Experts point out, however, that in hematological patients with secondary immune disorders resulting from the primary disease, and in particular in patients with lymphoid malignancies, HCV RNA testing should also be performed as part of screening because, in such patients, the anti-HCV assay result may be falsely negative. Currently, HCV RNA testing is only mandatory in patients before hematopoietic cell transplantation.

It should be emphasized that in patients with lymphoid malignancies, particularly MZL, WM and DLBCL, HCV infection may be one of the etiopathogenetic factors or a factor accelerating the transformation of iNHL to aggressive lymphomas. Therefore, iNHL patients with coexisting HCV infection who do not require immediate antitumor treatment should be treated first with DAA therapy, as it can lead to long-term remission of iNHL without the need for immunochemotherapy.

For hematological and lymphoid malignancy patients with coexisting HCV infection who do not require immediate hematological treatment, modern antiviral therapy should be the recommended treatment. On the other hand, in patients with acute hematological malignancies or aggressive lymphomas, such as DLBCL, coexisting with HCV infection, DAAs should be sought concurrently with chemotherapy or immunochemotherapy. Alternatively, DAAs can be administered sequentially, always taking into account possible drug interactions. In managing such cases, close cooperation between the hematologist and the infectious disease physician is essential.

Table III. Most commonly used drugs in hematooncological diseases and their possible interactions with pan-genotypic hepatitis C virus antiviral drugs, based on University of Liverpool Hep Drug Interactions (source [37])

Diseases and procedures	Possibility of deferring treatment	Most commonly used medications*	Potential interactions with antiviral drugs**	Direction of interaction
Acute myeloid leukemia	No	Daunorubicin	nd	
		Cytarabine	nd	
		Cladribine	nd	
		Mitoxantrone	GLE/PIB; SOF/VEL — monitoring	↑ mitoxantrone concentration
			VOX — contraindicated	
		Etoposide	No interaction	
		Midostaurin	nd	
		Venetoclax	nd	
		Azacitidine	nd	
Chronic myelogenous leukemia	Mostly yes	Imatinib	GLE/PIB; SOF/VEL — monitoring	↑ imatinib concentration
			VOX — contraindicated	
		Dazatinib	No interaction	
		Nilotinib	GLE/PIB; SOF/VEL — monitoring	↑ nilotinib concentration
			VOX — contraindicated	
		Ponatinib	nd	
		Bosutinib	GLE/PIB — monitoring	↑ bosutinib concentration
Polycythemia vera	Mostly yes	Hydroxycarbamide	nd	
Essential thrombocytopenia	Mostly yes	Hydroxycarbamide	nd	
		Anagrelid	No interaction	
Myelofibrosis	Mostly yes	Hydroxycarbamide	nd	
		Ruxolitinib	No interaction	
Myelodysplastic syndromes	Mostly yes	Azacitidine	nd	
		Lenalidomide	No interaction	
Acute lymphoblastic leukemia/lymphoma	No	Daunorubicin	nd	
		Vincristine	GLE/PIB; VOX — contraindicated SOF/VEL — monitoring	↑ vincristine concentration
		Dexamethasone	GLE/PIB; VOX — monitoring	↓ GLE; PIB; VOX concentration
		PEG-asparaginase	nd	
		Etoposide	No interaction	
		Methotrexate	VOX — contraindicated	↑ methotrexate concentration
			GLE/PIB; SOF/VEL — monitoring	
		Cytarabine	nd	
		Cyclophosphamide	No interaction	
		Fludarabine	No interaction	
		Mercaptopurine	No interaction	
Non-Hodgkin lymphoma	Variously	Doxorubicin	GLE/PIB — monitoring	↑ doxorubicin concentration
		Vincristine	GLE/PIB; VOX — contraindicated	↑ vincristine concentration
			SOF/VEL — monitoring	
		Prednisone	No interaction	

→

Table III (cont.). Most commonly used drugs in hematooncological diseases and their possible interactions with pan-genotypic hepatitis C virus antiviral drugs, based on University of Liverpool Hep Drug Interactions (source [37])

Diseases and procedures	Possibility of deferring treatment	Most commonly used medications*	Potential interactions with antiviral drugs**	Direction of interaction
		Cyclophosphamide	No interaction	
		Cisplatin	No interaction	
		Carboplatin	No interaction	
		Etoposide	No interaction	
		Ifosfamide	nd	
		Gemcitabine	No interaction	
		Bendamustine	Estramustine — no interaction	
		Fludarabine	No interaction	
		Ibrutinib	nd	
		Venetoclax	nd	
		Idelalisib	nd	
		Bortezomib	No interaction	
		Lenalidomide	No interaction	
		Chlorambucil	No interaction	
Hodgkin lymphoma	Sometimes yes	Doxorubicin	GLE/PIB — monitoring	↑ doxorubicin concentration
		Bleomycin	nd	
		Vinblastine	GLE/PIB; VOX — contraindicated	↑ vinblastine concentration
			SOF/VEL — monitoring	
		Dacarbazine	nd	
		Procarbazine	nd	
		Etoposide	No interaction	
		Vincristine	GLE/PIB; VOX — contraindicated	↑ vincristine concentration
			SOF/VEL — monitoring	
		Prednisone	No interaction	
		Ifosfamide	nd	
		Cisplatin	No interaction	
		Carboplatin	No interaction	
		Gemcytabine	No interaction	
		Brentixumab vedotin	GLE/PIB — monitoring	
Multiple myeloma	Sometimes yes	Bortezomib	No interaction	↑ MMAE concentration
		Carfilzomib	nd	
		Oxazomib	nd	
		Lenalidomide	No interaction	
		Thalidomide	No interaction	
		Pomalidomide	nd	
		Dexamethasone	GLE/PIB; VOX — monitoring	↓ GLE/PIB, VOX concentration
		Melphalan	nd	

→

Table III (cont.). Most commonly used drugs in hematooncological diseases and their possible interactions with pan-genotypic hepatitis C virus antiviral drugs, based on University of Liverpool Hep Drug Interactions (source [37])

Diseases and procedures	Possibility of deferring treatment	Most commonly used medications*	Potential interactions with antiviral drugs**	Direction of interaction
High-dose treatment (auto--HCT/allo-HCT)	Sometimes yes	Busulfan	nd	
		Cyclophosphamide	No interaction	
		Melphalan	nd	
		Thiotepa	nd	
		Carmutine	nd	
		Etoposide	No interaction	
		Cytarabine	bd	
		Bendamustine	Estramustine — no interaction	
		Fludarabine	No interaction	
Immunosuppression in patients after allo-HCT	No	Cyclosporine	VOX — contraindicated	↑ VOX concentration
			GLE/PIB — monitoring	↑ GLE/PIB concentration
		Tacrolimus	GLE/PIB; VOX — monitoring	↑↓ tacrolimus concentration, values should be monitored
		Sirolimus	GLE/PIB; VOX — monitoring	↑ sirolimus concentration
		Mycophenolate mofetil	No interaction	
		Methotrexate	VOX — contraindicated	↑ metothotrexate concentration
			GLE/PIB; SOF/VEL — monitoring	

*Biologics are not listed due to their low potential to cause drug interactions; **the most commonly used antiviral, pan-genotypic therapies are included, viz: GLE/PIB — glecaprevir/pibrentasvir, SOF/VEL — sofosbuvir/velpatasvir, VOX — voxilaprevir; allo-HCT — allogeneic hematopoietic cell transplantation; auto-HCT — autologous hematopoietic cell transplantation; MMAE — monomethyl aurostatin E; nd — no data

The authors of this paper believe that the recommendations presented should be included in the updated standards of diagnostic and therapeutic management for patients with hematological and lymphoid malignancies. We also believe there should be extensive education in this regard, similar to the recommendations regarding HBV infection in hematological patients treated with immunochemotherapy and inhibitors of cellular pathways, including tyrosine kinases.

Article information and declarations

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Conflict of interest
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References

1. World Health Organization. Hepatitis C. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c (July 18, 2023).
2. Torres HA, Shigle TL, Hammoudi N, et al. The oncologic burden of hepatitis C virus infection: a clinical perspective. CA Cancer J Clin. 2017; 67(5): 411–431, doi: 10.3322/caac.21403, indexed in Pubmed: 28683174.
3. Pawlotsky JM, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C: final update of the series. J Hepatology. 2020; 73(5): 1170–1218, doi: 10.1016/j.jhep.2020.08.018.
4. Halota W, Flisiak R, Juszczyk J, et al. Recommendations of the Polish Group of Experts for HCV for the treatment of hepatitis C in 2020. Clin Exp Hepatol. 2020; 6(3): 163–169, doi: 10.5114/ceh.2020.98606, indexed in Pubmed: 33145422.
5. Piekarska A, Tomasiewicz K, Halota W, et al. Searching for the optimal population for hepatitis C virus screening in Poland. Clin Exp Hepatol. 2020; 6(2): 74–76, doi: 10.5114/ceh.2020.94969, indexed in Pubmed: 32728622.
6. Flisiak R, Zarębska-Michaluk D, Ciupkeviciene E, et al. HCV elimination in central Europe with particular emphasis on microelimination in prisons. Viruses. 2022; 14(3), doi: 10.3390/v14030482, indexed in Pubmed: 35336889.
7. Persico M, Aglitti A, Caruso R, et al. Efficacy and safety of new direct antiviral agents in hepatitis C virus-infected patients with diffuse large B-cell non-Hodgkin's lymphoma. Hepatology. 2018; 67(1): 48–55, doi: 10.1002/hep.29364, indexed in Pubmed: 28714143.
8. Masarone M, Persico M. Hepatitis C virus infection and non-hepatocellular malignancies in the DAA era: a systematic review and meta-analysis. Liver Int. 2019; 39(7): 1292–1306, doi: 10.1111/liv.14119, indexed in Pubmed: 30983083.

9. Li YR, Chen WC, Tsai WL, et al. Severe acute exacerbation of HCV infection in cancer patients who undergo chemotherapy without antiviral prophylaxis. J Viral Hepat. 2020; 27(9): 873–879, doi: 10.1111/jvh.13302, indexed in Pubmed: 32301253.
10. Torres HA, Hosry J, Mahale P, et al. Hepatitis C virus reactivation in patients receiving cancer treatment: a prospective observational study. Hepatology. 2018; 67(1): 36–47, doi: 10.1002/hep.29344, indexed in Pubmed: 28653760.
11. Li YR, Hu TH, Chen WC, et al. Screening and prevention of hepatitis C virus reactivation during chemotherapy. World J Gastroenterol. 2021; 27(31): 5181–5188, doi: 10.3748/wjg.v27.i31.5181, indexed in Pubmed: 34497443.
12. Hosry J, Mahale P, Turturro F, et al. Antiviral therapy improves overall survival in hepatitis C virus-infected patients who develop diffuse large B-cell lymphoma. Int J Cancer. 2016; 139(11): 2519–2528, doi: 10.1002/ijc.30372, indexed in Pubmed: 27501007.
13. Mallet V, van Bömmel F, Doerig C, et al. ECIL-5. Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation: recommendations of the 5th European Conference on Infections in Leukaemia (ECIL-5). Lancet Infect Dis. 2016; 16(5): 606–617, doi: 10.1016/S1473-3099(16)00118-3, indexed in Pubmed: 27599653.
14. AASLD/IDSA HCV guidance: recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_January_21_2021.pdf (January 21, 2021).
15. Schillie S, Wester C, Osborne M, et al. CDC recommendations for hepatitis C screening among adults — United States, 2020. MMWR Recomm Rep. 2020; 69(2): 1–17, doi: 10.15585/mmwr.rr6902a1, indexed in Pubmed: 32271723.
16. Tomasiewicz K, Flisiak R, Jaroszewicz J, et al. Recommendations of the Polish Group of Experts for HCV for the treatment of hepatitis C in 2023. Clin Exp Hepatol. 2023; 9(1): 1–8, doi: 10.5114/ceh.2023.125957, indexed in Pubmed: 37064834.
17. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev. 2006; 15(11): 2078–2085, doi: 10.1158/1055-9965.EPI-06-0308, indexed in Pubmed: 17119031.
18. Nieters A, Kallinowski B, Brennan P, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study EPILYMPH. Gastroenterology. 2006; 131(6): 1879–1886, doi: 10.1053/j.gastro.2006.09.019, indexed in Pubmed: 17087949.
19. Giordano TP, Henderson L, Landgren O, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. JAMA. 2007; 297(18): 2010–2017, doi: 10.1001/jama.297.18.2010, indexed in Pubmed: 17488966.
20. Pozzato G, Mazzaro C, Dal Maso L, et al. Hepatitis C virus and non-Hodgkin's lymphomas: meta-analysis of epidemiology data and therapy options. World J Hepatol. 2016; 8(2): 107–116, doi: 10.4254/wjh.v8.i2.107, indexed in Pubmed: 26807206.
21. de Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol. 2008; 6(4): 451–458, doi: 10.1016/j.cgh.2008.02.011, indexed in Pubmed: 18387498.
22. Michot JM, Canioni D, Driss H, et al. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. Am J Hematol. 2014; 90(3): 197–203, doi: 10.1002/ajh.23889.
23. Arcaini L, Burcheri S, Rossi A, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol. 2007; 18(2): 346–350, doi: 10.1093/annonc/mdl388, indexed in Pubmed: 17071937.
24. Libra M, Polesel J, Russo AE, et al. Extrahepatic disorders of HCV infection: a distinct entity of B-cell neoplasia? Int J Oncol. 2010; 36(6): 1331–1340, doi: 10.3892/ijo_00000618, indexed in Pubmed: 20428756.
25. Mele A, Pulsoni A, Bianco E, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. Blood. 2003; 102(3): 996–999, doi: 10.1182/blood-2002-10-3230, indexed in Pubmed: 12714514.
26. Besson C, Canioni D, Lepage E, et al. Groupe d'Etude des Lymphomes de l'Adulte Programs. Characteristics and outcome of diffuse large B-cell lymphoma in hepatitis C virus-positive patients in LNH 93 and LNH 98 Groupe d'Etude des Lymphomes de l'Adulte programs. J Clin Oncol. 2006; 24(6): 953–960, doi: 10.1200/JCO.2005.01.5016, indexed in Pubmed: 16418500.
27. Zhang M, Gao F, Peng L, et al. Distinct clinical features and prognostic factors of hepatitis C virus-associated non-Hodgkin's lymphoma: a systematic review and meta-analysis. Cancer Cell Int. 2021; 21(1): 524, doi: 10.1186/s12935-021-02230-1, indexed in Pubmed: 34627251.
28. Michot JM, Canioni D, Driss H, et al. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. Am J Hematol. 2014; 90(3): 197–203, doi: 10.1002/ajh.23889.
29. Tsai Y-F, Liu Y-C, Yang C-I, et al. Poor prognosis of diffuse large B-cell lymphoma with hepatitis C infection. J Pers Med. 2021; 11(9), doi: 10.3390/jpm11090844, indexed in Pubmed: 34575621.
30. Gisbert JP, García-Buey L, Pajares JM, et al. Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection. Aliment Pharmacol Ther. 2005; 21(6): 653–662, doi: 10.1111/j.1365-2036.2005.02395.x, indexed in Pubmed: 15771751.
31. Arcaini L, Merli M, Volpetti S, et al. Indolent B-cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. Clin Dev Immunol. 2012; 2012: 638185, doi: 10.1155/2012/638185, indexed in Pubmed: 22956970.
32. Arcaini L, Besson C, Frigeni M, et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Blood. 2016; 128(21): 2527–2532, doi: 10.1182/blood-2016-05-714667.
33. Frigeni M, Besson C, Visco C, et al. Interferon-free compared to interferon-based antiviral regimens as first-line therapy for B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Leukemia. 2020; 34(5): 1462–1466, doi: 10.1038/s41375-019-0687-2, indexed in Pubmed: 31836855.
34. Musto P, Dell'Olio M, Sala ALa, et al. Diffuse B-large cell lymphomas (DBLCL) with hepatitis-C virus (HCV) infection: clinical outcome and preliminary results of a pilot study combining R-CHOP with antiviral therapy. Blood. 2005; 106(11): 2447–2447, doi: 10.1182/blood.v106.11.2447.2447.
35. Occhipinti V, Farina L, Viganò M, et al. Concomitant therapy with direct-acting antivirals and chemoimmunotherapy in HCV-associated diffuse large B-cell lymphoma. Dig Liver Dis. 2019; 51(5): 719–723, doi: 10.1016/j.dld.2018.10.019, indexed in Pubmed: 30502232.
36. Merli M, Frigeni M, Alric L, et al. Direct-Acting antivirals in hepatitis C virus-associated diffuse large B-cell lymphomas. Oncologist. 2018; 24(8): e720–e729, doi: 10.1634/theoncologist.2018-0331.
37. University of Liverpool. HEP drug interactions. https://www.hep-druginteractions.org (December 10, 2023).