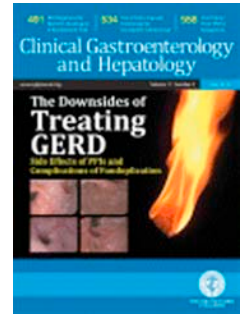


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**Does Chemotherapy Cause Viral Relapse in Cancer Patients with Hepatitis C Infection  
Successfully Treated with Antivirals?**

*Short title:* Relapse of HCV infection after chemotherapy

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*Author contributions:* H.A. Torres designed the study; P. Mahale collected the data; P. Mahale, and H.A. Torres analyzed, and interpreted the data; P. Mahale, and H.A. Torres drafted the manuscript; Pablo C. Okhuysen provided critical revision of the manuscript for important intellectual content; P. Mahale performed statistical analysis. All authors approved the final version of the manuscript.

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**Abstract**

Authors have reported conflicting results on the persistence of hepatitis C virus (HCV) infection in patients having sustained virological response (SVR) to treatment. Therefore, we sought to determine whether chemotherapy leads to viral relapse in 30 HCV-infected patients who had SVR before cancer diagnosis. Half of them had hematological malignancies. Most (60%) received HCV therapy with interferon and ribavirin. Chemotherapy was started at a median of 72 months after SVR and included rituximab (27%), cyclophosphamide (23%), cisplatin (17%), or corticosteroids (37%). No patient had post-SVR viral relapse. Therapeutically induced resolution of HCV appears to be permanent and not affected by chemotherapy.

*Keywords:* Hepatitis C Virus; SVR; Chemotherapy; Interferon; Ribavirin

The goal of therapy for hepatitis C virus (HCV) infection is attainment of a sustained virological response (SVR).<sup>1</sup> Whether HCV can be completely eradicated after an SVR has been a topic of debate. Some studies have demonstrated absence of residual HCV RNA in plasma or peripheral blood mononuclear cells (PBMCs) in patients who had SVR, thus implying a “cure” of HCV infection.<sup>2-4</sup> However, others reported detection of residual HCV RNA in such blood components as “occult” HCV infections.<sup>5-9</sup> The existence of post-SVR reservoirs of HCV RNA is a concern because it suggests that viral relapse is possible after immunosuppression.

Cancer chemotherapy leads to HCV reactivation in patients with chronic infections,<sup>10</sup> but to our knowledge, data on the effect of chemotherapy on HCV infection after an SVR are lacking. Therefore in the present study, we sought to determine whether chemotherapy leads to relapse of HCV infection in cancer patients who have SVR before cancer diagnosis and treatment.

## **Materials and Methods**

### *Study Design and Patient Population*

In this retrospective study, the medical records of cancer patients with HCV infections seen at The University of Texas MD Anderson Cancer Center from January 1, 2008, to December 31, 2011, were reviewed. All patients positive for anti-HCV antibodies were identified by searching our institutional database. Only patients who received HCV infection therapy and had SVRs before their cancer diagnoses were included. The information collected included demographic data, underlying cancer type, clinical presentation, laboratory data including HCV viral load and genotype, and details of HCV infection therapy and cancer treatment. All patients underwent HCV infection therapy with standard interferon monotherapy, or a combination of interferon (pegylated or standard) plus ribavirin between 1994 and 2009.

Since direct-acting antivirals including telaprevir and boceprevir were approved by the US Food and Drugs Administration in 2011, none of our patients received them. Patients who received chemotherapy or immunosuppressive therapy after their SVRs were further analyzed to identify residual viremia (HCV RNA). Chemotherapy agents used included alkylating agents (cyclophosphamide, melphalan, bendamustine, temozolomide), antimetabolites (methotrexate, 5-Fluorouracil, fludarabine, gemcitabine, hydroxyurea, capecitabine, cladribine, pemetrexed), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine), platinum analogues (cisplatin, carboplatin, oxaliplatin), anthracycline antibiotics (doxorubicin), targeted therapy (rituximab, bortezomib, bevacizumab, sorafenib, imatinib), immunomodulatory agents (thalidomide, lenalidomide), and miscellaneous agents (denileukin diftitox, folinic acid). Immunosuppressive agents administered included tacrolimus and systemic corticosteroids. The protocol for this study was approved by the MD Anderson Institutional Review Board.

#### *HCV RNA Quantification*

HCV RNA in serum was quantified using a commercially available polymerase chain reaction method (COBAS TaqMan HCV test, version 1; Roche Molecular Systems, Branchburg, NJ) with a quantification range of 43-69,000,000 IU/mL (1.63-7.84 log<sub>10</sub> IU/mL).

#### *Definitions*

An SVR was defined as the absence of HCV RNA in serum at 6 months after discontinuation of HCV infection therapy.<sup>1</sup> Post-SVR relapse of HCV infection was defined as detectable HCV RNA in serum after an SVR. A low HCV viral load was defined as HCV RNA level  $\leq$  800,000 IU/L in serum. Normal range for alanine aminotransferase was 7-56 IU/L and for aspartate aminotransferase was 15-46 IU/L.

### *Statistical analyses*

Characteristics of all patients were analyzed using descriptive statistics. Categorical variables were reported as number with frequencies (as percentages). Continuous variables were reported as median with range. Durability of an SVR was determined by repeated testing of serum samples for HCV RNA after cancer therapy was completed. Duration from achievement of an SVR to initiation of chemotherapy and repeated testing of serum for HCV RNA was analyzed. All analyses were conducted using STATA IC software, version 12.0 (StataCorp LP, College Station, TX).

### **Results**

We analyzed 30 cancer patients who had SVRs and underwent subsequent chemotherapy or immunosuppressive therapy (Table 1). Most of them were male (63%) and white (73%), with a median age of 58 years (range, 43-80 years). Half of the patients had hematological malignancies, mostly non-Hodgkin lymphoma (53%) followed by multiple myeloma (27%). The most common solid tumors were hepatocellular carcinoma (20%) and rectal cancer (13%). Three (10%) patients underwent stem cell transplantation.

HCV genotype data were available for only 3 (10%) patients; all of them had genotype 2. Cirrhosis at the time of HCV diagnosis was present in 2 of 25 (8%) patients with available data. Before starting antiviral therapy, most patients (n=10/12 [83%]) had low HCV viral load ( $\leq$  800,000 IU/L), and most (n=22/26 [85%]) had normal baseline alanine aminotransferase and aspartate aminotransferase levels (n=19/23 [83%]). Twelve (40%) patients received monotherapy for HCV infection with standard interferon, whereas 18 (60%) received combination therapy with interferon (pegylated or standard) plus ribavirin (Table 1). The patients underwent treatment

of HCV infection before cancer diagnosis from 1994 to 2009. The median duration of HCV infection therapy was 48 weeks (range, 16-72 weeks).

Physicians started cancer chemotherapy at a median of 72 months (range, 2-166 months) after SVR. The chemotherapeutic agents administered, either alone or in combination, included rituximab (27%), cyclophosphamide (23%), cisplatin (17%), 5-fluorouracil (13%), doxorubicin (13%), melphalan (13%), bortezomib (10%), fludarabine (10%), paclitaxel (10%), sorafenib (10%), lenalidomide (10%), and vincristine (10%) (Table 1). Eleven (37%) patients received corticosteroids. The patients underwent a median of 3 cycles (range, 1-12 cycles) of chemotherapy. Other treatment modalities used for cancer in these patients were chemoradiation (17%), radiation therapy (7%), and radiofrequency ablation (3%).

No post-SVR relapses of HCV infection occurred in the patients following any form of cancer therapy. The median time from SVR to repeat HCV RNA testing was 96 months (range, 18-168 months), with a median number of 2 serum samples (range, 1-11 samples) tested per patient. Last HCV RNA testing was performed at a median of 6.8 months (range, 1 day-108 months) after chemotherapy discontinuation.

## **Discussion**

The current data in the literature on the durability of SVRs after treatment of HCV infection are conflicting and information regarding SVR longevity after cancer chemotherapy is lacking. Our findings confirm that the virological cure of HCV is not affected after chemotherapy or immunosuppressive therapy in cancer patients.

Researchers have detected HCV RNA in liver cells and PBMCs after SVRs.<sup>5-9</sup> However, the clinical significance of such “occult” HCV infections remains unknown. In a large



prospective cohort of 1343 patients enrolled in 9 randomized multicenter trials of pegylated interferon alfa-2a (administered alone or in combination with ribavirin), only 12 (0.9%) patients had post-SVR HCV infection relapses.<sup>11</sup> The relapses occurred at a mean of 1.8 years (range, 1.1-2.9 years) after treatment completion. Intravenous drug use, presence of HCV genotype 1 infection, and high baseline alanine aminotransferase levels were the only predictors of relapse. Of 100 patients with human immunodeficiency virus (HIV)/HCV co-infection in that study, only one had a post-SVR infection relapse, demonstrating the durability of SVRs even in immunocompromised patients. Likewise, in a systematic review of 44 studies conducted to analyze the durability of SVR after HCV infection therapy, only 2% of 399 immunocompromised subjects (mostly recipients of solid organ transplants or patients with HIV/HCV co-infections) had post-SVR HCV infection relapses.<sup>12</sup> In addition, few case reports have documented post-SVR relapse of HCV infection after immunosuppressive events such as kidney transplantation, hypogammaglobulinemia, and HIV/HCV co-infection (supplementary table 2).<sup>13-15</sup>

In theory, “virological cure” of HCV infection after an SVR may be reversed once the patient becomes immunosuppressed.<sup>5</sup> However, none of our 30 patients who had SVRs and received cancer chemotherapy had viral relapses. These clinical findings support recent observations by Fujiwara et al.<sup>2</sup> who did not identify residual HCV RNA in plasma samples or PBMCs obtained from subjects who had SVRs. The patients in our study had either solid or hematological malignancies. They also received different types of chemotherapeutic agents after their SVRs, including rituximab, the use of which has been associated with reactivation of chronic HCV infection.<sup>10</sup> Several patients also received systemic corticosteroids as a part of their chemotherapy regimens without having relapses of their HCV infections. In our study, we did

not observe late relapse of HCV infections, as the SVR statuses of the 30 patients remained unchanged upon testing up to 14 years after starting immunosuppressive therapy for cancer.

Our study had some limitations including the sample size which was small. Also, we did not look for residual HCV RNA in PBMCs, as we based our definition of HCV infection relapse on detection of HCV RNA in serum using commercially available assays. Baseline characteristics associated with favorable treatment outcome were presented in some patients (e.g., Caucasian race, genotype 2 infection, lack of cirrhosis, and low HCV viral load). It remains unknown, therefore, if our findings may be generalized to all cancer patients with a history of successfully treated HCV infection.

In conclusion, our findings suggest that HCV infection is curable and that eradication of this virus appears to remain unaffected even after a patient undergoes post-SVR cancer chemotherapy. Physicians should aim for early identification and treatment of HCV infection before starting chemotherapy in cancer patients.

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ACCEPTED MANUSCRIPT

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**Table 1.** Characteristics of 30 HCV-Infected Patients Who Had SVRs Before Cancer Diagnosis and Treatment and Received Subsequent Chemotherapy or Immunosuppressive Therapy

Characteristic	Number of patients (%)
Median age, years (range)	58 (43-80)
Sex	
Male	19 (63)
Female	11 (37)
Race/ethnicity	
White	22 (73)
Black	3 (10)
Hispanic	3 (10)
Asian	2 (7)
Type of cancer	
Hematological	15 (50)
Non-Hodgkin lymphoma	8 (53)
Multiple myeloma	4 (27)
Leukemia	2 (13)
Myelofibrosis	1 (7)
Solid tumor	15 (50)
Hepatocellular carcinoma	3 (20)
Rectal cancer	2 (13)
Other <sup>a</sup>	10 (67)

HCV treatment modality	
Monotherapy	12 (40)
Interferon (pegylated or standard)	12 (100)
Combination therapy	18 (60)
Standard interferon and ribavirin	11 (61)
Pegylated interferon and ribavirin	7 (39)
Median duration of HCV therapy, weeks (range)	48 (16-72)
Chemotherapeutic and immunosuppressive agents <sup>b</sup>	
Systemic corticosteroids	11 (37)
Rituximab	8 (27)
Cyclophosphamide	7 (23)
Cisplatin	5 (17)
5-Fluorouracil	4 (13)
Doxorubicin	4 (13)
Melphalan	4 (13)
Bortezomib	3 (10)
Investigational agents	3 (10)
Fludarabine	3 (10)
Lenalidomide	3 (10)
Paclitaxel	3 (10)
Sorafenib	3 (10)
Vincristine	3 (10)
Gemcitabine	2 (7)

Temozolomide	2 (7)
Other <sup>c</sup>	16 (53)
Median number of chemotherapy cycles (range)	3 (1-12)
Median duration from SVR to repeat HCV RNA testing, months (range)	96 (18 – 168)
Median duration from SVR to administration of first dose of chemotherapy, months (range)	72 (2-166)
Median duration from chemotherapy discontinuation to HCV RNA testing, months (range)	6.8 (0.03 – 108)
Other modes of cancer therapy	
Chemoradiation <sup>d</sup>	5 (17)
Radiation therapy	2 (7)
Radiofrequency ablation	1 (3)

<sup>a</sup>Anal cancer, breast cancer, cholangiocarcinoma, gastric cancer, glioblastoma multiforme, laryngeal cancer, lung cancer, melanoma, pancreatic cancer, and prostate cancer in one patient each.

<sup>b</sup>Administered either alone or in combination with other agents.

<sup>c</sup>Bendamustine, bevacizumab, capecitabine, carboplastin, cladribine, denileukin diftitox, docetaxel, folinic acid, hydroxyurea, imatinib, methotrexate, metoxantrone, oxaliplatin, pemetrexed, tacrolimus, and thalidomide in one patient each.

<sup>d</sup>Drugs administered during chemoradiation consisted of 5-fluorouracil (n = 2), cisplatin (n = 2), temozolomide (n = 1), and paclitaxel (n = 1).