Clinical features of hepatitis E infections in patients with hematologic disorders

Susanne Ghandili,[1*] Cecilia Lindhauer,[1*] Sven Pischke,[2] Julian Schulze zur Wiesch,[2] Philipp H. von Kroge,[3] Susanne Polywka,[4] Carsten Bokemeyer,[1] Walter Fiedler,[1] Nicolaus Kröger,[5] Francis Ayuk,[5] Raissa Adjallé[5#] and Franziska Modemann[1,6#]

[1]Department of Oncology, Hematology and Bone Marrow Transplantation with Section Pneumology, University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf; [2]The I. Department of Internal Medicine, Division of Infectious Diseases, University Medical Center Hamburg-Eppendorf; [3]Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf; [4]The Institute of Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf; [5]Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf and [6]Mildred Scheel Cancer Career Center, University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

**SG and CL contributed equally as co-first authors.*
#RA and FM contributed equally as co-last authors.

Correspondence:
F. Modemann
f.modemann@uke.de

R. Adjallé
r.adjalle@uke.de

Received: February 13, 2022.
Accepted: June 16, 2022.
Prepublished: June 30, 2022.

https://doi.org/10.3324/haematol.2022.280853

Abstract

Hepatitis E virus is increasingly being reported to cause chronic infection in immunocompromised patients. However, less is known about patients with an underlying hematologic disease. In particular, the impact of hepatitis E infection on oncological therapy has been poorly described. In this retrospective single-center study, we analyzed 35 hematologic patients with hepatitis E, including 20 patients under active oncological treatment and 15 patients who were in the post-treatment follow-up or under active surveillance. The primary aim was to describe the clinical courses with particular focus on any hepatitis E-related therapy modifications of cancer-directed therapy. In the majority (60%) of patients who were under active oncological treatment, hepatitis E-related therapy modifications were made, and 25% of deaths were due to progression of the hematologic disease. In patients receiving concomitant oncological treatment, no hepatitis E-related deaths occurred. In contrast, two patients in the follow-up group died from hepatitis E-associated acute-on-chronic liver failure. Chronic hepatitis E was observed in 34% of all cases and 43% received ribavirin therapy; of those, 27% achieved a sustained virological response. CD20-directed therapy was the only independent risk factor for developing chronic hepatitis E. We conclude that CD20-directed treatment at any time point is a risk factor for developing chronic hepatitis E. Nevertheless, since mortality from the progression of hematologic disease was higher than hepatitis E-related mortality, we suggest careful case-by-case decisions on modifications of cancer treatment. Patients in the post-treatment follow-up phase may also suffer from severe courses and hepatitis E chronicity occurs as frequently as in patients undergoing active therapy.

Introduction

Hepatitis E virus (HEV) is one of the most common causes of acute hepatitis worldwide, with more than 20 million estimated new infections per year, about 3.3 million cases of symptomatic infections, and approximately 44,000 HEV-related deaths each year.[1] In immunocompetent patients, HEV causes a self-limiting acute hepatitis which is usually asymptomatic or runs a mild course and acute fulminant hepatitis with acute liver failure or acute-on-chronic liver failure (ACLF) is rare, whereas more severe courses with ACLF are observed in patients with other pre-existing liver diseases and during pregnancy.[2-5] In contrast to their course in immunocompetent patients, HEV infections in strongly immunosuppressed patients, such as solid organ and hematopoietic stem cell transplant recipients, progress into chronic hepatitis E in about 50% of cases.[5-13] Overall, there are limited data from Europe on the prevalence of HEV in hematologic patients. However, in a Chinese population, the seroprevalence of HEV was significantly higher in cancer patients (26%) than in healthy controls (13%), with the highest prevalence of 32.2% being found in patients with leukemia.[14]

Most of the available data on HEV infections in patients with hematologic disorders are derived from single case reports and small case series.[7,15-34] Even in the current ver-

sion of the European Conference on Infection in Leukemia (ECIL) and the European Association for Study of the Liver (EASL) guidelines,[35,36] questions such as whether HEV infection makes changes of systemic cancer therapy necessary in patients with hematologic disorders, how often hepatitis E-related therapy modifications are performed in patients with hematologic disorders, what kind of therapy modifications are made and what their impact on the overall treatment schedule is remain unanswered. Additionally, it is not known yet whether hematologic patients during follow-up potentially have a higher hepatitis E-associated mortality rate or are at higher risk of developing chronic hepatitis E. Another unresolved issue is the feasibility of off-label treatment of chronic hepatitis E with ribavirin, a nucleoside analog used as a virostatic agent for the treatment of chronic hepatitis C, in patients with hematologic disorders who usually suffer from pre-existing, prolonged and profound cytopenia.

One of the few larger analyses that reported on a population of hematologic patients is a European multicenter, retrospective, cohort study that investigated the burden of HEV infections in 50 patients with hematologic malignancies: in 2019, von Felden and colleagues documented a hepatitis E-related overall mortality, defined as death with ongoing hepatitis E, of 16% (8/50), an overall acute liver failure rate of 8% (4/50) and an overall progression rate into chronic hepatitis E of 37% (17/50).[7]

Here, we evaluated the impact of HEV infections on oncological treatment in patients with hematologic disorders by investigating the frequency, the dose modifications and delays of therapy courses as well as the overall mortality in a large, retrospective, single-center cohort. Additionally, we report on the clinical course of hepatitis E as well as response to virological treatment in hematologic patients during the follow-up period after chemotherapy and the special features of virological assessments in patients with hematologic disorders.

Methods

Study design and population

This single-center retrospective study included patients who met all the following criteria: (i) aged ≥18 years; (ii) laboratory-confirmed diagnosis of hepatitis E made by polymerase chain reaction; and (iii) a co-existing or previously existing underlying hematologic disorder. For further analysis, patients were divided into two groups: group A consisted of HEV-infected patients with hematologic disorders under active oncological treatment, defined as treatment in the last 6 months prior to hepatitis E infection or during hepatitis E infection, while group B consisted of HEV-infected patients with hematologic disorders during active surveillance or post-treatment follow-up. Thirty-five patients met the study inclusion criteria, 20 were assigned to group A, and 15 group B (Figure 1).

Clinical data collection

All patients were identified by having been tested positive for HEV-RNA in blood samples at the University Medical Center Hamburg-Eppendorf, Germany between January 2012 and December 2021. Clinical data regarding treatment and disease characterization were collected from the patients' electronic medical records. The data cut-off was January 2022.

The Common Terminology Criteria for Adverse Events, version 5, was used to assess toxicity.[37] Remission status was defined according to international remission criteria.[38-42] Chronic hepatitis E was defined as the persistence of HEV viremia for more than 3 months.[35] Hepatitis E mortality was defined as death due to HEV-associated acute liver failure or ACLF. Acute liver failure and ACLF were defined as the development of hepatic encephalopathy and impaired synthetic liver function (International Normalized Ratio >1.4) in patients without or with pre-existing liver disease, respectively. The dosage and duration of off-label ribavirin treatment were not standardized. A sustained virological response (SVR) was defined as the absence of detectable HEV-RNA in blood samples and/or, if available, in stool or urine samples 24 weeks after the completion of antiviral therapy.

Data were collected in compliance with local legislation requirements and the collection procedure was reviewed and approved by the ethics committee of the Medical Council of Hamburg (WF-138/20). Informed consent was waived by the ethics committee since only anonymous data were analyzed and published. Some patients included in this study have already been investigated and the findings were published by von Felden *et al.* and Mikulska *et al.*[7,13]

Virological assessments

An in-house test was used for the detection of HEV-RNA, as described earlier.[43,44] Since 2017 the fully automated Cobas® HEV test has been used on a Roche Cobas 6800 platform according to the manufacturer's instructions (Roche Diagnostics, Mannheim, Germany) for the detection of HEV in blood, stool, and urine samples.

Statistical analysis

All statistical analyses were performed, and figures were designed using the Statistical Package for Social Sciences statistical software, version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism, version 9 (GraphPad Software, La Jolla, CA, USA). Continuous values are presented as medians with interquartile ranges (IQR). Nominal variables are expressed as numbers with percentages and compared by Cramér's V. For evaluation of associations between nominal and metric variables of interest, the Eta (η) correlation

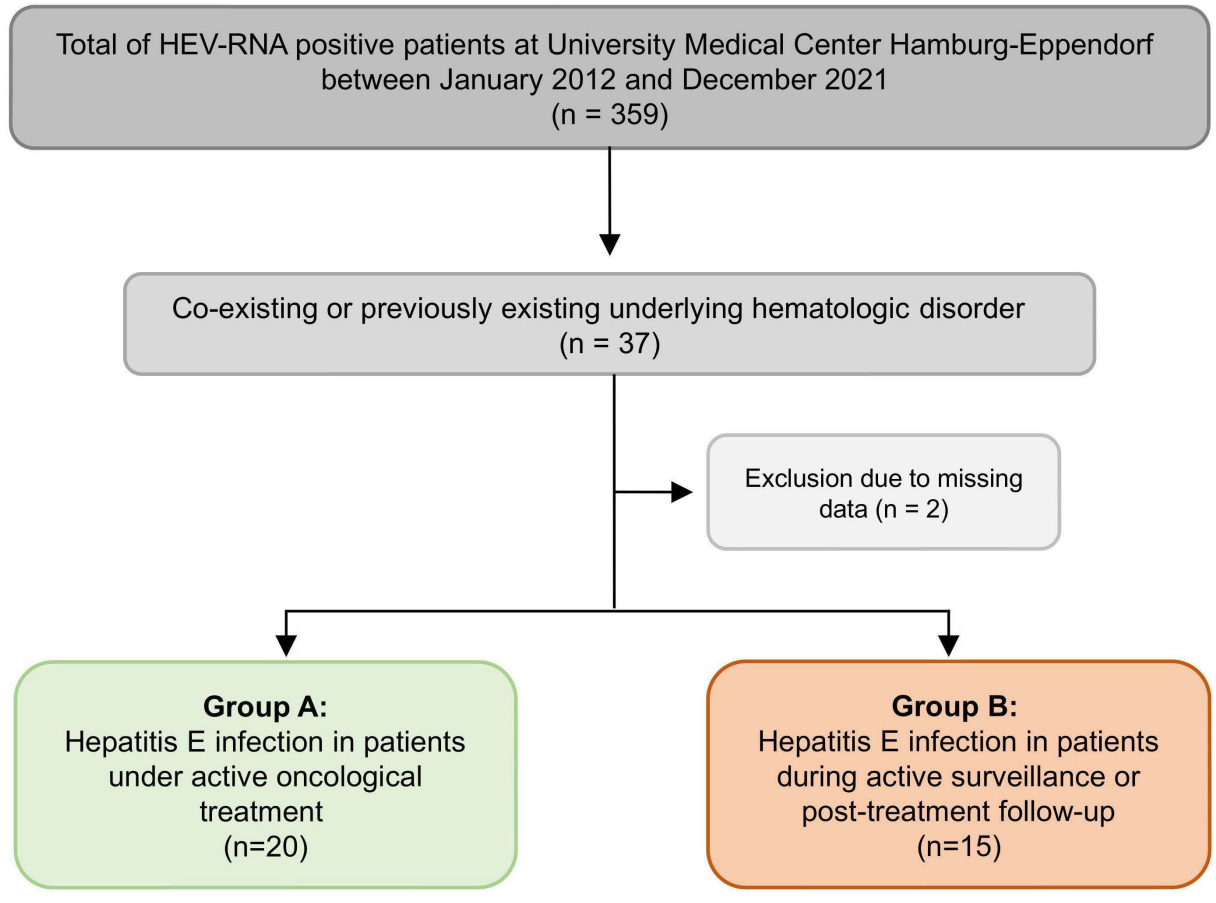

Figure 1. Flow chart of the study design and population. HEV: hepatitis E virus.

coefficient was calculated, and statistical significance was tested with analysis of variance. A multivariant linear regression analysis was carried out. The association of metric variables of interest was compared using the Pearson correlation coefficient. Significant differences in means between two groups were calculated by using a *t*-test. A two-sided *P* value <0.05 was considered statistically significant.

Endpoints

The primary aim was to evaluate the impact of HEV infections on oncological treatment in patients with hematologic disorders. Secondary aims were to investigate the clinical courses and virological features of HEV-infected patients with hematologic disorders.

Results

Characteristics of groups A and B

A total of 35 patients were included in this retrospective analysis. At the time of laboratory-confirmed hepatitis E infection, 20 patients (57%) were receiving systemic oncological treatment (group A). Of the remaining 15 patients (group B), 11 were diagnosed with hepatitis E during post-treatment follow-up and four were under active surveillance. Detailed information about the patients' demographics and characteristics are presented in Table 1.

Transmission of hepatitis E virus

In four patients, blood products were identified as the source of HEV infection. Three patients had been infected by red blood cell concentrates and one by a peripheral blood allogeneic stem cell concentrate containing HEV. In one patient, contaminated food was identified as the source of HEV infection, whereas in 30 patients, the transmission route remains unknown.

Virological findings

At the time of the first laboratory-confirmed diagnosis of HEV infection, the median viral load in EDTA blood samples from patients in group A was 87,675 IU/mL (IQR: 1,415-575,367) or 1,000,000 copies/mL (IQR: 740-13,000,000). In patients of group B, the median viral load in EDTA blood samples at first laboratory-confirmed diagnosis was 730,000 IU/mL (IQR: 7,421-9,882,778) or 176,500 copies/mL (IQR: 2,105-541,250). In group A, stool samples were available for 17 patients and urine samples for ten patients at variable time points during the entire duration of the HEV infection. HEV was detectable in the stool or urine samples in 15 (88%) and five (50%) of these patients, respectively. In group B, stool samples were available for nine patients and urine samples for two patients at variable time points. HEV was detectable in stool and urine samples in four (44%) and one (50%) of these patients, respectively.

The median time to viral clearance in EDTA blood samples and/or other tested samples was 55 days (IQR: 41-190) in group A patients and 45 days (IQR: 16.5-327) in group B patients. In three patients in group A (18%), HEV-RNA was still detectable in stool or urine samples, although no HEV-RNA could be detected in repeated tests of blood

Table 1. Patients' characteristics.

	Total cohort (N=35)			
	Group A: under active treatment (N=20)		**Group B: under active surveillance and post-treatment follow-up (N=15)**	
Age in years, median (IQR)	56 (47-67)			
	55 (46.3-64.5)		58 (49-69)	
Male, N (%)	23 (64.7)			
	12 (60)		11 (73.3)	
CCI	2.5		3	
Pre-existing liver diseases*, N	5		5	
Hematologic disorders	Myeloid neoplasm (n=6) Lymphoid neoplasm (n=22) Plasmacell-related dyscrasia (n=6) Other (n=1)			
		N		N
	AML	3	AML	1
	CML	1	ET-related MF	1
	ALL	1	Hodgkin lymphoma	3
	Indolent B-NHL	6	Indolent B-NHL	6
	Aggressive B-NHL	1	Aggressive B-NHL	2
	Indolent B-NHL with transformation into aggressive B-NHL	2	Indolent B-NHL with transformation into aggressive B-NHL	1
	MM	5	MGUS	1
	Hypocellular refractory cytopenia	1	Other	NA
Remission status	Newly diagnosed	12	Under active surveillance	4
	Relapsed/refractory	8	Post-treatment follow-up	11
Lines of therapy	1	9	1	7
	2	4	2	3
	3	4	3	1
	≥ 3	3	≥ 3	0
	NA	0	NA	4
Treatment regimen under active HEV infection**	Monoclonal antibody therapies	10	NA	
	Chemotherapy-based regimens	13		
	Autologous PBSCT	1		
	Allogeneic PBSCT	6		
	CAR T-cell therapy	1		
	Checkpoint inhibitor-based treatment	1		
	Oral signal transduction inhibitors treatments	3		
	Proteasome inhibitor-based treatments	6		
	Immunomodulatory drug-based	3		

Continued on following page.

	Total cohort (N=35)			
	Group A: under active treatment (N=20)		Group B: under active surveillance and post-treatment follow-up (N=15)	
Previous systemic therapies***	CD20-directed treatments	8	CD20-directed treatments	5
	Chemotherapy-based treatments	11	Chemotherapy based treatments	10
	Autologous PBSCT	4	Autologous PBSCT	2
	Allogeneic PBSCT	1	Allogeneic PBSCT	3
	Oral signal transduction inhibitors	6	Oral signal transduction inhibitors	2
	Proteasome inhibitor	2	Proteasome inhibitor	0
	Without systemic oncological treatment	8	Without systemic oncological treatment	4

*Including steatosis, drug-related hepatotoxicity, infiltration by underlying disease, liver transplantation, hepatitis B or C infection, liver cirrhosis. **Defined as active oncological treatment in the last 6 months prior to hepatitis E infection or during hepatitis E infection. ***Defined as active surveillance or post-treatment follow-up. IQR: interquartile range; CCI: Charlson Comorbidity Index;[48] AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ET: essential thrombocythemia; MF: myelofibrosis; ALL: acute lymphoblastic leukemia; B-NHL: B-cell non-Hodgkin lymphoma; MGUS: monoclonal gammopathy of unknown significance; MM: multiple myeloma; PBSCT: peripheral blood stem cell transplantation; CAR: chimeric antigen receptor; HEV: hepatitis E virus.

samples. In one patient in group B (11%), HEV-RNA was detected in stool samples despite viral clearance in blood samples.

Clinical course

In group A, 12 of the 20 patients (60%) developed acute hepatitis; further virological assessment was lacking for one case. Chronic hepatitis E occurred in seven of the 20 patients (35%) and two patients (10%) developed ACLF. HEV relapse after temporary clearance of the virus was observed in two of 20 patients (10%). In all 20 patients (100%), an elevation of liver enzymes, particularly alanine-aminotransferase (ALT) and gamma-glutamyl-transferase (GGT), was observed during hepatitis E infection with a median peak ALT of 326.5 U/L (IQR: 125.3-943.3) and a median peak GGT of 285 U/L (IQR: 181-570). In group A, neutrophil and lymphocyte counts at the time of the first laboratory-confirmed hepatitis E infection were available for 15 patients. Of these, two patients (13%) had grade 3 or 4 decreased neutrophil and lymphocyte counts. Seven out of the 20 patients in group A died, leading to an overall mortality of 35%, with five deaths due to cancer progression and one due to intracerebral bleeding and secondary malignancy. No hepatitis-related death occurred in group A (Table 2).

In group B, the median time from the first diagnosis of the hematologic disorder until the first diagnosis of HEV infection was 4 years (range, 1-33 years). Ten patients (67%) developed acute hepatitis. Chronic hepatitis E occurred in five of the 15 patients (33%) in group B, including two patients who died of ACLF. One patient in complete remission after high-dose chemotherapy with autologous stem cell transplantation, performed to treat aggressive lymphoma, died of HEV-associated ACLF and, together with hepatorenal syndrome, developed spontaneous bacterial peritonitis. The second patient in complete remission after treatment with six cycles of rituximab and bendamustine, again given to treat an aggressive lymphoma, died due to a combination of ACLF and septic shock. Neither of the two patients had. any other relevant comorbidities. HEV relapse after transient viral clearance was observed in two of the 15 patients (13%) in group B. In 14 of 15 patients (93%), elevation of liver enzymes, particularly ALT and GGT, was observed during the hepatitis E infection with a median peak ALT of 403 U/L (IQR: 136-1,039) and a median peak GGT of 203.5 U/L (IQR: 98.3-381.3). Data on neutrophil and lymphocyte counts were not routinely assessed in patients in group B. Two of the 15 patients died, leading to an overall mortality of 13%. Both patients died due to hepatitis E-related ACLF. No cancer-related death occurred in group B (Table 2).

Impact of hepatitis E infection on oncological treatment in patients with hematologic disorders

We analyzed hepatitis E-related therapy modifications which occurred in 12 of the 20 patients (60%) in group A (Table 3). In six patients, there was a delay of 6 to 8 weeks in the administration of high-dose therapy and autologous PBSCT, because of HEV-contaminated autologous grafts or pending HEV clearance, which led to the need for bridging therapies in three cases. Moreover, two patients were diagnosed with hepatitis E infection immediately prior to allogeneic PBSCT, leading to a delay of the allogeneic transplant until HEV clearance. In one patient, the first relapse of multiple myeloma was diagnosed simultaneously with the hepatitis E infection, leading to a 6-week delay of second-line therapy until HEV clearance was achieved. Furthermore, in one case of aggressive B-cell non-Hodgkin lymphoma, immunochemotherapy was terminated prematurely due to HEV positivity, as was CD20-directed

Table 2. Treatment and hepatitis E-related parameters.

	Total cohort (N=35)	
	Group A: under active treatment (N=20)	**Group B: under active surveillance and post-treatment follow-up (N=15)**
Form of hepatitis E, N (%)		
Acute	12 (60)	10 (67)
Chronic	7 (35)	5 (33)
HEV relapse	2 (10)	2 (13)
ACLF	2 (10)	2 (13)
Unknown	1 (5)	NA
Viral load* in copies/mL, median (IQR)	310,000 (1,720-2,700,000)	
	1,000,000 (740-13,000,000)	176,500 (2,105-541,250)
Viral load* IU/mL, median (IQR)	297,060 (3,723-764,672)	
	87,675 (1,415-575,367)	730,000 (7,421-9,882,778)
Days to virus clearance, median (IQR)	52.5 (35.7-160)	
	55 (41-190)	45 (16.5-327)
Peak GGT in U/L, median (IQR)	254 (159-445)	
	285 (181-570)	203.5 (98.3-381.3)
Peak ALT in U/L, median (IQR)	391 (137-973)	
	326.5 (125.3-943.3)	403 (136-1039)
Ribavirin therapy, N (%)	9 (45)	6 (40)
Days of treatment with ribavirin, median (IQR)	154 (49-210.5)	
	162 (50.3-309.5)	121 (9.8-181.3)
Time to treatment start with ribavirin in days, median (IQR)	40 (13-81)	
	30 (11.5-73.3)	49.5 (28.5-121.3)
Sustained virological response, N (%)	3 (33)	1 (17)
Overall mortality, N (%)	7 (35)	2 (13)
HEV-related deaths, N (%)	0 (0)	2 (13)
Cancer-related deaths, N (%)	5 (25)	0 (0)
Death from other causes, N (%)	2 (10)	0 (0)

*Defined as viral load at first laboratory-confirmed detection of hepatitis E infection. HEV: hepatitis E virus; ACLF: acute-on-chronic liver failure; IQR: interquartile range; GGT: gamma-glutamyl transferase; ALT: alanine aminotransferase.

maintenance therapy in two other patients for the same reason. Dose modifications did not occur. No hepatitis E-related deaths occurred in these 12 patients. However, four of those whose treatment schedules were modified subsequently became refractory to treatment or relapsed and three cancer-related deaths occurred (Table 3, Figure 2).

Next, we compared the clinical courses between the two groups of patients. We did not observe significant differences regarding the rate of acute and chronic hepatitis, the viral load, the duration of HEV clearance, and the increase of liver enzymes. However, the only two HEV-related deaths both occurred in group B (Table 2).

Hepatitis E infection in patients undergoing allogeneic stem cell transplantation

Ten patients underwent allogeneic PBSCT. The median duration between the allogeneic transplant and laboratory-confirmed HEV infection was 3.5 months (IQR: 0-13.8). Chronic hepatitis was observed in five of ten patients (50%) and one patient had a HEV relapse. No acute liver failure or ACLF occurred and there were no hepatitis E-related deaths in this subgroup. The median time to HEV clearance was 110 days (IQR: 53.5-613). In all eight tested patients, HEV-RNA was detectable in stool samples and in three of six (50%) in urine samples. Importantly, in one case HEV was transmitted by allogeneic PBSCT in a patient who then developed chronic hepatitis E with spontaneous HEV clearance without requiring modification of immunosuppressive therapy. In one patient, immunosuppressive therapy was interrupted until HEV clearance. Likewise, in eight other patients, no change in graft-*versus*-host disease (GvHD) prophylaxis was required. No patient developed signs of acute or chronic liver GvHD.

Table 3. Overview of the hematologic outcome of all patients with hepatitis E virus-related cancer-directed treatment modifications.

Case	Sex	Age, years	Underlying hematologic disease	Systemic treatment prior to HEV infection	Last response prior to HEV infection	Systemic treatment during HEV infection including treatment modification	Response after end of treatment	Outcome	Cause of death
1	M	66	CLL transformation into DLBCL	6 cycles of FCR 6 cycles of R-Benda Ibrutinib	PR	5 cycles of R-CHOP, treatment delay, R-Ven, allogeneic PBSCT	PD	Dead	Cancer-related
2	F	60	MM	None	sCR	4 cycles of IsaKRd (EMN24 trial), cyclophosphamide mobilization, instead of high-dose melphalan and autologous PBSCT bridging with 2 cycles of VRd	NA	Alive	NA
3	F	55	MCL	None	CR	2 cycles of R-CHOP, 1 cycle of R-DHAP, 1 cycle of R-DHAOx, premature discontinuation of therapy, delay of high-dose TEAM	CR	Alive	NA
4	M	58	MM	None	VGPR	4 cycles of VCd, CE-mobilization, delay of high-dose melphalan and autologous PBSCT	VGPR	Alive	NA
5	F	42	GZL	6 cycles of R-CHOP	PR	2 cycles of R-DHAP, 2 cycles of R-ICE, ofatumumab-BEAM and autologous PBSCT, autologous stem cell support due to ribavirin toxicity, delay of allogeneic PBSCT	CR	Alive	NA
6	F	51	MM	4 cycles of VCd, high-dose melphalan and autologous PBSCT	VGPR	Delay of second high-dose melphalan and autologous PBSCT during first relapse and bridging with Vd	Unknown, lost to follow-up	Alive	NA
7	F	57	MM	None	Unknown	2 cycles of Vd, steady-state mobilization, delay of high-dose melphalan and autologous PBSCT and 2 cycles of Vd for bridging	PD	Dead	Cancer-related
8	M	59	sAML	None	PD	Non-intensive induction with azacytidine and delay of allogeneic PBSCT	n.a.	Dead	Intracranial bleeding
9	M	46	MCL	None	CR	3 cycles of R-CHOP, 3 cycles of R-DHAP, one additional cycle of R-DHAP and delay of high-dose R-BEAM	CR	Alive	NA

Continued on following page.

Case	Sex	Age, years	Underlying hematologic disease	Systemic treatment prior to HEV infection	Last response prior to HEV infection	Systemic treatment during HEV infection including treatment modification	Response after end of treatment	Outcome	Cause of death
10	M	52	MM	4 cycles of VCd, high-dose melphalan and autologous PBSCT, MMY2060 trial	PR	VCd and premature discontinuation of therapy	PD	Dead	Cancer-related
11	M	55	FL	6 cycles of Obi-Benda, 3 cycles of Obi-maintenance	CR	Obinutuzumab maintenance, premature discontinuation of therapy	Unknown, lost to follow-up	Alive	NA
12	M	70	MCL	5 cycles of R-CHOP, 1 cycle of R-DHAP, autologous PBSCT, R-ICE, high-dose BEAM, autologous PBSCT, ibrutinib, 6 cycles of R-Benda	CR	Rituximab maintenance, premature discontinuation of therapy, VR-CAP and CAR T-cell therapy during relapse	Relapse	Alive	NA

M: male; F: female; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; MM: multiple myeloma; MCL: mantle cell lymphoma; GZL: gray zone lymphoma; sAML: secondary acute amyloid leukemia; FL: follicular lymphoma; FCR: fludarabine, cyclophosphamide, rituximab; R-Benda: rituximab, bendamustine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VCd: bortezomib, cyclophosphamide, dexamethasone; PBSCT: peripheral blood stem cell transplantation; MMY2060 trial: NCT01286077; Obi-Benda: obinutuzumab, bendamustine; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; R-BEAM: rituximab, carmustine, etoposide, cytarabine, melphalan; PR: partial remission; CR: complete remission; sCR: stringent complete remission; VGPR: very good partial remission; PD: progressive disease; R-Ven: rituximab, venetoclax; IsaKRd: isatuximab, carfilzomib, lenalidomide, dexamethasone; VRd: bortezomib, lenalidomide, dexamethasone; R-DHAOx: rituximab, dexamethasone, cytarabine, oxaliplatin; TEAM: thioptepa, etoposide, cytarabine, melphalan; CE: cyclophosphamide, etoposide; Vd: bortezomib, dexamethasone; VR-CAP: rituximab, cyclophosphamide, doxorubicin, prednisolone, bortezomib; CAR: chimeric antigen receptor; NA: not applicable.

Analysis of factors influencing hepatitis E infection

As CD20-directed therapy is known to have an impact on immune responses, we assessed a possible relation between CD20-directed treatment and the time to HEV clearance. CD20-directed treatment during the period of HEV-RNA positivity and/or during the last 12 months prior to the first laboratory confirmation of hepatitis E infection (group A) correlated significantly with the development of chronic hepatitis (*P*=0.035) (Figures 3 and 4). Furthermore, we observed a significant correlation between CD20-directed therapy alone or in combination with chemotherapy and a prolonged time to HEV clearance in uni- and multivariate analyses (*P*=0.01 and P=0.009, respectively) (Figure 3). In contrast, in patients treated with chemotherapy-based approaches, no significant correlation with slow HEV clearance was observed (*P*=0.149).

Next, we assessed other possible reasons and risk factors for the development of chronic hepatitis E. However, no other risk factors could be identified, including pre-existing liver disease, allogeneic stem cell transplantation, underlying hematologic disorder, and remission status (Table 4).

As in group A patients, chronic hepatitis E correlated significantly with previous CD20-directed therapy (*P*=0.007) with a significant correlation between CD20-directed therapy alone or in combination with chemotherapy and prolonged time to HEV clearance in uni- and multivariate analyses (*P*=0.049 each) in group B patients (Figures 3 and 4). Since rituximab can be detected for up to 12 months in the plasma, only patients with CD20-directed therapy 12 months before first confirmation of HEV were assigned to group B. Again, in chemotherapy-based treatment approaches, no significant correlation regarding a prolonged time to HEV clearance was observed (*P*=0.434).

As in group A patients, no other risk factors for developing chronic hepatitis E could be found (pre-existing liver dis-

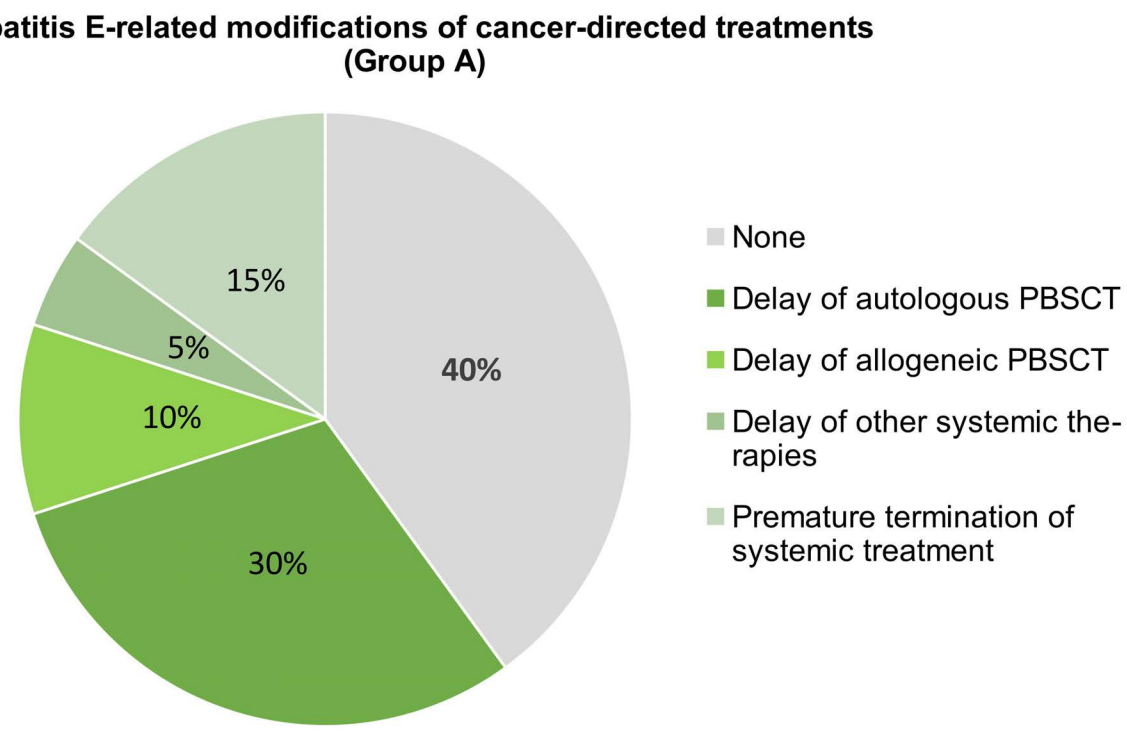

Figure 2. Overview of hepatitis E virus-related modifications of cancer treatment in group A. PBSCT: peripheral blood stem cell transplantation.

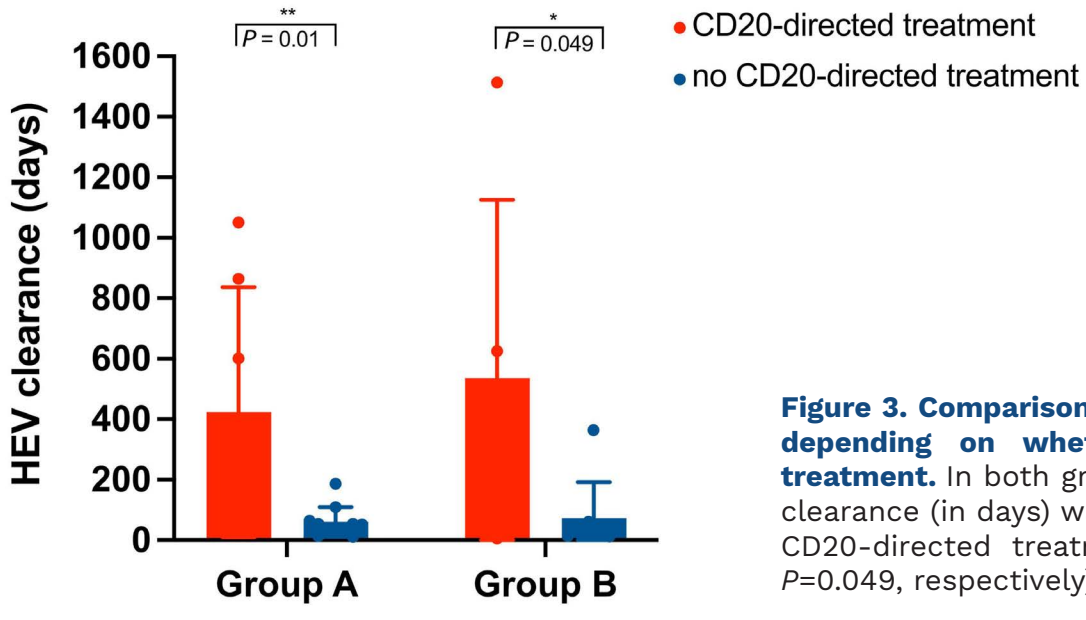

Figure 3. Comparison of the time to achieve hepatitis E virus clearance depending on whether the patient had received CD20-directed treatment. In both groups A and B, the time to achieve hepatitis E virus clearance (in days) was significantly longer in patients who had received CD20-directed treatments than in those who had not (*P*=0.01 and *P*=0.049, respectively).

Table 4. Analysis of disease- and treatment-specific factors and their impact on the risk of progression into chronic hepatitis E infection.

	Patients without progression to chronic hepatitis E (N=22)	Patients with progression to chronic hepatitis E (N=12)	*P* value[c]
Male, N	15	7	0.56
Age in years, median	55	67	0.14
Underlying hematologic disease,* N			
Myeloid neoplasm	5	1	0.34
Lymphatic disease	12	9	0.24
Plasma-cell dyscrasia	5	1	0.34
In remission,[a] N	6**	7**	0.45
CD20-directed treatment,[b] N	4	9	0.001
CD20-directed induction treatment,[b] N	3	8	NA
CD20-directed maintenance treatment,[b] N	1	1	NA

[a]Defined as complete remission and very good partial remission (in the case of multiple myeloma). [b]As part of the following treatment regimens: R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; Rituximab and venetoclax; R-DHAP: Rituximab, dexamethasone, cytarabine, cisplatin; R-BEAM: Rituximab, carmustine, etoposide, cytarabine, melphalan; R-ICE: Rituximab, ifosfamide, carboplatin, etoposide; Ofatumumab, R^2: Rituximab-Lenalidomide, rituximab and bendamustine, rituximab maintenance; VR-CAP: Rituximab, cyclophosphamide, doxorubicin, prednisolone, bortezomib; R-DHAOx: Rituximab, dexamethasone, cytarabine, oxaliplatin; Obinutuzumab. [c]*P* value for assessing the risk factor for progression to chronic hepatitis E. *One patient not assessable and one other hematologic disease. **One patient not assessable. PBSCT: peripheral blood stem cell transplantation, NA: not assessable.

eases, allogeneic stem cell transplantation, or underlying hematologic disorder) in group B patients (Table 4).

Treatment of hepatitis E virus infection

Nine patients (45%) in group A received off-label treatment with ribavirin: three of them (33%) achieved a SVR, two have not undergone assessment for SVR and two others continue to be treated with ribavirin at data cutoff. It should be noted that one patient was treated with sofosbuvir, because of refractoriness to ribavirin and ribavirin-associated cytopenia with the need for a PBSCT boost. The median duration of ribavirin treatment was 162 days (IQR: 50.3-309.5) with a median maximal dose of ribavirin of 800 mg/day (Table 2).

Six of 15 patients (40%) in group B received off-label treatment with ribavirin. One of these six patients achieved a SVR (17%) and two have not yet reached the time for SVR assessment; three patients did not have a response to ribavirin treatment (defined as a SVR). The median duration of ribavirin treatment was 121 days (IQR: 9.8-181.3) with a median maximal dose of ribavirin of 600 mg/day. Pre-existing liver disease was less frequently observed in patients responding to ribavirin than in patients who did not achieve SVR (0/4 *vs*. 4/5). Other possible influencing factors predicting response to ribavirin could not be identified.

Discussion

Although hepatitis E is known to be one of the most common causes of self-limiting acute hepatitis, the risk of developing chronic hepatitis E is increased in immunocompromised patients.[9-12] Little is known about the impact of hepatitis E infection in patients with hematologic disorders under active oncological treatment and in patients under active surveillance or during post-treatment follow-up.

By investigating the clinical course of 20 patients with hematologic disorders undergoing systemic oncological treatment with concomitant hepatitis E infection, we observed hepatitis E-related therapy modifications, particularly delays, in more than half of the patients (60%). Interestingly, we did not observe any hepatitis E-related deaths in this group, whereas 25% died of cancer-related causes, and included nearly two-thirds of patients whose therapy had been modified. One of the few publications reporting the burden of HEV infections in 50 patients with hematologic malignancies is a European multicenter retrospective analysis by von Felden *et al*.[7] With an overall rate of hepatitis E-related therapy modifications of 12%, the authors reported a significantly lower proportion of modified cancer therapies compared to ours, which may be explained by a lack of subdivision into patients under active systemic oncological treatment and those under active surveillance or post-treatment follow-up.[7]

Overall, the hepatitis E-related mortality rate was 6% in our cohort, which is in line with liver-associated death rates of 8% and 9% previously reported for European patients.[7,13] It is worth noting that in our study population, while two deaths happened in the post-treatment follow-

up patients, no hepatitis E-related deaths occurred in the group of patients undergoing active treatment. Both patients who died from ACLF had been previously treated with rituximab. Furthermore, no patient who underwent allogeneic stem cell transplantation died from hepatitis E. In this cohort, hepatitis E infection did not lead to acute or chronic GvHD of the liver. Adjustment of immunosuppressive therapy after allogeneic stem cell transplantation was required in only one patient. In contrast to the study by von Felden *et al.,* in which reduction of immunosuppressive therapy was associated with fulminant GvHD, the patient in our cohort did not develop GvHD.[7]

Chronic hepatitis E occurred in 34% of all the patients, while corresponding percentages in group A, group B, and the group of allogeneic stem cell recipients were 35%, 33%, and 50%, respectively. Our results are in line with previously reported results showing high rates of chronic hepatitis E (41-62%) in allogeneic stem cell recipients.[7,8,13] The rate of chronic hepatitis E in our cohort is higher than that reported by Tavitian *et al.* who observed chronic hepatitis in 23% of a cohort of 26 patients with hematologic disorders.[6] To the best of our knowledge, we were able to show for the first time that the proportion of patients with chronic hepatitis among patients with hematologic disorders is just as high among those undergoing post-treatment follow-up/active surveillance as among those receiving active systemic therapy. Based on the high rate of chronicity in both subgroups, consideration should be given to performing regular liver assessments in previously infected patients, due to the residual risk of developing chronic hepatitis E-related liver cirrhosis and to screen for HEV relapse.

Interestingly, we were able to show that in about 15% of all cases HEV-RNA was detectable longer in stool or urine samples, remaining present after clearance from blood samples. We, therefore, propose intensified monitoring including stool and urine samples on a regular basis.

Given the absence of established guidelines, the indication for ribavirin in hematologic patients is still based on a case-by-case decision.[35,36,45] In our cohort, 43% of patients received antiviral treatment with ribavirin after a median time to start this treatment of 40 days. Of these patients, 27% achieved a SVR which is in contrast to previously reported SVR rates of up to 90%.[6,7,11,46] Interestingly, the majority of ribavirin non-responders had pre-existing liver disease (including one patient with drug-related hepatotoxicity, one patient with chronic hepatitis B infection, one patient with liver cirrhosis of unknown origin and one patient with previous hepatitis C infection), which might explain the comparably large differences in SVR between our cohort and previously described SVR rates. However, due to the small number of available SVR assessments in our patients, reliable statistical analysis of factors predicting response are not possible. Cytopenia is a frequently ob-

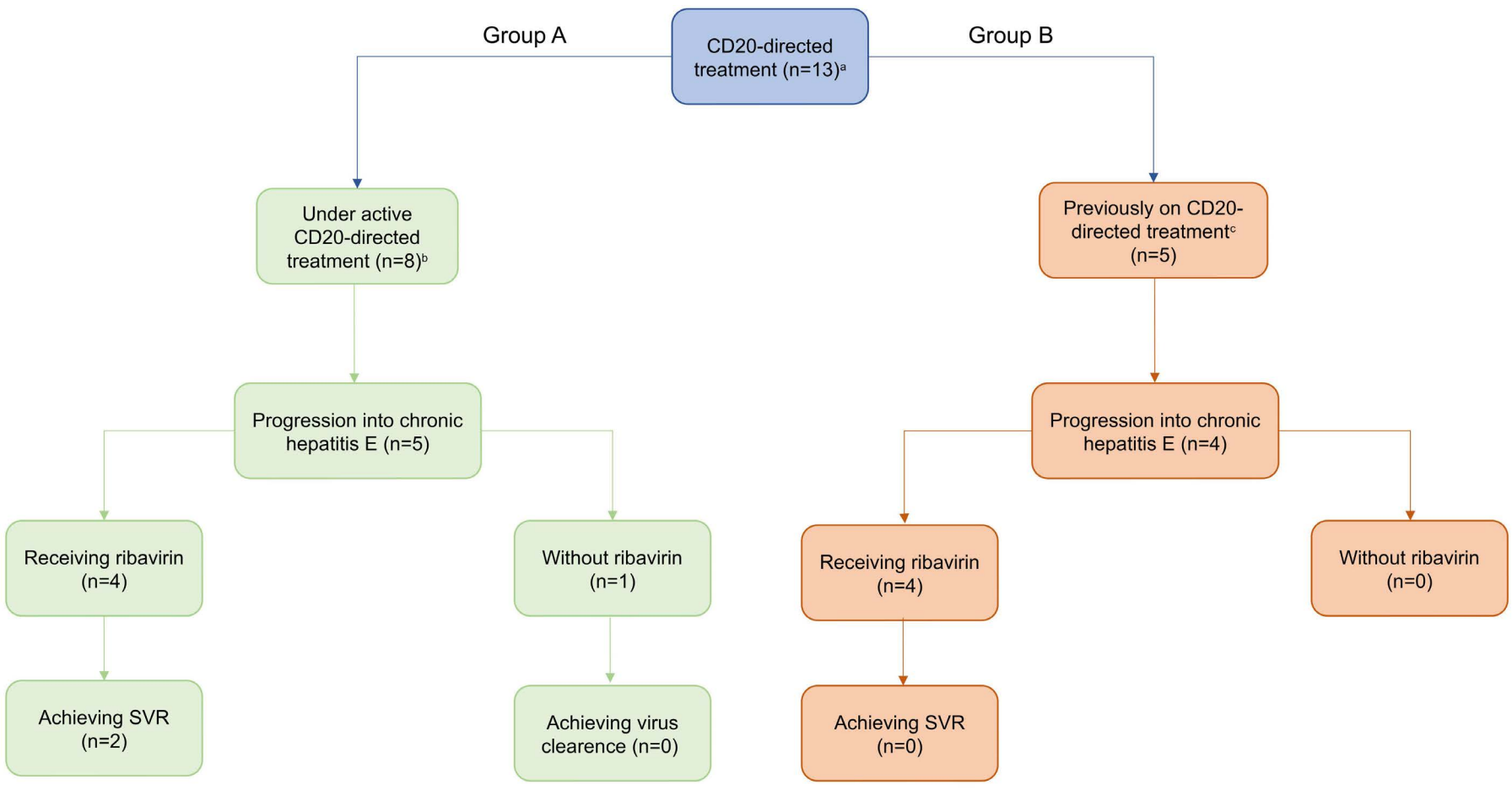

Figure 4. Overview of the clinical courses of hepatitis E in patients under active CD20-directed treatment (group A) and in patients previously treated with CD20-directed monoclonal antibodies. SVR: sustained virological response. [a]All patients receiving CD20-directed treatment at any timepoint; [b]Patients who received CD20-directed treatment during the last 12 months prior to hepatitis E infection; [c]Patients who received CD20-directed treatment more than 12 months before hepatitis E infection.

served ribavirin-related adverse reaction.[47] We observed only one case of ribavirin-associated cytopenia, which may indicate the feasibility of ribavirin treatment in hematologic patients.

Remarkably, we found a significant correlation between CD20-directed treatment and a prolonged time to HEV clearance not only in patients under current treatment but also in patients previously treated with CD20-directed monoclonal antibodies, leading to the conclusion that CD20-directed therapy at any time seems to be a risk factor for chronic hepatitis E and underlining the importance of B-lymphocytes in the cellular immune response. This finding seems similar to the already known significantly increased rate of hepatitis B virus reactivation after exposure to rituximab.[36] Consistently, the longest duration of HEV positivity, 1,051 days, was observed in a patient who underwent long-term CD20-directed therapy. Overall, this analysis of hepatitis E in patients with hematologic disorders highlights the impact of CD20-directed treatment as a risk factor for chronic hepatitis E (P=0.001 overall).

Based on our results for HEV-infected patients, we suggest that, in particular in patients with a pronounced need for systemic oncological therapy, the initiation of chemotherapy should not be delayed, but that the efficacy and risks of CD20-directed therapy should be discussed exhaustively. Since cancer-related mortality outweighed hepatitis E-related mortality in our cohort of patients receiving systemic oncological treatment, we suggest a careful case-by-case decision of cancer-treatment modification and/or delays. We also suggest, especially in patients with HEV-contaminated autologous stem cells, that ribavirin treatment should be considered at an early stage for rapid HEV clearance in order to avoid long therapy delays and to enable further stem cell harvest. Furthermore, based on our results concerning HEV monitoring, we suggest intensifying HEV-RNA monitoring by including stool and urine samples to identify the time point of definite virological clearance more precisely in patients, even when HEV-RNA is no longer detectable in blood samples. Moreover, we conclude that hematologic patients during post-treatment follow-up or those under active surveillance are at risk of developing chronic hepatitis E or ACLF even if the oncological treatment has been completed several years previously.

Due to the relatively small cohort of this study, its retrospective design, the heterogeneous timing of HEV-RNA testing and non-systematic screening, there is a risk of potential selection biases and residual confoundings in our analysis. Furthermore, due to missing reliable data on the dosage and duration of ribavirin treatment, no conclusions about the efficacy and safety of this drug can be made in patients with hematologic disorders. Furthermore, flow cytometric analyses of lymphocytes at defined timepoints were not part of clinical routine. For this reason, no further information on any relationship between lymphopenia and the development of chronic hepatitis E can be gained from this study. Overall, several questions remain unaddressed: is antiviral prophylaxis for HEV recommended and if so, for how long should it be administered, particularly in patients with CD20-directed treatments? Should ribavirin-induced cytopenia not be considered a dose-limiting toxicity in these patients? National and international registers are urgently needed to collect reliable data and provide evidence-based recommendations on the treatment of HEV infection in hematologic patients.

To our knowledge, we report here on the largest single-center cohort of patients with hematologic disorders and concomitant HEV infections. We observed that hepatitis E-related therapy modifications were made in the majority of patients who were under active oncological treatment. Interestingly, the mortality from progression of the hematologic disease significantly outweighed HEV-related mortality. Chronicity of HEV was seen in one-third of patients and we were the first to identify CD20-directed treatment as the only independent risk factor for developing chronic HEV. With our data, we hope to contribute to the development of recommendations for the management of hepatitis E infection in hematologic patients, an important combination for hemato-oncologists worldwide.

Disclosures

SG, CL, JSzW, PHvK, SP, NK, FA and RA have nothing to declare. SP received honoraria from MSD, Abbvie, the Government of Hong Kong, Falk Foundation, Gilead, Diarsorin and Shionogi. CB received speaker's honoraria from AOK Germany, Bristol Myers Squibb, Med update, Merck Serono, Roche Pharma, Sanofi Aventis and participated on advisory boards for Astra Zeneca, Bayer Healthcare, Berlin Chemie, Bristol Myers Squibb, GSO Research Organisation, Jansen Cilag, Merck Serono, Merck Sharp Dohme, Novartis, and Sanofi Aventis. WF participated in advisory boards for Morphosys, AbbVie, Pfizer, Amgen, Jazz Pharmaceuticals and Clinigen; received support for meeting attendance from Amgen, Jazz Pharmaceuticals, Daiichi Sankyo Oncology, Bristol-Myers Squibb and Servier; and received support for medical writing from Amgen, Boehringer Ingelheim, Pfizer, and AbbVie. FM received support for meeting attendance from Servier, Abbvie, Incyte, Gilead, Jazz Pharmaceuticals, Novartis, Teva, Pfizer and Amgen; received support for medical writing from Servier; received research grants from Apis Technologies and Daiichi Sankyo; and received speaker's honoraria from Servier, Jazz Pharmaceuticals and Abbvie.

Contributions

SG, CL, PvK, SP, RA and FM collected the clinical and epi-

demiological data. SG, CL, RA and FM summarized all the data. SG, CL, RA and FM drafted the manuscript; SG, CL, SP, JSzW, PHvK, SP, CB, WF, NK, FA, RA and FM revised the final version. All authors read and agreed to the published version of the manuscript.

Data-sharing statement

The datasets generated during and/or analyzed in the current study are available from the corresponding authors on reasonable request.

References

1. WHO. Hepatits E. 27th July 2021. Available from: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-e Accessed May 19, 2022.
2. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med. 2007;147(1):28-33.
3. Hamid SS, Atiq M, Shehzad F, et al. Hepatitis E virus superinfection in patients with chronic liver disease. Hepatology. 2002;36(2):474-478.
4. Kamar N, Bendall R, Legrand-Abravanel F, et al. Hepatitis E. Lancet. 2012;30;379(9835):2477-2488.
5. European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406-460.
6. Tavitian S, Peron JM, Huguet F, et al. Ribavirin for chronic hepatitis prevention among patients with hematologic malignancies. Emerg Infect Dis. 2015;21(8):1466-1469.
7. von Felden J, Alric L, Pischke S, et al. The burden of hepatitis E among patients with haematological malignancies: a retrospective European cohort study. J Hepatol. 2019;71(3):465-472.
8. Versluis J, Pas SD, Agteresch HJ, et al. Hepatitis E virus: an underestimated opportunistic pathogen in recipients of allogeneic hematopoietic stem cell transplantation. Blood. 2013;122(6):1079-1086.
9. Haagsma EB, van den Berg AP, Porte RJ, et al. Chronic hepatitis E virus infection in liver transplant recipients. Liver Transpl. 2008;14(4):547-553.
10. Abravanel F, Lhomme S, Chapuy-Regaud S, et al. Hepatitis E virus reinfections in solid-organ-transplant recipients can evolve into chronic infections. J Infect Dis. 2014;209(12):1900-1906.
11. Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med. 2008;358(8):811-817.
12. Haagsma EB, Niesters HG, van den Berg AP, et al. Prevalence of hepatitis E virus infection in liver transplant recipients. Liver Transpl. 2009;15(10):1225-1228.
13. Mikulska M, Penack O, Wendel L, et al. HEV infection in stem cell transplant recipients-retrospective study of EBMT Infectious Diseases Working Party. Bone Marrow Transplant. 2022;57(2):167-175.
14. Bai MJ, Zhou N, Dong W, Li GX, Cong W, Zhu XQ. Seroprevalence and risk factors of hepatitis E virus infection in cancer patients in eastern China. Int J Infect Dis. 2018;71:42-47.
15. Boudin L, Patient M, Tsitsi Nding Tsogou P, Roméo E, Bladé JS, de Jauréguiberry JP. Successful treatment with ribavirine for chronic hepatitis E in chronic lymphocytic leukemia treated with Ibrutinib. Bull Cancer. 2019;106(1):84-85.
16. Alric L, Bonnet D, Beynes-Rauzy O, Izopet J, Kamar N. Definitive clearance of a chronic hepatitis E virus infection with ribavirin treatment. Am J Gastroenterol. 2011;106(8):1562-1563.
17. Chandak S, Mandot A, Rathi S. An unusual case of chronic hepatitis E in haematological malignancy. J Ass Physicians India. 2018;66(6):97-98.
18. Field Z, Russin M, Murillo Alvarez RM, Madruga M, Carlan S. Acute hepatitis E: a rare cause of acute liver failure in a patient with acute myeloid leukemia. Cureus. 2020;12(9):e10628.
19. Fuse K, Matsuyama Y, Moriyama M, et al. Late onset post-transfusion hepatitis E developing during chemotherapy for acute promyelocytic leukemia. Int Med. 2015;54(6):657-661.
20. Gauss A, Wenzel JJ, Flechtenmacher C, et al. Chronic hepatitis E virus infection in a patient with leukemia and elevated transaminases: a case report. J Med Case Rep. 2012;6:334.
21. Geng Y, Zhang H, Huang W,et al. Persistent hepatitis E virus genotype 4 infection in a child with acute lymphoblastic leukemia. Hepat Mon. 2014;14(1):e15618.
22. Giordani MT, Fabris P, Brunetti E, Goblirsch S, Romanò L. Hepatitis E and lymphocytic leukemia in man, Italy. Emerg Infect Dis. 2013;19(12):2054-2056.
23. Haboubi HN, Diyar R, Benton A, Ch'ng CL. A case of acute hepatitis E infection in a patient with non-Hodgkin lymphoma treated successfully with ribavirin. Case Rep Gastrointest Med. 2017;2017:8941218.
24. Kootte RS, Faber LM. Hepatitis E during lenalidomide treatment for multiple myeloma in complete remission. Neth J Med. 2017;75(3):117-121.
25. Lemons-Estes FM, Capt HP, Skelton H, Smith KJ. A clonal cutaneous CD30+ lymphoproliferative eruption in a patient with evidence of past exposure to hepatitis E. Int J Dermatol. 2000;39(7):521-527.
26. Mainardi V, Gerona S, Ardao G, et al. Locally acquired chronic hepatitis E followed by Epstein-Barr virus reactivation and Burkitt lymphoma as a suspected extrahepatic manifestation in a liver transplant recipient. Am J Case Rep. 2019;20:1016-1021.
27. Mallet V, Bruneau J, Zuber J, et al. Hepatitis E virus-induced primary cutaneous CD30(+) T cell lymphoproliferative disorder. J Hepatol. 2017;67(6):1334-1339.
28. Okano H, Nakano T, Ito R, et al. The spontaneous clearance of hepatitis E virus (HEV) and emergence of HEV antibodies in a transfusion-transmitted chronic hepatitis E case after completion of chemotherapy for acute myeloid leukemia. Clin J Gastroenterol. 2020;13(2):252-259.
29. Pfefferle S, Frickmann H, Gabriel M, Schmitz N, Günther S, Schmidt-Chanasit J. Fatal course of an autochthonous hepatitis E virus infection in a patient with leukemia in Germany. Infection. 2012;40(4):451-454.
30. Tessé S, Lioure B, Fornecker L, et al. Circulation of genotype 4 hepatitis E virus in Europe: first autochthonous hepatitis E infection in France. J Clin Virol. 2012;54(2):197-200.
31. Verbeeck A, De Becker A, Reynaert H. An unexpected cause of recurrent jaundice after resolution of acute hepatitis E. Case Rep Gastroenterol. 2020;14(2):415-419.
32. Ollier L, Tieulie N, Sanderson F, et al. Chronic hepatitis after hepatitis E virus infection in a patient with non-Hodgkin lymphoma taking rituximab. Ann Intern Med. 2009;150(6):430-431.
33. Desai R, Singh S, Zalavadia D, Bansal P, Goyal H. Burden of hepatitis E infection and associated healthcare resource utilization among

hematological malignancy-related hospitalizations: a national perspective in the United States, 2007-2014. J Hepatol. 2019;71(6):1266-1268.
34. Alnuaimi K, Lavole J, Lascoux-Combes C, et al. Chronic hepatitis E in patients with indolent lymphoma after treatment with rituximab and bendamustine. Hepatology. 2018;67(6):2468-2470.
35. European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis E virus infection. J Hepatol. 2018;68(6):1256-1271.
36. Mallet V, van Bommel F, Doerig C, et al. 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 Infec Dis. 2016;16(5):606-617.
37. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf Accessed May 19, 2022.
38. Cheson BD, Bennett JM, Kopecky KJ, et al. Reporting Standards for Therapeutic Trials in Acute Myeloid L. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-4649.
39. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
40. Gökbuget N. Recommendations of the European Working Group for Adult ALL, available from https://www.uni-med.de/recommendations-of-the-european-working-group-for-adult-all.html Accessed May 19, 2022.
41. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
42. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.
43. Westholter D, Hiller J, Denzer U, et al. HEV-positive blood donations represent a relevant infection risk for immunosuppressed recipients. J Hepatol. 2018;69(1):36-42.
44. Garson JA, Ferns RB, Grant PR, et al. Minor groove binder modification of widely used TaqMan probe for hepatitis E virus reduces risk of false negative real-time PCR results. J Virol Methods. 2012;186(1-2):157-160.
45. O'Gorman J, Burke A, O'Flaherty N. Hepatitis E virus - key points for the clinical haematologist. Br J Haematol. 2018;181(5):579-589.
46. Xhaard A, Roque-Afonso AM, Mallet V, et al. Hepatitis E and allogeneic hematopoietic stem cell transplantation: a French nationwide SFGM-TC retrospective study. Viruses. 2019;11(7):622.
47. Ribavirin SmPC. 2021 29.01.2022. Available from: https://www.medicines.org.uk/emc/product/7108/smpc Accessed May 19, 2022.
48. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383.