Digestive and Liver Disease 51 (2019) 719–723

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Concomitant therapy with direct-acting antivirals and chemoimmunotherapy in HCV-associated diffuse large B-cell lymphoma

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ARTICLE INFO

Article history:
Received 3 September 2018
Accepted 23 October 2018
Available online 3 November 2018

Keywords:
Chemoimmunotherapy
Diffuse large B-cell lymphoma
Direct-acting antivirals
Hepatitis C virus
Rituximab
Safety

ABSTRACT

Introduction: The association between hepatitis C virus (HCV) infection and B-cell non-Hodgkin's Lymphomas (NHL) is well established. Antiviral therapy (AVT) is the first-line treatment for HCV-related indolent NHL whereas diffuse large B-cell lymphoma (DLBCL) requires immediate start of chemoimmunotherapy (CIT), usually deferring AVT. However, an early HCV elimination may reduce the risk of CIT-induced liver toxicity and consequent CIT interruption or withdrawal. To date few data are available on safety and efficacy of concomitant administration of direct-acting antivirals (DAA) and CIT in HCV-associated DLBCL.
Methods: 7 consecutive patients (5 males, median age 65 years) with HCV infection (four genotype 2a/2c, two genotype 1b, one genotype 4; one patient with compensated cirrhosis) and DLBCL received different DAA regimens concurrently with CIT.
Results: All patients completed the scheduled AVT and CIT with neither interruption nor withdrawal of the latter. One case of neutropenia was observed during concomitant therapy, no liver toxicity occurred. All patients achieved sustained virological response and complete DLBCL response (median follow-up of 12 months).
Conclusions: Concomitant administration of DAA and CIT for HCV-associated DLBCL is safe and may prevent CIT-induced liver toxicity. Large, prospective studies are needed to confirm these preliminary data and to assess prognostic implications.

1. Introduction

The association between hepatitis C virus (HCV) infection and lymphoprolipherative disorders such as Mixed Cryoglobulinemia and B-cell non-Hodgkin's Lymphomas (NHL) is supported by several epidemiological, biological and therapeutic studies. An increased prevalence of HCV infection among patients with NHL compared to general population has been widely described, with a 2–10-fold increased risk according to different metanalysis and systematic reviews [1–5]. Although a direct oncogenic effect of HCV on infected lymphocytes has been postulated [6], the most accepted mechanism to explain the HCV-induced lymphomagenesis is the chronic antigenic stimulation on B-cells [3] leading to expansion of specific clones and subsequent acquisition of genetic mutations [7]. HCV infection has been associated either with indolent NHL, such as marginal zone lymphoma (MZL) and lymphoplasmacytic lymphoma, or with aggressive subtypes and, in particular, diffuse large B-cell lymphoma (DLBCL) [5,8–10]. The most convincing evidence for a causal relationship between HCV infection and NHL is the observation of indolent NHL response to antiviral therapy (AVT). Interferon (IFN)-based AVT in patients with HCV-related indolent NHL translated to a high rate of lymphoma regression as well as to a reduction of relapse risk after complete remission [11–18]. A similar efficacy has been shown in some preliminary experiences with the new direct-acting antiviral agents (DAA) [19–23], thus confirming the hypothesis of a direct effect of viral eradication by removing the antigenic stimulation that drives the lymphoid proliferation, rather than an IFN-mediated anti-proliferative activity.

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https://doi.org/10.1016/j.dld.2018.10.019
1590-8658/

On the contrary, aggressive NHL are unlikely to respond to AVT alone thus requiring the immediate start of chemotherapy, usually in association with anti-CD20 antibody Rituximab (chemoimmunotherapy, CIT) [24]. However, even in this setting an early eradication of HCV may be useful not only for a direct effect on the hematological outcome, but also to potentially reduce the risk of CIT-induced hepatotoxicity. Indeed, a higher risk of liver toxicity and subsequent need for modifications or withdrawal of the scheduled CIT has been reported in HCV-positive patients with DLBCL compared to uninfected patients [25,26], probably as a result of Rituximab-mediated HCV reactivation.

While IFN-based therapies are not suitable for a concurrent administration with chemotherapy for the high incidence of side effects [27], DAA appear an appealing opportunity allowing short, well-tolerated and highly effective AVT.

In this study we explored safety and efficacy of a concomitant administration of CIT and AVT with DAA in patients with HCV infection and DLBCL.

2. Patients and methods

Between March 2016 and February 2018, we treated with DAA concomitantly with CIT 7 consecutive patients with HCV infection and DLBCL.

HCV infection was confirmed by HCV-RNA positivity by real-time PCR (Abbott Real Time HCV assay, lower limit of quantification 12 IU/ml). Determination of HCV genotype, complete liver function tests and non-invasive assessment of liver fibrosis with Fibroscan® (EchoSens, Paris, France) were performed at the hepatological screening visit.

Hepatitis B virus (HBV) status (HBsAg, HBsAb, HBcAb) was determined before starting CIT to individuate patients needing for antiviral prophylaxis or treatment to prevent HBV reactivation.

The CIT schedule was primarily chosen by the hematologists according to guidelines [24], patient age and comorbidities. The DAA were chosen by the hepatologists according to the national [28] and international [29] guidelines. The presence of known potential drug–drug interactions (DDI) between the specific chemotherapeutic agents and all the available DAA was checked on the HEP drug interactions online database (www.hep-druginteractions.org, University of Liverpool) in order to reduce risk of toxicity or lower efficacy of both therapies.

During AVT, the patients were monitored monthly with liver function tests and HCV RNA quantification, with additional controls scheduled by the hematologists to monitor CIT effects and NHL outcome. Serious adverse events (SAE), defined as grade 3 or 4 toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [30], were reported.

Efficacy of AVT was defined as the negativity of HCV-RNA 12 weeks after the end of AVT (sustained virological response, SVR). DLBCL response to CIT was assessed according to Cheson criteria [31].

3. Results

3.1. Patients characteristics

Clinical features of the enrolled patients are summarized in Table 1; individual data are resumed in Supplementary Table 1. The seven enrolled patients were five males and two females, with a median age of 65 years (range 50–78). At baseline, median ALT level was 56 (range 8–277) U/L and five of seven patients had ALT values above the upper limit of normal (33 U/L). Albumin, bilirubin and coagulation were normal in all patients.

Table 1
Clinical features of the patients at the hepatological screening visit.

Age (years)[a]	65 (52–78)
Male/Female	5/2
Haemoglobin (g/dL)[a]	13 (10.1–15.6)
White blood cells (/mm^3)[a]	5100 (1460–11700)
Platelets (x10^3/mm^3)[a]	97 (18–234)
ALT (U/L)[a]	56 (8–277)
ALT > 33 U/L[b]	5/7
HCV genotype[b]	
1b	2/7
2a/2c	4/7
4	1/7
HCV RNA > 750000 U/mL[b]	5/7
Previous HBV infection[b]	2/7
Liver stiffness (kPa)[a]	6.1 (5.3–23)
Liver cirrhosis[b]	1/7
DLBCL[b]	
De novo	6/7
Transformed	1/7
Ann-Arbor stage[b]	
I–II	0/7
III–IV	7/7
IPI score[b]	
1–2	6/7
3–4	1/7

Abbreviations: ALT, alanine aminotransferase; DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index.
[a] Median (range).
[b] Number/total.

HCV genotype was 2a/2c in four patients, 1b in two patients and 4 in one. Baseline viral load was high (>750,000 IU/mL) in five patients. One patient had compensated cirrhosis according to liver stiffness measurement (23 kPa), while the others had low to moderate fibrosis. The cirrhotic patient was the only one previously treated with an IFN-based regimen, which failed due to a virological breakthrough several years before the diagnosis of lymphoma. In two patients with a resolved HBV infection (HBsAg negative, anti-HBc positive, anti-HBs negative) 100 mg/day lamivudine prophylaxis as prevention of HBV reactivation was concomitantly started with CIT.

All patients were affected by DLBCL (de novo in six patients, transformed in one). All patients had stage III–IV lymphoma and the International Prognostic Index (IPI) was ≥2 in five out of seven patients. Three patients had bone marrow involvement, one patient had liver involvement. Performance status was excellent (ECOG 0) in all the patients.

3.2. Treatments

All patients were in first-line therapy for NHL with Rituximab-based CIT, scheduled as 6 cycles every 21–28 days. Five patients received Rituximab plus cyclophosphamide, doxorubicin (or liposomal doxorubicin in order to reduce cardiotoxicity), vincristin and prednisone (R-CHOP or R-COMP). One patient was initially treated with Rituximab plus gemcitabin and oxaliplatin (R-GemOx), due to significant comorbidities (ischemic cardiopathy, previous chemotherapies for a Hodgkin's lymphoma and a malignant melanoma). However, after the first cycle, gemcitabin was reduced and then permanently interrupted due to a severe hepatic flare (ALT up to 927 IU/L) that resolved before the start of AVT. Last patient received R-DA-EPOCH (dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab).

After evaluating the possible DDIs between the chemotherapeutic agents and all the available DAA (resumed in Table 2), a sofosbuvir (SOF)-based AVT was chosen in all patients but one. In the latter case elbasvir/grazoprevir regimen was preferred to a

Table 2
Potential drug–drug interactions between CIT regimens and all available DAAs at the time of the study[a,b].

Chemotherapeutic agent	Sofosbuvir	Daclatasvir	Sofosbuvir-ledipasvir	Sofosbuvir-velpatasvir	Elbasvir-grazoprevir	Ritonavir-boosted paritaprevir- ombitasvir-dasabuvir
Rituximab	◆	◆	◆	◆	◆	◆
Cyclophosphamide	■	■	■	■	■	■
Doxorubicin	◆	◆	◆	◆	◆	◆
Vincristin	◆	◆	◆	△	△	△
Prednisone	◆	◆	◆	◆	◆	△
Oxaliplatin	◆	◆	◆	◆	◆	△
Etoposide	◆	◆	◆	◆	◆	△

[a] Data from HEP drug interactions (www.hep-druginteractions.org, University of Liverpool). In all cases the potential drug interactions are derived from metabolism and clearence data and not from direct study of coadministration.
[b] Legend of symbols: ◆ no interactions expected; △ potential interactions; ■ drug not included in HEP drug interactions.

Table 3
Antiviral therapy and chemoimmunotherapy, side effects and outcomes.

Antiviral therapy[a]	
Sofosbuvir/Daclatasvir	3/7
Sofosbuvir/Ledipasvir	2/7
Sofosbuvir/Velpatasvir	1/7
Elbasvir/Grazoprevir	1/7
Previous AVT[a]	1/7
CIT scheme[a]	
R-CHOP	3/7
R-COMP	2/7
R-DA-EPOCH	1/7
R-Oxaliplatin[b]	1/7
AVT started after CIT[a]	5/7
SAE before start of AVT[a]	4/5 (2 neutropenia, 1 ALT increase, 1 neuropathy)
SAE during concomitant therapy[a]	1/7 (neutropenia)
CIT dose reduction/delay during AVT[a]	0/7
Completion of planned CIT[a]	7/7
Negative HCV-RNA at week 4[a]	6/7
SVR[a]	7/7
Lymphoma complete response (months of follow-up)[a]	7/7 (12, 5–20)

Abbreviations: AVT, antiviral therapy; CIT, chemoimmunotherapy; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-COMP, Rituximab, cyclophosphamide, vincristine, liposomal doxorubicin, prednisone; R-DA-EPOCH, dose adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone and rituximab; SAE, seriuous adverse events; SVR, sustained virological response.
[a] Number/total.
[b] Therapy started as Rituximab, Gemcitabin and Oxaliplatin; Gemcitabin stopped for liver toxicity, resolved before start of AVT.

SOF-based regimen due to impaired renal function of the patient (estimated glomerular filtration rate, eGFR 34 ml/min). Ribavirin was not included in any of the used regimens. In two patients AVT was started before CIT; in the other cases AVT was started after two or three of the six programmed cycles of CIT.

Both AVT and CIT were completed as planned in all patients, without the need for any chemotherapy dose delay. During concomitant therapy only one serious adverse event (grade 3 neutropenia) was observed. No cases of liver toxicity were observed, and ALT levels normalized in all patients at week 4 of AVT. At the same time, HCV-RNA was not detectable in all patients but one, and in the latter case it became undetectable at week 8.

All patients achieved both SVR and a complete remission of lymphoma at the end of the first-line CIT. All patients remained disease-free at the last available follow-up, 12 months (range: 5–20) from the end of CIT.

AVT and CIT regimens, grade 3–4 toxicities, virological and hematological outcomes are summarized in Table 3; individual data are showed in Supplementary Table 2.

4. Discussion

Our results suggest that concomitant administration of AVT with DAAs and Rituximab-based CIT in patients with HCV infection and DLBCL is safe and effective. We did not observe any clinically significant DDI between any DAA and CIT regimens applied. Three patients experienced SAE (one case of liver toxicity, two cases of neutropenia) of CIT before start of AVT, while only one case of neutropenia was observed during the concomitant therapy. Most relevantly, no patient showed ALT flares during the concomitant therapy (neither did the patient who had previously experienced a severe liver toxicity), thus allowing the completion of the scheduled cycles of CIT without any need of administration delays. The different DAA regimens translated to SVR achievement in all patients, associated to a complete radiological response of lymphoma. No evidence of disease recurrence was observed after a median time of 12 months from the end of CIT.

AVT alone is generally effective in HCV-related indolent NHL, and it is recognized as a possible first-line therapy in this subset of patients [32]. On the contrary, in patients with high-grade NHL a primary treatment with chemotherapy is required. Once remission is achieved, AVT should be introduced also in aggressive NHL, since the eradication of HCV with IFN-based AVT has been shown to reduce or to eliminate the risk of lymphoma recurrence [27,33]. This sequential approach has been the most used therapeutic strategy in the last years, despite a potential increased risk of liver toxicity induced by chemotherapy in patients with HCV active infection. In this regard, previously published data are discordant. Standard chemotherapy without Rituximab in HCV patients with hematological malignancies has been reported by some authors as relatively safe [34–36], while others [37] described a higher rate of liver toxicity and a worse outcome among HCV-positive DLBCL patients receiving aggressive regimens compared to patients without infection. More recently, further concerns arised on the use of Rituximab in combination with chemotherapy agents, that in the last decades has become the standard of care in DLBCL. In fact, depletion of B cells by Rituximab may induce a loss of immune control on viral replication [38–40] with a sudden rise of HCV viral load and liver damage.

Rituximab and high dose steroids were found as independent risk factors for viral reactivation in a recent prospective study of HCV patients with different malignancies, reporting 36% of HCV reactivation rate in patients with hematological malignancies compared to 10% of patients with solid tumors [41]. Zaky et al. [42] even observed more liver toxicity and a worse overall survival in HCV-patients with DLBCL who received CIT with Rituximab compared to standard chemotherapy, while this was not confirmed by other authors [43]. Overall, severe (grade 3 or 4) hepatotoxicity occurs in 16–28% of HCV-patients affected by DLBCL undergoing R-CHOP [25,26,42,44]. Studies in which a direct comparison was made, con-

firmed a higher risk in infected patients compared to non-infected matched controls [25,26].

Liver toxicity is frequently cause of CIT dose delays or discontinuation in HCV patients [25,26,41,44], thus increasing the risk of lymphoma recurrence. In fact, a significantly shorter progression-free survival has been observed in HCV patients that experienced liver toxicity during chemotherapy compared to those who did not [44]. Specific clinical approaches to limit liver toxicity and improve survival in HCV patients with aggressive NHL are therefore strongly needed.

An early combination of AVT and CIT may reduce the risk of liver toxicity, particularly those secondary to HCV reactivation, but IFN-based therapies were not suitable for this purpose because of unacceptable haematological side effects [27]. On the contrary, DAA allow very high SVR rates with short and generally well-tolerated treatments [45], making them potentially appealing for a concomitant administration with CIT. The possibility, with newer DAA, to avoid the use of ribavirin, further increases the haematological safety of AVT reducing the risk of anemia. While the efficacy of DAA has already been confirmed in patients with HCV-related DLBCL after completion of first-line CIT [21,46], to date only few data have been published on their concurrent administration with Rituximab-based CIT. In this context, the major concern is represented by the possible presence of unknown DDI. International guidelines underline the importance of a check for possible DDI before starting any AVT [29], but contemporary administration of DAA and chemotherapeutic drugs has not been studied. Information available in online databases is only derived from metabolism and clearance data, and some drugs (like cyclophosphamide) are not even included. A prospective study performed on 21 HCV-infected cancer patients included only one DLBCL [47] and a retrospective study included 6 patients treated with DAAs after autologous hematopoietic stem-cells transplantation for different hematological malignancies. Merli et al. [48] reported one case of a patient with HCV-related DLBCL who started AVT with SOF-ledipasvir, after two interruptions of first-line R-CHOP therapy due to two severe ALT flares (accompanied by an increase in viral load) and before safely resuming and completing CIT. Similarly to patient 3 of our study, this report clearly shows the possible preventive role of AVT against CIT-induced liver damage. In our case, the absence of a quantitative determination of HCV RNA before the start of CIT does not allow to completely clarify the cause of the hepatic flare, but the very high viremia detected before the start of AVT, only few weeks after the acute event, strongly suggests a contribution of viral reactivation induced by CIT combined to gemcitabine hepatic toxicity.

Recently, a wider experience was reported by Persico et al. [49] who described 20 DLBCL patients infected with genotype 1b HCV who received SOF-Ledipasvir concomitantly with R-CHOP or CHOP, with excellent virological outcome (100% SVR, even if one patient prematurely stopped AVT for a lymphoma-associated adverse event). In the latter paper, a comparison with a matched historical control showed an advantage in disease free survival (but not in overall survival) for treated patients. These results are encouraging despite the limits of the analysis, such as the different follow-up of the two groups and the increased use of Rituximab in the AVT group. No safety concerns were observed, in particular no cases of severe liver toxicities were reported either in treated patients or in historical control.

Despite the limited number of patients, our results confirm the efficacy and safety of a concomitant administration of DAA and CIT. Our experience is the first reported with HCV-genotype different to 1b and in particular with genotype 2. This is of particular interest because genotype 2 virus has been associated to higher risk of hepatitis flare with respect to genotype 1b in untreated patients [50]. All the cases of HCV reactivation with hepatitis flares during chemotherapy reported by Torres et al. occurred in patients infected by genotype 2 HCV [41], like the single case described in our series. These evidences seem to suggest that patients infected with genotype 2 HCV may particularly benefit from an early AVT before or at least during the first phases of chemotherapy. We also report for the first time the use of a non-SOF-based regimen, suggesting that the concomitant therapy can be applied in all HCV patients, also in those with impaired renal function that cannot be treated safely with SOF. The recent approval of second-generation multigenotypic DAA with different mechanisms of action, increased potency, higher genetic barrier and eventually, shorter treatment duration, might allow to further simplify the algorithms of HCV therapy also in this setting.

The patients attending our Hepatology Unit were evaluated monthly, as ordinary patients with HCV infection, without the need for a closer follow-up during AVT. The concomitant therapy had no impact on severity and management of a typical CIT-related toxicity like severe neutropenia, while possibly prevented liver toxicity and subsequent delays or early interruptions of CIT. Large, prospective studies are needed to confirm our preliminary data and to assess prognostic implications of the concomitant administration of DAA and CIT.

Conflict of interest

M Viganò is on the speakers' bureau of Roche, Gilead and Bristol Myers Squibb. MG Rumi has served as a consultant for AbbVie, Gilead Sciences, Merck. Other authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.10.019.

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