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Concurrent Therapy of Hepatitis C and Primary CNS Lymphoma: A Case Report

K. Xhaxho[1]; E. Aydilek[1]; R. Akdas[1]; K. Becker[1]; H. Schwörer[2]; T. Huckhagel[3]; L. Stork[4]; C. Stadelmann[4]; G. Wulf[1]; N. Brökers[1]*

[1]*Department of Hematology and Medical Oncology,University Göttingen, Göttingen, Germany.*

[2]*Department of Gastroenterology, Gastrointestinal Oncology and Endocrinology University Medical Center Göttingen, Göttingen, Germany.*

[3]*Department of Diagnostic and Intervention al Neuroradiology, 37075 Göttingen, Germany.*

[4]*Institute of Neuropathology, 37075 Göttingen, Germany.*

***Corresponding Author(s): K Xhaxho**

Department of Hematology and Medical Oncology, University Göttingen, Göttingen, Germany.

Tel: +49-551-39-65465;

Email: kristin.xhaxho2@med.uni-goettingen.de

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Abstract

At diagnosis of primary central nervous system lymphoma (PCNSL), the patient was tested positive for hepatitis C. Curative therapy for cerebral lymphoma includes high-dose methotrexate. Direct antiretroviral (DAA) drugs are highly effective in the treatment of hepatitis C. Methotrexate therapy is hepatotoxic and exhibits a high potential for drug-drug interactions. No standard treatment exists for this dilemma situation. Here we describe successful HCV treatment with glecaprevir and pibrentasvir (Maviret®) in an HCV-infected patient with PCNSL. To reduce drug-induced liver injury and the risk of drug-drug interactions during treatment with DAA, the patient received concomitant methotrexate-free I-CT.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare aggressive extranodal non-Hodgkin lymphoma. The standard-of-care treatment consists of induction immunochemotherapy (I-CT) (high-dose methotrexate, rituximab and other cytostatic agents able of crossing the blood–brain barrier) followed by consolidation high-dose chemotherapy with autologous stem cell transplantation (HD-AST) [1]. At diagnosis, our patient tested positive for hepatitis C (HCV) infection. Hepatitis C Infection is detected in 1,5 to 32% of cancer patient around the word [2]. Up to now there are no reports of patients with PCNSL who suffer from HCV-Infection. Although direct-acting antiviral (DAA) treatment is highly efficient and sustained virologic response (SVR) can improve general outcome, there is no standard of care to guide the treatment schedule in patients with HCV and PCNSL [3]. Furthermore coadministration of glecaprevir and pibrentasvir (Maviret®), and methotrexate has not been studied.

Here, we describe successful HCV treatment with Maviret®, in an HCV-infected patient with PCNSL. To reduce drug induced liver injury and the risk of drug-drug interaction during medication with DAA the patient received in between times methotrexate-free I-CT.

Case Report

A 54-year-old immunocompetent woman with no significant past medical history presented with transient left-sided paralysis. The patient denied behavior and personality changes and did not show symptoms of increased intracranial pressure. The physical and neurologic examination revealed no further pathologies.

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An initially extern performed cCT showed multiple lesions of the right frontal lobe whereas a brain MRI detected four homogeneously contrast enhancing foci with significant perifocal edema and mild midline shift and markedly restricted diffusion, suggestive of CNS Lymphoma (Figure 1).

Due to the urgency of imaging signs suggestive of increased intracranial pressure, therapy with dexamethasone was initiated and symptoms improved rapidly afterwards.

Before performing stereotactic brain biopsy, steroid treatment was stopped. The biopsy sample revealed diffuse large B cell lymphoma (Ki-67 proliferative index 90%, EBV negative) (Figure 2). Contrast-enhanced CT of chest and abdomen detected no tumorous lesions. Bone marrow infiltration was absent. The constellation of findings confirmed the diagnosis of PCNSL.

To complete diagnostic work-up, a hepatitis profile was obtained, the patient tested positive for hepatitis C (viral load 9.77 e*06 IU/ml, genotype 1b, most likely sporadic infection).

A co-infection with either HAV, HBV or HIV was not present. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, prothrombin time (PT %), and albumin levels were all within normal ranges. An abdominal ultrasound showed a grade I hepatic steatosis as well as hepato- and splenomegaly, but no liver cirrhosis.

The case was discussed in our multidisciplinary tumor board, consenting prompt PCNSL treatment consisting of induction therapy analog the MARiTA trial (Rituximab 375 mg/m2 d0, d4; MTX 3,5 g/m2 d1; Cytarabin 2 g/m2 every 12 h d2, d3, repeated d22) and followed by consolidation therapy with high dose therapy and autologous hematopoietic stem cell transplantation.

For the first cycle, the dose of MTX was reduced due to renal insufficiency. MTX elimination was not prolonged. Consequent to MTX toxicity, the liver enzymes were elevated (CTCAE Grade 4) (Figure 3). After the first cycle of I-CT DAA therapy was initiated. The patient was treated according to the guidelines with Maviret® for 8 weeks. The treatment was straightforward and uneventful, usual side effects (headache, fatigue, nasopharyngitis and nausea) were denied.

In order to minimize toxicity and potential drug-drug interactions between DAAs and MTX (bone marrow depression, nephrotoxicity, mucositis) the patient underwent MTX-free I-CT according to a modified Freiburger NHL ZNS regime for the two following cycles (Rituximab 375 mg/m^2 d1; Cytarabin 3g/ m^2 d1, d2; Thiotepa 40mg/m^2 d2, repeated on day 22) (Figure 4) [4].

After achieving HCV-RNA levels <10 IU/ml MTX was administrated again (dose was reduced due to previous liver toxicity und reduced ECOG of 3) and stem-cell harvest was successfully performed.

Three months after the initiation of DAA treatment SVR was documented (Figure 2). Although initial cMRI studies showed treatment response, the neurologic symptoms progressively worsened. A later performed cMRI showed tumor growth and ifosphamide and carboplatin based salvage therapy (R-DeVIC6: Rituximab 375 mg/m^2 d0; dexamethasone 40 mg d1-3; etoposide 100 mg/m^2 d2-3; ifosfamide 1500 mg/m2 d1-3; carboplatin 300 mg/m^2 d1; repeated on day 22) was administered. Consistent with the clinical neurological exacerbation, another later performed MRI showed tumor growth, so that afterwards the patient opted for a best supportive care approach (Figure 1).

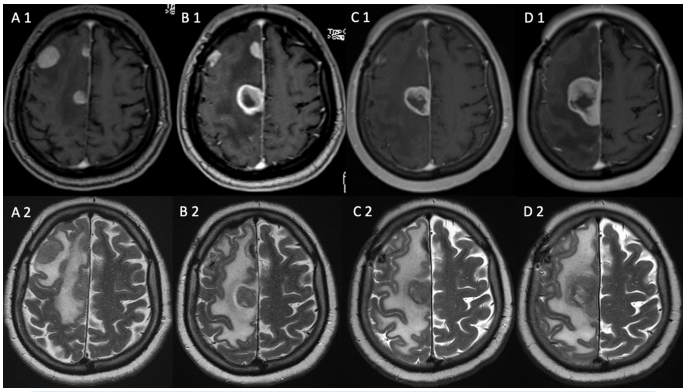

Figure 1: MRI illustration of disease course under therapy from left to right (**A**: October 2021; **B**: December 2021; **C**: January 2022; **D**: March 2022). Top row: contrast enhanced T1 weighted imaging in the transverse plane. Bottom row: T2 weighted imaging in the transverse plane.

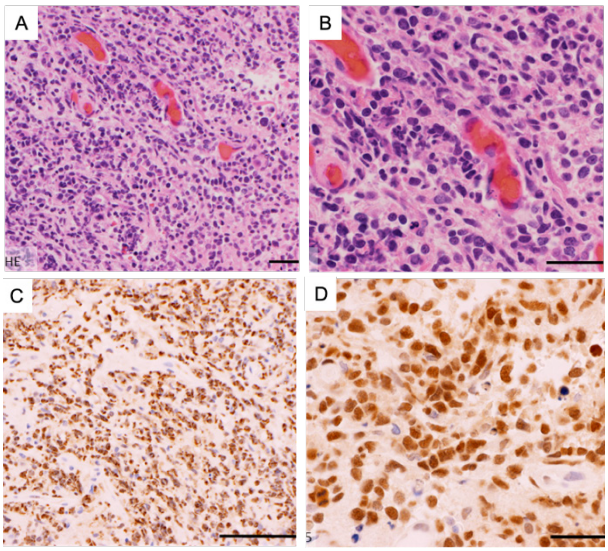

Figure 2: HE staining shows highly cellular, pleomorphic, diffusely growing tumor with infiltration of the perivascular space **(A)**. In the same staining with a higher magnification tumor cells with large round-oval nuclei und scant cytoplasm could be distinguished; numerous mitosis and apoptosis are also seen **(B)**. Ki67-staining shows proliferation index of almost 90% **(C)**. Tumor cells express mature B-cell marker Pax5, **(C)**. Scale bars 50µm.

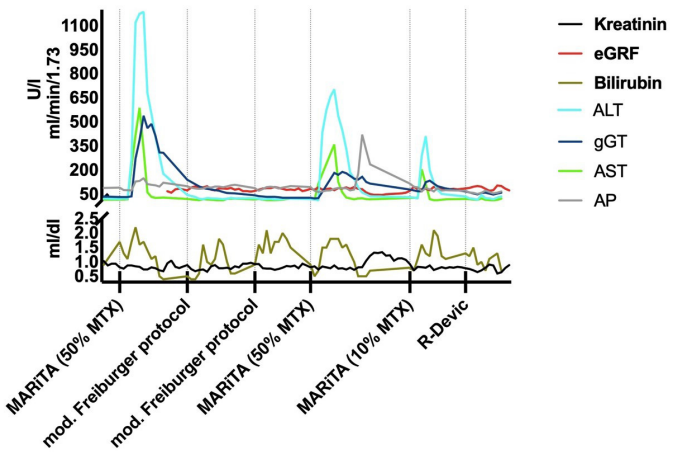

Figure 3: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma.glutamyl transferase (gGT), alcaline phosphatase (AP) Bilirubin, Kreatinin and eGRF before und during CT-I and DAA Treatment.

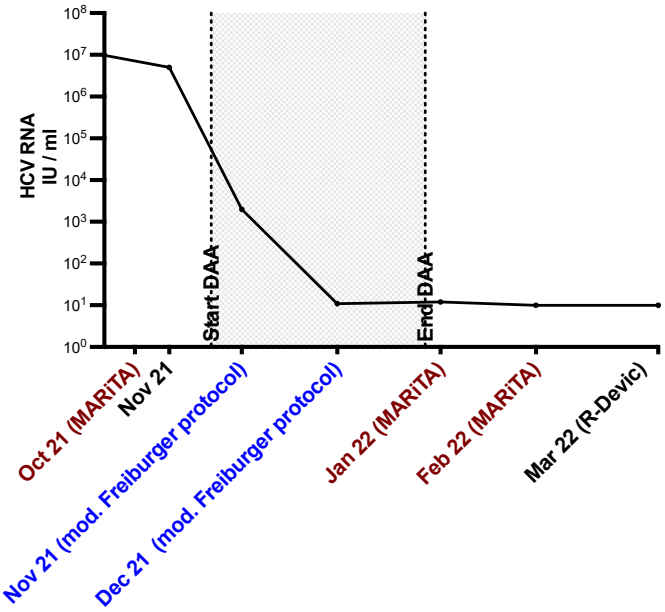

Figure 4: Hepatitis C viremia.

Discussion

Current guidelines support testing for HCV in patients with hematologic malignancies and hematopoietic cell transplant recipients. HCV infection in patients with cancer represents a great therapeutic challenge, including liver disease progression, occurrence of occult HCV infection or viral reactivation. Moreover, time administration (simultaneous or successive treatment) and drug-drug-interaction (DDI) between DAAs and chemotherapy pose further difficulties in treating these patients [6].

HCV infection is associated with B-cell non-Hodgkin lymphoma (B-NHL), especially marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL) and diffuse large B-cell lymphoma (DLBCL). The pathogenic role of HCV in NHL has been further confirmed by the response to antiviral therapy (AVT).[7] In cases of indolent B-NHL, especially MZL, a complete regression has been observed after sole treatment of HCV with interferon plus ribavirin or DAAs [8].

DAA treatment should be initiated without significant delay except in cases of uncontrolled cancer. When faced with life expectancy of <12 months, intolerance to DAAs, pregnancy or anticipated major interactions with cancer treatment, then DAA treatment can be initiated either before, after or in long term treatment (months to years) even simultaneously [9].

In a trial comparing DLBCL/HCV-infected patients, receiving sofosbuvir/ledipasvir and chemotherapy to a retrospective cohort, that did not receive AVT, there was no statistical difference in overall survival (OS) after 52 weeks, whereas a statistically significant higher diseasefree survival (DFS) was achieved in treated patients. A limitation of this study was that the retrospective historical control cohort included patients enrolled at a time in which Rituximab-containing protocols were less common [10].

Another prospective study showed HCV reactivation (defined as increase in HCV-RNA level of ≥1 log10IU/mL from baseline HCV-RNA) under rituximab alone or in combination with high-dose steroids, suggesting that close monitoring is needed. Although none of the patients experienced liver failure or liver-related death, dose reduction or therapy discontinuation was required. Patient with HCC, liver metastases or treated infection with undetectable HCV RNA were excluded [11]. On the other hand a retrospective study with 30 patients Mahale et al. reported no post-SVR relapses of HCV infection in the patients receiving any form of cancer therapy, including rituximab [12]. Different studies showed improved OS rates in DLBCL patients who received AVT and achieved SVR. However, in these studies the most used therapy approach was IFN-based, a potent antitumor agent when combined with rituximab [3]. Merli et al. shows in a retrospective international study that HCV-positive DLBCL patients receiving IFN-free AVT with DAAs during or after I-CT (mainly R-CHOP) had an improved 2-year OS and PFS, respectively. A concurrent DAAs and I-CT administration is favored to a sequential one in order to prevent hepatic toxicity of I-CT [13]. Nevertheless, it is very import to acknowledge that even though morphologically undistinguishable PCNSL and extracerebral DLBCL are two distinct lymphoma entities [14]. As scientists investigate further on mechanisms of pathogenesis and resistance in PCNSL promising novel treatment strategies are being developed and tested in clinical trials [14,15].

In the present case, an increase in ALT, AST, gGT, and AP was observed following treatment with MARiTA because of MTX toxicity. MTX can cause significant elevation of serum transaminases or/and drug-induced liver injury. According to the Liverpool Hep Drug there is no evidence of interaction between Maviret® and MTX. Nevertheless, MTX is a substrate of BCRP (breast cancer resistance protein) and its concentrations could increase due to inhibition of BCRP by Maviret®. On these grounds we decided on a MTX-free regimen during DAA treatment and until HCV-RNA dropped below 10 IU/l. In any case, patients should be closely monitored for MTX associated toxicities.

In conclusion, we presented (to the best of our knowledge) the first case of treating a patient with PCNSL and simultaneous HepC infection with high-dose MTX and consecutive simultaneous application of DAA and MTX-free chemotherapy, showing that it might be safe and successful.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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