

## CASE REPORT

# Feasibility of all-oral anti-HCV treatment during DHAP chemotherapy and autologous stem cell transplantation for T-cell lymphoma

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## SUMMARY

The role of anti-HCV direct-acting agents (DAAs) is well described in HCV-related lymphoproliferative disorders, whereas few data are available on their use in other malignancies, such as aggressive T-cell lymphomas requiring autologous stem cell transplantation (ASCT). We describe two oncologic cirrhotic patients treated with DAAs who underwent ASCT achieving cure for both diseases. Co-administration of sofosbuvir with cisplatin led an unexpected severe kidney impairment that did not resolve 30 weeks after drug exposure. The optimal timing of DAA administration in the ASCT setting has yet to be defined: our experience shows that co-administration is feasible, but requires close monitoring for adverse events.

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## INTRODUCTION

In the “post-screening” era, the prevalence of HCV infection in hematopoietic stem cell transplantation (HSCT) candidates before transplant is still around 6.0% (Locasciulli *et al.*, 1999). Liver disease is a well-known major complication after HSCT: HCV-infected recipients are at risk for accelerated liver disease progression, acute HCV exacerbation, viral reactivation and liver-related death (Ramos *et al.*, 2009; Ljungman *et al.*, 2012). Additionally, HCV is a risk factor for drug-induced liver toxicity, treatment delays and reduced dose intensity (Ennishi *et al.*, 2010; Chen *et al.*, 2015), with some evidence of a negative prognostic impact on survival (Hosry, 2016). For these reasons, HCV-infected patients are often excluded from bone marrow transplantation procedures (Locasciulli *et al.*, 1994; Klingeman *et al.*, 1991). However, nowadays HCV-infected patients might benefit from direct-acting agents (DAAs), which have proved to be highly effective and safe.

Some reports are available on the use of DAA before, during or soon after chemotherapy, including HSCT, but no data have been published on the feasibility of DAA treatment during peripheral blood progenitor cell mobilization and autologous stem cell transplantation (ASCT). Here we describe two patients who underwent ASCT for aggressive T-cell lymphoma while on treatment with sofosbuvir (SOF) and daclatasvir (DCV).

## Patient #1

In May 2015 a 43-year-old man referred to an external Oncologic Center for Peripheral T-Cell Lymphoma, Not Otherwise Specified, stage IVA according to the Ann-Arbor system. Baseline PET scan showed disseminated nodal and focal gastric involvement. Age-adjusted International Prognostic Index score was 1 (low-intermediate). HCV infection was detected at baseline by serology, but no further tests were performed. Six courses of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and methylprednisone) at standard dose were administered achieving a complete remission (CR), confirmed by PET negativity. The patient was then referred to our Center in March 2016 for consolidation with ASCT, but he was considered ineligible due to high level of transaminases (above 3xULN) and HCV RNA (7.25 log<sub>10</sub> UI/mL); bilirubin and creatinine were within normal ranges. HCV genotype 1a was identified, and liver cirrhosis was documented (stiffness 12.3 kPa; Child-Pugh Class A, MELD 8; portal hypertension). It was decided to treat HCV infection before chemotherapy, so he started SOF 400 mg and DCV 60 mg on March 23, 2016. After two weeks of antiviral treatment, HCV RNA dropped to 1.45 log<sub>10</sub> UI/mL with transaminases normalization. The hematological plan was resumed, and a single DHAP course (dexamethasone, high-dose cytarabine and cisplatin), both for consolidation and stem cell mobilization purpose, was administered on April 15. Granulocyte growth-stimulating factor (G-CSF) at a dose of 10 µg/kg/day subcutaneously was started on day +1 and adequate stem cell harvest by single leukapheresis was obtained on April 28 (5.1x10<sup>6</sup> CD34+/kg). After DHAP chemotherapy, acute renal failure occurred (grade 3 defined as Common Terminology Criteria for Adverse Events, CTCAE, version 4.03). The estimated glomerular filtration rate (eGFR) dropped from baseline 155 to 22.4 mL/min, with con-

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comitant severe hypomagnesemia and hypokalemia. SOF dose was reduced to 400 mg every other day. Non-oliguric acute renal failure with concomitant severe hypomagnesaemia and hypokalemia was consistent with a typical cisplatin-related kidney toxicity, as confirmed by nephrologist evaluation: despite prompt rehydration, at discharge eGFR was still low (34.8 mL/min) but SOF dose returned to 400 mg daily (Figure 1).

He started the conditioning phase with the CEAM regimen (lomustine, cytarabine, etoposide and melphalan) on August 03 and underwent ASCT on August 10 (day 0). The aplastic phase was complicated by oral mucositis (grade 3) and by right lobe pneumonia. Time to engraftment was 9 days for neutrophils and 11 days for platelet. He was discharged on day +16.

The anti-HCV treatment was stopped on September 07 2016 after a 24 week course with no major toxicities; the patient achieved sustained virological response after 12 weeks (SVR12) remaining with a reduced eGFR (54.0 mL/min). At the hematological evaluation on March 2017, the patient was asymptomatic with an ECOG performance status of 0; CT scan confirmed CR. Nevertheless, more than 30 weeks after the exposure to cisplatin, renal function did not fully recover (eGFR 61.0 mL/min).

## Patient #2

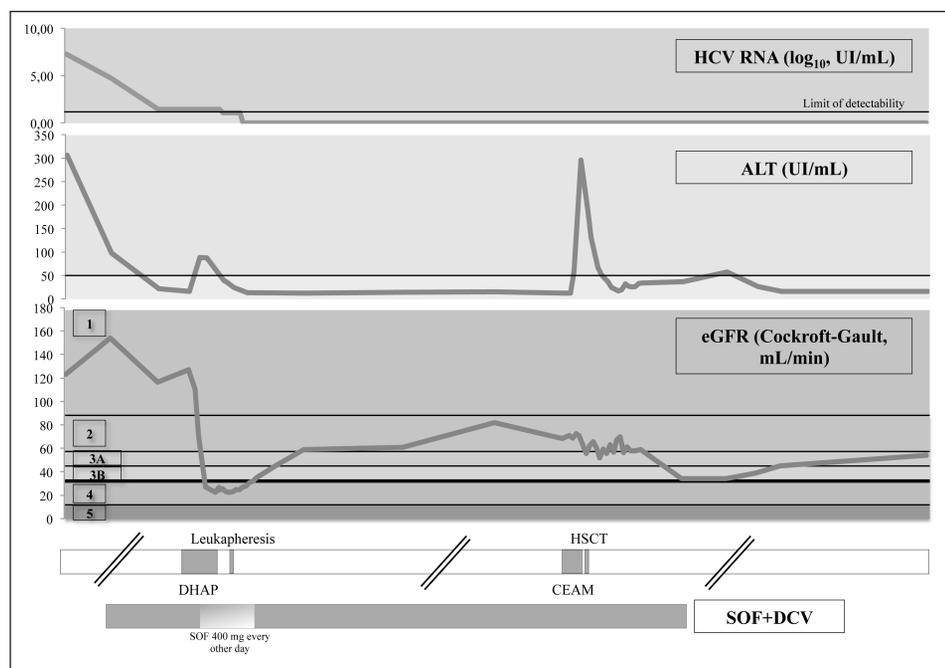
In 2013 a 52-year-old man was diagnosed in an external Oncologic Center with Follicular Lymphoma grade 1, clinical stage IIIB according to the Ann Arbor system. He underwent six courses of R-CVP (rituximab, cyclophosphamide, vincristine and prednisone) from August to November 2013 obtaining a partial remission (PR). Then he received maintenance therapy with rituximab every 8 weeks for 24 months, achieving CR. In March 2015 he presented with enlarged lymph nodes and multiple skeletal lesions. During the assessment for the hematologic malignancy, he was tested for HCV and resulted negative. A

follicular lymphoma recurrence was postulated, and the patient received six Rituximab-CHOP courses, achieving a second CR. In May 2016, while on follow-up, the patient presented with novel left inguinal lymphadenopathy, and after a few weeks also B symptoms appeared. In July he was referred to our Hospital, and histologically proven diagnosis of Anaplastic Large Cell Lymphoma (ALCL) Alk-positive was made. Restaging procedures showed IIB clinical stage. Due to his peculiar clinical history and previous anthracycline-containing treatment, the patient was a candidate for high-dose chemotherapy and ASCT despite the Alk positivity. On July 30, he received the first DHAP course with a grade 2 as CTCAE cisplatin-induced kidney toxicity that recovered after hyper-hydration; he underwent leukapheresis on August 12, and  $17.3 \times 10^6$  CD34+/kg were collected. Before DHAP administration transaminases were slightly increased, so he repeated serology for HCV that tested positive. The route of transmission was not established, but a potential healthcare assistance-associated infection could not be ruled out. Liver disease was due to a genotype 1a virus with a viral load of  $5.65 \log_{10}$  UI/mL. Transient elastography was suggestive of liver cirrhosis (stiffness 14.3 kPa; Child-Pugh Class A, MELD 6).

Given the previous kidney toxicity, he shifted to DHAOx chemotherapy (dexamethasone, high-dose cytarabine and oxaliplatin) and received two additional courses, completed on 12 October. Restaging showed a PR, and a consolidation with ASCT was planned. In order to minimize transplant-related hepatic toxicity, the patient started a 24 week course of SOF 400 mg and DCV 60 mg on October 17 2016 achieving viral undetectability after 8 weeks of therapy.

He started CEAM conditioning on December 16 and underwent ASCT on December 23 (day 0). The aplastic phase was complicated by fever of unknown origin. Time to engraftment was 8 days for neutrophils and 11 days for platelets. He was discharged on day +13.

At the last hematological evaluation, the patient was in



**Figure 1** - Virologic, Alanine Amino Transferase (ALT) and estimated creatinine clearance (eGFR) trend over time in Patient #1.

good clinical conditions with a CT scan showing CR. The DAA treatment was stopped on 02 April 2017 with no major toxicities and SVR12 was achieved.

## DISCUSSION

We present two cases of T-cell lymphomas treated with SOF and DCV simultaneously with DHAP chemotherapy, peripheral blood progenitor cells mobilization and ASCT. DAAs allowed the patients to undergo full-dose regimens with no liver-related adverse events. So far, the combined hematologic and antiviral treatments have achieved a full response for both diseases.

Few data are available on drug-drug interactions between DAAs and antineoplastic agents. No interactions are expected with most of the drugs used, with the exception of dexamethasone, which may decrease DCV concentrations: co-administration is contraindicated. On the other hand, a possible combined renal toxicity between cisplatin and SOF could not be completely ruled out. Cisplatin-induced nephrotoxicity has been well known since the first studies in 1971 (Kociba and Sleight, 1971). The incidence of renal insufficiency is around 20-30% (Hartmann *et al.*, 1999). Generally, non-oliguric renal failure begins several

days after cisplatin administration, with the increase in serum creatinine and blood urea nitrogen concentrations, mild glycosuria and proteinuria, indicative of proximal tubular dysfunction. Recovery usually occurs over a period of 2-4 weeks; permanent nephrotoxicity can result only after repeated administrations (Taguchi *et al.*, 2005). In our case a single cisplatin dose of 100 mg/m<sup>2</sup> (173 mg) induced persistent renal failure. SOF is mainly eliminated by the kidney, primarily as its metabolite GS-331007: the prescription of SOF in patients with eGFR below 30 mL/min is not recommended because GS-331007 AUC is increased by 55%, 88% and 451% in cases of mild, moderate and severe renal insufficiency, respectively. SOF and GS-331007 mechanisms of renal elimination are not well described, but tubular excretion might be speculated given the structural analogy with HBV and HIV nucleotide analogs. Therefore, competitive risks with other drugs that are toxic for the tubule - antivirals, anti-calceinurins and cisplatin - could be expected (Carrier *et al.*, 2013).

While DAA-based treatment in HCV-related indolent lymphomas has been well described (Rossotti *et al.*, 2015; Sultanik *et al.*, 2015; Arcaini *et al.*, 2016), few case series have been published on other lymphoproliferative disorders (Table 1 summarizes published data). Carrier *et al.*

**Table 1.** Clinical features of hematologic patients treated with DAA so far published.

Author	N	Histology	DAA regimen	Chemotherapy regimen	Timing of DAA	Toxicity	SVR	Complete response
Carrier	5	Marginal zone lymphoma (2)	SOF+SMV	Rituximab	During rituximab infusion	G3 asthenia	100% (5/5)	100% (5/5)
		Marginal zone lymphoma (1)	SOF+DCV			No		
		DLBCL (2)	SOF+DCV	4 R-ACVBP, 2 Methotrexate, 4 R-VP16	After CT	G3 liver toxicity		
Merli	2	DLBCL (1)	SOF+SMV	R-CHOP, R-mini-DHAP followed by RT	After CT, during RT	No	100% (2/2)	100% (2/2)
		DLBCL (1)	SOF/LDV	R-CHOP	Contemporary			
Economides	9	Multiple myeloma (2); Myelodysplastic syndrome (2)	SOF/LDV±RBV (52%) SOF+RBV (29%) SOF+SMV (14%) SOF+DCV (5%)*	No detailed data	Contemporary	Serious adverse events: 38% (8/21): G3: Anemia Neutropenia Thrombocytopenia Fatigue Weight loss Headache G4: Abdominal pain Fatigue	95% (20/21)*	No data
		Acute myelogenous leukemia (1)						
		DLBCL (1)						
		Follicular lymphoma (1)						
		Waldenström macroglobulinemia (1)						
		Mycosis fungoides/T cell lymphoma (1)						
Kyvernitakis	14	Leukemia (14); Non-Hodgkin lymphoma (20); Hodgkin lymphoma (9); Multiple myeloma (25); other (1)*	SOF+RBV (6)	No detailed data	After HSCT	G3 anemia	85% (11/13)	32/64 (50%)*
			SOF+SMV (2)			No		
			SOF/LDV±RBV (6)			G3 hyperbilirubinemia		
Total	30					29% (12/42)*	90% (18/20)**	55% (39/71)^

\* Including the full study population; \*\* excluding patients described by Economides for whom no distinction between oncologic and hematologic subjects is available; ^: including the full population described by Kyvernitakis and excluding the subjects described by Economides.

SMV: simeprevir; LDV: ledipasvir; DLBCL: Diffuse Large B-cell Lymphoma; R-ACVBP: rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin and cytarabine; R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone; CT: chemotherapy; RT: radiotherapy; G3/G4: grade 3/grade 4 toxicity according to Common Terminology Criteria for Adverse Events, CTCAE, version 4.03 published in 2010).

(2016) and Merli *et al.* (2017) reported some cases of diffuse large B-cell lymphomas (DLBCL), concluding that DAAs could be introduced very early to prevent lymphoma relapse, improve the hematological prognosis and reduce the liver toxicity of chemotherapy (allowing full-dose and on time treatment administration). Economides *et al.* (2016) described nine heterogeneous hematologic disorders: no DAAs or chemotherapy discontinuation or serious adverse events occurred. Nevertheless, very different anti-HCV and anti-cancer regimens were used and no distinction between solid and hematologic malignancies was made. As a consequence, the generalizability of the results needs caution. Only one paper described the use of DAAs in the field of HSCT: Kyvernitakis *et al.* (2016) published 64 transplant candidates or recipients who underwent anti-HCV therapy. Only 14 cases were treated with DAAs and all after transplantation because of the recent availability of these agents (median time between HSCT and anti-HCV treatment: 649 days). Patients who received anti-HCV therapy had fewer relapses with a significantly higher 5-year survival rate (77% versus 36%;  $p=0.005$ ).

No data on DAAs during peripheral blood progenitor cell mobilization and conditioning for ASCT are available: the optimal timing of antiviral administration in this setting has yet to be defined. Current international treatment guidelines do not include any specific recommendations for HSCT candidates or recipients. The cited papers by Merli *et al.* and Kyvernitakis *et al.* proposed to defer DAA administration to after the completion of chemotherapy to prevent overlapping toxicity and potential drug-drug interactions. If HSCT could be postponed, the authors proposed to start antiviral treatment before HSCT spacing a sufficient amount of time - at least 3 months - between the two procedures. Our experience showed that concomitant administration of antivirals with mobilization chemotherapy and conditioning regimen to ASCT is feasible without delays, but potential drug-drug interactions should be taken into consideration. Thus close monitoring for adverse events is warranted.

### Competing interests

All authors approved the final version of the manuscript and none of them has any conflict of interest to declare. No financial support was granted for this work. A preliminary version of these data has been presented at the 16<sup>th</sup> National Congress of the Italian Society of Infectious and Tropical Diseases (SIMIT), Salerno, 15-18 October 2017.

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