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Research Article

Treatment Outcome of Chronic Hepatitis C Virus Infection with Directly Acting Antivirals in Patients with Current or Previously Treated Extrahepatic Malignancies

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Abstract

Introduction: Concurrent treatment of chronic hepatitis C and extrahepatic malignancies exacerbates the symptoms of cancers and the adverse effects of the treatment. It is expected that DAA (Directly Acting Antiviral) therapies may be safe in this group of patients.

Aim: To assess the outcome of HCV treatment with DAA in patients with extrahepatic cancers either on treatment or completed treatment.

Methods: A retrospective audit of Chronic HCV patients for the period of April 2015 - December 2017 was done. Data were collected regarding demography, cancer site, cancer treatment, prior anti HCV treatment, current anti HCV treatment, adverse events, possible drug-drug interaction, status of underlying liver function and treatment response for anti HCV therapy. HCV therapy was in accordance with AASLD/EASL.

Results: Out of total 48 patients assessed, 38 patients were included in the analysis (7 lost to follow up, 2 died, 1 stopped therapy). 6 (16%) patients were cirrhotic. One patient was treatment experienced with PEG-IFN. Most common associated malignancies were Hematolymphoid, Gynaecological and Gastrointestinal. 7 patients had HBV coinfection. 1/3rd of patients received cancer therapy concomitantly with anti HCV therapy. All 38 patients had achieved ETR and SVR 12. Overall adverse event rate was 38%, most common being anaemia requiring modification of ribavirin therapy (n = 5). No modification for either anti HCV therapy or cancer therapy was required. No drug-drug interaction was noted.

Discussion: This study demonstrates that SVR rate is excellent (100%) in this cohort of patients with chronic HCV infection. Concomitant cancer therapy and DAA are safe without significant adverse events.

Keywords: *HCV; HBV; DAA; Cancer chemotherapy; SVR; ETR; DDI*

Abbreviations

AASLD: American Association of Study of Liver Disease; EASL: European Association of Study of Liver; NCCN: National Comprehensive Cancer Network; ESMO: European Society of Medical Oncology; DAA: Directly Acting Antivirals

Introduction

Treatment of chronic hepatitis C virus (HCV) infection has been a challenge for gastroenterologists prior to availability of directly acting antivirals (DAA). The prevalence of HCV infection is estimated to be 0.7% overall in all types of cancer [1] and as high as 15% in hematolymphoid malignancies [2-5]. In patients with leukaemia and chronic HCV infection, it was found that final prognosis is worse in spite of complete chemotherapy due to development of liver dysfunction [6]. In hematopoietic stem cell transplant recipients with concurrent HCV infection, increased rate of sinusoidal obstruction syndrome, hepatic inflammation, liver decompensation and mortality were noted in early post-transplant period. A shorter interval of progression from hepatitis to cirrhosis was also seen in them [7]. On the other hand, HCV reactivation and hepatitis flare is known to occur in patients receiving chemotherapy requiring modification of chemotherapy, which in turn can adversely affect oncological outcomes [8]. Hence, there is a need to treat chronic HCV infection in cancer patients but was dif-

ficult due to side effect of Interferons and drug-drug interaction with chemotherapy. With the availability of DAAs, treatment has become convenient and feasible for these patients. However, there is a paucity of data on regarding safety and effectiveness of HCV treatment with DAA in patients with malignancy. In this study, we analysed the response to treatment of HCV infection in patients with extrahepatic malignancy.

Methods

Study design

This is a retrospective observational study. Data was retrieved from the prospectively maintained database of Hepatology Clinic of Tata Memorial Hospital, a high-volume cancer centre, from April 2015 to December 2017. We analysed data of patients having extrahepatic malignancy with concurrent HCV infection. Baseline parameter data was collected about demography, cancer site, cancer treatment, prior anti HCV treatment, current anti HCV treatment and status of underlying liver function. We analysed the treatment response of both chemotherapy and anti HCV therapy. Drug related adverse events and possible events of drug-drug interaction (DDI) were documented. Any modification of therapy if needed was done as per attending physician's discretion and was documented as well. Only patients treated with DAAs were included in the study irrespective of whether they were treatment naïve or experienced. Anti-HCV treatment was prescribed according to the latest AASLD/EASL guidelines, based on the availability of medications in India. Ribavirin (RBV) was usually started at a dose of 600 mg daily if haemoglobin was more than 10 gm/dl and was avoided in patients with haemoglobin less than that. RBV dose was escalated every week by an increment of 200 mg to a maximum dose of 1000 mg daily. When the dose of RBV could not be increased up to 1000 mg daily due to side effects, patient was continued at maximum tolerated dose until the completion of anti HCV treatment. No patient was prescribed RBV at a dose of 1200 mg, as previous experience showed poor tolerance and a higher rate of adverse effects with that dose in Indian patients. Cancer treatment mostly followed current NCCN/ESMO guidelines and decision of cancer treatment were taken in a multidisciplinary board. All patients, underwent biopsy confirmation (except HCC), and baseline staging of their cancer. Waiver from approval of institutional review board was granted as it is a retrospective study.

HCV infection was defined as any level of detectable HCV RNA in patients' serum. Adverse events are defined as per Common Terminology Criteria for Adverse Events (CTCAE v 4.0). Sustained virological response at 12 weeks (SVR12) i.e. undetectable HCV RNA at 12 weeks after the completion of treatment was considered as surrogate of cure from HCV infection in our study. End of therapy response (ETR) defined as undetectable HCV RNA at completion of anti HCV therapy was noted. Treatment failure was defined as the absence of either the ETR or SVR12. When available, SVR at 24 weeks and 48 weeks were also recorded. Cirrhosis was assessed by liver ultrasonography (USG) or CT scan in all patients. Patients underwent Fibroscan™, liver biopsy or any other test when as per discretion of treating gastroenterologists. Patients with Hepatitis B (HBV) coinfection received concurrent anti HBV therapy.

Patients were followed up monthly or once in two months for assessment of treatment compliance and adverse events. Also, they were provided with Hepatology Clinic Phone number to intimate and seek telephonic advice for any adverse events perceived by them. For patients who were treated with RBV, weekly follow up was done for 3 weeks or until one week after attaining maximum dose of RBV. Potential DDI was checked using current databases (https://www.drugs.com and https://reference.medscape.com).

Statistical analysis

Patients' demography, HCV genotype and primary cancer were analysed by descriptive variables. Variables checked and analysed were age, sex, cancer, ongoing cancer treatment, Haemoglobin, Platelets, liver function assessment by AST, ALT, Albumin, composite liver status assessed by ChildPugh score and MELD score for cirrhotics, presence of decompensation of cirrhosis, quantitative HCV RNA, HCV genotype, SVR, treatment failure and retreatment. Other conditions considered were comorbid condition i.e. coinfection of HBV, HIV, diabetes, hypertension, ischemic heart disease and chronic kidney disease, alcohol addiction, adverse events during concomitant treatment of DAA and chemotherapy, modifications of chemotherapy regimen or anti HCV therapy and its reason. Statistical analysis was done with the help of SPSS software (v 23.0, IBM Corp, NY, USA).

Results

48 patients were included in the analysis. 7 patients could neither be contacted nor returned back after starting anti HCV therapy and hence SVR could not be assessed. 2 patients died while on anti HCV treatment (Figure 1). One had metastatic prostatic carcinoma who died after 3 months of starting anti HCV therapy due to progressive cancer. The other patient had lymphoma and was receiving Bendamustine along with anti HCV therapy. He died after 4 weeks of starting anti HCV therapy resulting from neutropenic sepsis. In one patient with metastatic Gallbladder cancer, concurrent chemotherapy (GEMCIS) and anti HCV therapy was started in view of very good ECOG performance (ECOG PS 1) status at presentation. However, patient had aggressive cancer and rapidly progressed to poor performance status (ECOG PS 4) and hence anti HCV therapy was stopped when multidisciplinary team considered to withdraw chemotherapy in view of limited life expectancy.

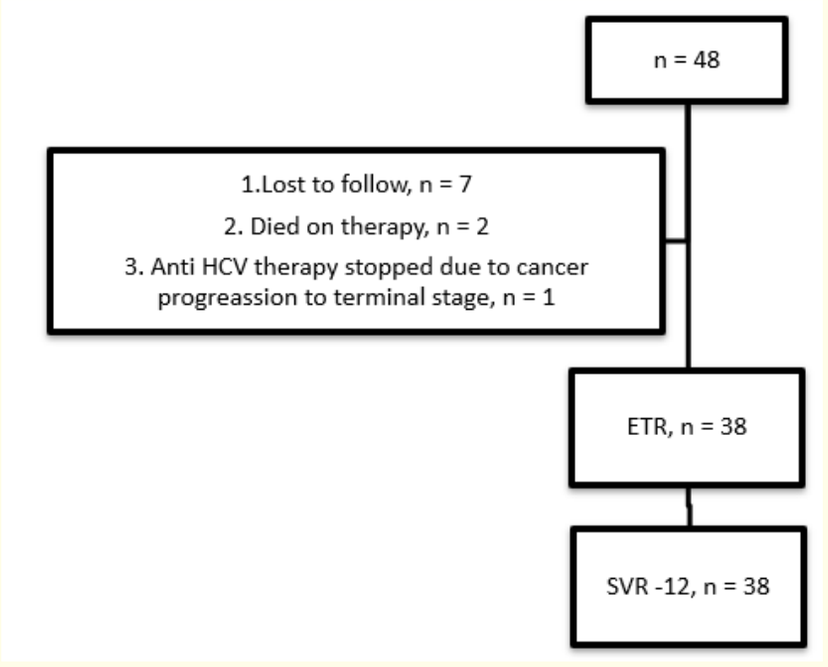

Figure 1: *Flow diagram of study population.*

38 patients were evaluated till ETR. Mean age of the population was 45.5 years (Range 18 - 72 years; SD 14.2 years). 1 patient had prior treatment for HCV (PEG-IFN + RBV) while rest were treatment naïve. 10 (26%) had hematolymphoid malignancy, 5 (13%) had cancer breast, 8 (21%) had gynaecological malignancy, 1 (2%) had urinary bladder cancer, 7 (18%) had gastrointestinal cancers, 4 (10%) had cancers of musculo-skeletal system and 3 (7%) of patients had cancer of head-neck region. 14 (37%) patients receiving cancer chemotherapy while rest (n = 24, 63%) were either not receiving cancer treatment or on surveillance after completion of cancer therapy. None of the patients treated for HCV had history of alcoholism as per DSM -IV criteria. 2 patients had both diabetes and hypertension. 1 patient had ischemic heart disease. 7 patients had HBV coinfection. All of them are receiving concomitant anti HBV therapy (Entecavir, n = 4; Tenofovir, n = 1; and Lamivudine, n = 2). 10 patients had genotype 1 HCV infection, 27 had genotype 3 and one had genotype 4. Mean baseline RNA is > 5 lac IU/ml. 32 patients were non-cirrhotic and 6 were cirrhotic. Among cirrhotics, 5 were Child Pugh A while one was Child Pugh score B (9/15).

6 (15%) patients were treated with Sofosbuvir with Ribavirin regimen before availability of any other drug in India. All of them had genotype 3 infection and were non-cirrhotic. Other treatment regimen used were Sofosbuvir with Daclatasvir (n = 15; 39%), Sofosbuvir with Daclatasvir and Ribavirin (n = 3; 8%), Sofosbuvir with Velpatasvir (n = 4; 10%) and Sofosbuvir with Ledipasvir (n = 10, 26%). Adverse events were noted in 13 patients (38%). Most common side effect was Anaemia (n = 4; 10.5%) requiring reduction of RBV dose (n = 3) or stopping it (n = 1). One patient had skin rash (grade 2). Others had dyspepsia, nausea, occasional vomiting or non-specific constitutional symptoms. 14 patients were receiving cytotoxic chemotherapy or immunotherapy concurrently with anti HCV therapy. No DDI was noted. No grade 3/4 adverse event were noted with chemotherapy. All 38 patients achieved ETR and SVR.

Parameters		N = 38 (%)	Remarks
Age in years (Mean ± SD)		45.53 (± 14.23)	
Male		17 (45%)	
Female		21 (55%)	
Cirrhotic		6 (16%)	
Non-cirrhotic		32 (84%)	
Genotype	1	10 (26%)	
	3	27 (72%)	
	4	1 (2%)	
Mean Baseline RNA (IU/ml)		> 5 Lac IU/ml	
Treatment naïve		37	
Treatment experienced		1	PEG IFN + RBV
Concurrent cancer Breast, n = 5 Genitourinary, n = 9 Gastrointestinal, n =7 Head and neck region, n =3 Musculo-skeletal, n = 4		Hematolymphoid, n = 10	ALL, n = 4; Chronic myeloproliferative disease, n =1; Plasma cell leukemia, n = 1; Plasmacytoma, n = 1 Non-Hodgkin's lymphoma, n =2 Multiple myeloma, n =1
		Cervix cancer, n = 5; Ovarian cancer, n = 2; Uterine cancer, n = 1; Urinary bladder, n = 1	
		Stomach adenocarcinoma, n =4; Stomach GIST, n = 1;Colon cancer, n =2	
		Buccal mucosa squamous cell cancer, n = 2; Thyroid cancer, n=1	
		Osteosarcoma, n = 1; Fibromatosis, n = 1; Rhabdomyosarcoma, n = 1 Paediatric neuro-ectodermal tumour, n = 1	
Intent of cancer therapy Palliative, n = 4 (10%) Surveillance, n = 22 (58%) Benign, n = 1 (2.4%)		Curative, n = 12 (32%)	
Ongoing cancer treatment No, n = 24 (63%)		Yes, n =14 (37%)	
Comorbid conditions Hypertension, n = 2 Ischemic heart disease, n = 1		Diabetes, n = 2	
Co-infection HIV, n = 0		HBV, n = 7	
Anti HCV therapy SOF + LDV, n = 10 (26%) SOF + DCV + RBV, n = 3 (8%) SOF + VEL, n = 4 (10%) SOF + RBV, n = 6 (15%)		SOF + DCV, n = 15 (39%)	
Ribavirin dose		Median = 800 mg (Range: 600 -1000 mg)	

Concurrent chemotherapy	n = 14 Pacli-Crabo, n = 1 (Ca Breast) Paclitaxel, n = 2 Imatinib, n =3 R-CHOP, n = 2 FOLFIRI, n =1 Cyclophosphamide-Adriyamycin, n =1 Gem -Carbo, n =1 VCD, n = 2	CAPOX, n =1
Adverse events requiring drug modification of HCV therapy	Anaemia, n = 4 (44% among those receiving RBV, Overall 10%)	
Adverse events not requiring drug modification of HCV therapy or cancer therapy	Dyspepsia, nausea or vomiting, n= 6 (15%) Constitutional, n = 2 (5%) Skin rash, n = 1 (2%)	
Adverse events requiring drug modification of cancer therapy	Cytotoxic or immunotherapy = None;	Grade 1 nausea was seen in patient on CAPOX Grade 2 vomiting and diarrhoea was seen in patient on Pacli-Carbo. No grade 3/4 adverse events noted requiring drug modification.

Table 1: *Study Population parameters.*

Baseline parameters	Mean (SD)
Haemoglobin (gm/dl)	12.3 (1.5)
Platelet	2 lac (1.21 lac)
Bilirubin (mg/dl)	0.92 (0.49)
Albumin (gm/dl)	3.8 (0.6)
AST (IU/ml)	75.93 (74.8)
ALT (IU/ml)	65.50 (55.1)
Creatinine (mg/dl)	0.8 (0.2)

Table 2: *Laboratory parameters.*

Discussion and Conclusion

Real life data of concomitant cancer chemotherapy and therapy for Hepatitis C is scarce. HCV infected cancer patients comprise a special population as both chemotherapy and anti HCV therapy is complicated by effect of the drugs on each other. Previously, treatment for HCV was deferred usually until the completion of chemotherapy. Availability of DAA provides a unique opportunity to treat HCV infected cancer patient with ongoing chemotherapy, as the duration of treatment is short, easy to administer and is associated with fewer side effects. However because of limited data scepticism prevails among gastroenterologists and oncologists about concomitant therapy.

HCV antibody, in hematolymphoid cancer patients, anti HCV antibody test may be falsely negative posing unique problem [9]. Hence, in these patients, use of HCV RNA PCR to detect chronic hepatitis C is recommended when there is persistently abnormal liver function tests. Treatment of HCV in pre DAA era also posed a unique problem as many patients had advanced liver disease, which made them ineligible for interferon based therapy [10]. Significant adverse events of interferon therapy such as granulocytopenia, thrombocytopenia, depression, suicidal tendency and autoimmune phenomena hampered successful continuation of anti-cancer treatment. Coexistence of HCV and malignancy suggested poor prognosis in these patients as the HCV infection affected oncologic outcomes adversely affecting their chemotherapy. Moreover, a rapid progression of liver disease to cirrhosis was observed in some HCV infected cancer patients- particularly in those who underwent hematopoietic stem cell transplant [11]. In a study on HCV infected Breast Cancer patients, more toxicity and treatment delays or discontinuation were reported during chemotherapy [12]. Hepatitis C reactivation is known to occur in 23% patients with ongoing chemotherapy [8]. Hence there has been a need to treat hepatitis C in this cohort of patients. The availability of DAA, especially second generation DAAs, treatment of HCV has become simplified and there is now greater enthusiasm among gastroenterologists to treat HCV infection along with cancer chemotherapy. Data regarding safety and efficacy of concurrent use of anti-HCV treatment and anti-cancer treatment are rare [13].

Most of our patients had Genotype 3 Hepatitis C infection, as was seen in previous studies from India [14]. All our patients achieved ETR and SVR. 38% of our patients had concomitant ongoing chemotherapy. Although data on use of DAA with chemotherapy is sparse, a study in patients in Non-Hodgkin's lymphoma demonstrated the safety and efficacy of simultaneous treatment [15]. While previous data showed that more than 50% of patients with incidentally detected Hepatitis C had cirrhosis at baseline, our study showed only 16% had cirrhosis [16]. Although, cirrhotics are known to have lower rates of SVR, especially with genotype 3, all our cirrhotic patients achieved SVR [17]. This audit demonstrates that SVR rate is excellent (100%) in patients with HCV infection who is suffering from cancer presently or had cancer previously. Previous treatment experience with PEG-IFN did not result in DAA treatment failure. We found concomitant cancer therapy and DAA is effective in curing HCV infection without hampering cancer treatment.

Previous studies have demonstrated adverse reactions in up to 40% patients with severe adverse reactions in up to 3% [18]. Our data revealed a similar rate of adverse events (38%), although no serious adverse events were seen and did not mandate cessation of either cancer therapy or HCV therapy. 80% of patients could tolerate full dose of RBV. 44% of those who received ribavirin developed anaemia and needed dose modification. A previous small study reported use of DAAs during chemotherapy in 15 patients with a SVR rate of 90%, with no reported drug interactions [19]. No drug-drug interactions were noted in this study.

Major limitations of the study were being retrospective in nature, small sample size and a significant attrition rate on therapy. This is the first study from India after availability of DAA to assess the effect of anti HCV therapy among cancer patients and cancer survivors. It is also the first report from India about feasibility and safety of concomitant cancer therapy and HCV therapy. To conclude, anti-HCV therapy with DAAs is both safe and effective in a patient with extrahepatic malignancy even when receiving anticancer therapy concomitantly. There is need for guidelines to direct anti-HCV therapy in this special cohort of patients.

Bibliography

1. Kose S., *et al*. "Seroprevalence of hepatitis B and C among oncology patients in Turkey". *Journal of Health, Population and Nutrition* 29.6 (2011): 652-655.

2. Silvestri F., *et al*. "Prevalence of Hepatitis C virus infection in patients with lymphoproliferative disorders". *Blood* 87.10 (1996): 4296-301.

3. Faggioli P., *et al*. "Acute hepatic toxicity during cyclic chemotherapy in non Hodgkin's lymphoma". *Haematologica* 82.1 (1997): 38-42.

4. Markovic S., *et al*. "Reactivation of hepatitis B but not hepatitis C in patients with malignant lymphoma and immunosuppressive therapy. A prospective study in 305 patients". *Hepatogastroenterology* 46.29 (1999): 2925-2930.

5. Fujii Y., *et al*. "Hepatitis C virus infection in patients with leukemia". *American Journal of Hematology* 46.4 (1994): 278-282.

6. Borchardt RA and Torres HA. "Challenges in managing hepatitis C virus infection in cancer patients". *World Journal of Gastroenterology* 20.11 (2014): 2771-2776.

7. Torres HA., *et al*. "Hepatitis C Virus Infection among Hematopoietic Cell Transplant Donors and Recipients: American Society for Blood and Marrow Transplantation Task Force Recommendations". *Biology of Blood and Marrow Transplantation* 21.11 (2015): 1870-1882.

8. Torres HA., *et al*. "Hepatitis C virus reactivation in patients receiving cancer treatment: A prospective observational study". *Hepatology* 67.1 (2018): 36-47.

9. Locasciulli A., *et al*. "Hepatitis C Virus Serum Markers and Liver Disease in Children With Leukemia During and After Chemotherapy". *Blood* 82.8 (1993): 2564-2567.

10. Puri P., *et al*. "Consensus Statement of HCV Task Force of the Indian National Association for study of the liver (INASL). Part II: INASL recommendations for management of HCV in India". *Journal of Clinical and Experimental Hepatology* 4.2 (2014): 117-140.

11. Peffault de Latour R., *et al*. "Long-term outcome of hepatitis C infection after bone marrow transplantation". *Blood* 103.5 (2004): 1618-1624.

12. Morrow PKH., *et al*. "Effects of chronic hepatitis C infection on the treatment of breast cancer patients". *Annals of Oncology* 21.6 (2010): 1233-1236.

13. Economides MP., *et al*. "Concomitant use of direct-acting antivirals and chemotherapy in hepatitis C virus-infected patients with cancer". *Alimentary Pharmacology and Therapeutics* 44.11-12 (2016): 1235-1241.

14. Christdas J., *et al*. "Genotypes of hepatitis C virus in the Indian sub-continent: a decade-long experience from a tertiary care hospital in South India". *Indian Journal of Medical Microbiology* 31.4 (2013): 349-353.

15. Persico M., *et al*. "Efficacy and safety of new direct antiviral agents in hepatitis C virus-infected patients with diffuse large B-cell non-Hodgkin's lymphoma". *Hepatology* 67.1 (2018): 48-55.

16. Gupta V., *et al*. "Most Patients of Hepatitis C Virus Infection in India Present Late for Interferon-Based Antiviral Treatment: An Epidemiological Study of 777 Patients from a North Indian Tertiary Care Center". *Journal of Clinical and Experimental Hepatology* 5.2 (2015): 134-141.

17. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu European Association for the Study of the Liver. "EASL Recommendations on Treatment of Hepatitis C 2018". Journal of Hepatology 69.2 (2018): 461-511.

18. Banerjee D and Reddy KR. "Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy". *Alimentary Pharmacology and Therapeutics* 43.6 (2016): 674-696.

19. Mahale P., *et al*. "Concomitant use of chemotherapy and antivirals in hepatitis C virus infected cancer patients [abstract]". Proceedings from the 66th Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, CA. Abstract 1160 (2015).

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