



# Tumor recurrence in patients treated with direct-acting antivirals for hepatitis C following curative therapy: a cause for concern?

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Comment on: Reig M, Mariño Z, Perelló C, *et al.* Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. *J Hepatol* 2016. [Epub ahead of print].

Submitted Jun 22, 2016. Accepted for publication Jul 05, 2016.

doi: 10.21037/tcr.2016.08.06

View this article at: <http://dx.doi.org/10.21037/tcr.2016.08.06>

Liver cancer is one of the most common malignancies in the world, the incidence ranking fifth in men and seventh in women and the mortality second for total number of cancer deaths worldwide (1). Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections accounts for over 80% of HCC diagnosed (2). Hepatocarcinogenesis promoted by HCV is a complex and progressive multistep process, whereby 80% of newly infected patients develop chronic infection; an estimated 10% to 20% develop cirrhosis and 1–5% progress to HCC over a period of 20 to 30 years (3). HCV induced tumorigenesis is believed to occur mainly indirectly, as a result of longstanding hepatic inflammation and fibrosis (most with HCV and HCC have established cirrhosis) and potentially also directly, by interaction of viral proteins with host oncogenes and pro-vascular factors (4). Since 2002, a 24–48 weeks course of pegylated interferon (peg-IFN) and ribavirin (RBV) has been used to treat chronic HCV infection. However the probability of success, defined as undetectable HCV PCR 24 weeks post treatment, or sustained virological response (SVR), was low and side effects of treatment were severe, especially in those with cirrhosis (5). Long term follow-up studies have shown a decreased risk of HCC in cirrhotic non-cancer patients who have achieved an SVR (6). In those with history of HCC, IFN exposure itself may lower the risk of HCC recurrence even when SVR is not achieved (7–10). Since 2014, IFN-free regimens, such as sofosbuvir-ledipasvir (SOF-LDV), paritaprevir/ritonavir-ombitasvir and dasabuvir (PrOD), sofosbuvir-simeprevir (SOF-SMV), and simeprevir-daclatasvir (SMV-DCV) have eliminated the need for IFN therapy for those with HCV genotype 1

infection—the most common type of HCV infection (3). Successful treatment is now defined as undetectable HCV PCR after 12 weeks of treatment (SVR12) (11). SVR12 is expected in almost all patients who can complete the prescribed treatment regime. The question of whether SVR12 translates to real clinical benefits for those with the most advanced disease, such as those with a history of HCC, remains to be seen as individuals with HCC were specifically excluded from studies.

Reig *et al.*, have reviewed a Spanish cohort after observing an unexpected rise in early HCC recurrence after HCV treatment (12). A total of 58 cases met inclusion criteria for this uncontrolled cohort study: (I) HCC treatment with ablation (55.2%), resection (34.5%), or chemoembolization (TACE, 10.3%); (II) complete response to curative HCC therapy as well as an absence of “non-characterized nodules” at imaging before DAA treatment; (III) DAA therapy in the absence of IFN treatment (36.2% SOF-LDV, 25.9% PrOD, 25.2% SOF-SMV, 10.3% SOF-DCV, 7% SMV-DCV); and (IV) one tumor status assessment following antiviral therapy. HCC surveillance for recurrence was performed with magnetic resonance (MR) or computed tomography (CT) every 6 months post HCC treatment. In the ablation group, a contrast ultrasound was also performed at 1 and 3 months post ablation. This is an early report as only 40 (69%) have finished DAA treatment and have had the 12 weeks post treatment blood test to determine if HCV treatment was successful or not (SVR12 was 97.5% in the 40).

Of the 58 cases, the Barcelona Clinic Liver Cancer classification (BCLC) characterized 42 (72.4%) as stage

A (a single HCC or <3 nodules, smaller than 3 cm in size, Child-Pugh score A–B and performance status 0). Due to the limited sample size of the study, wide distribution of baseline hepatic functions was also observed, for example the median value for albumin was 40 g/L with a range of 20–50 g/L, Bilirubin was 1.00 mg/dL with a range of 0.3–6.0, platelets was  $101 \times 10^9$  with a range of  $33\text{--}229 \times 10^9$ , suggesting that outliers within the cohort may have had more advanced liver cirrhosis and therefore may have an increased propensity for recurrence—patients with bad biology (13,14).

After a median follow up of 5.7 months, 16 of 58 (27.6%) cases developed radiological tumor recurrence following DAA treatment. Patients treated with ablation, potentially those with the best HCC treatment characteristics, experienced the highest rate of recurrence with 9 of 16 cases (56.3%) while surprisingly, none treated with TACE, potentially those with the worst HCC treatment characteristics, have shown HCC recurrence to date.

Does HCV treatment with IFN-free regimens paradoxically lead to higher HCC recurrence risk? An abstract by Buonfiglioli *et al.*, have reported a second cohort from Italy that also suggests that HCC recurrence may be more frequent following DAA treatment (15). HCC was detected in 7.6% of patients within a 24-week period following DAA treatment for HCV. In the 17 patients with a prior history of HCC, recurrence was observed in 29% and of these cases 3.2% were novel cancers. Among patients with HCC recurrence the median age was younger (56 *vs.* 73 years of age) and more frequently treated for HCC (88.2% *vs.* 61.9%), suggesting that these patients had more severe liver disease and were higher risk for HCC recurrence irrespective of DAA treatment (13,14).

The majority of HCC recurrence in this cohort had ablation as curative therapy. Ablation is therapy that is specifically targeted to the visualized HCC. Although it is less invasive compared to resection, there is higher potential for incomplete treatment leading to local recurrence that might not be recognized for a few months post treatment. Treatment response in the first 3 months was assessed by contrast ultrasound, an examination targeted to the visualized ablation zone. In the Spanish cohort, the median time from HCC treatment to start of DAA treatment was 11.2 months but some started treatment just 3.6 months post HCC treatment—before the first CT or MRI scans that might have detected metachronous lesions missed by contrast ultrasound. Local HCC recurrence was only observed in 6/16 (37.5%)—the majority had

HCC recurrence in an untreated area. More with tumor recurrence had HCV treatment early, within the first year of HCC treatment (9/28 or 32%) compared to a lower proportion of those treated beyond 1 year had HCC recurrence (7/30 or 23%).

In the absence of a control group, the authors note that the observed recurrence rate is higher than historical controls of 15–20% post curative HCC (6). The authors also note that the HCC recurrence following HCV treatment is higher than what was observed in the control arm of STORM trial (16). However, HCV only accounted for 24.2% cases of HCC in the STORM trial, while majority were HBV infected patients at 49% (16). Clearly, neither ablation nor resections are perfect cures for HCC. Other groups have reported higher HCC recurrence rates, as high as 76.2% of patients following resections in first 24-month (17) and 20% to 49% after a mean or median follow-up of 9 to 34 months post ablation (18). In a large study where 110 with HCC were treated with ablation, recurrence rates as high as 49% after median follow-up of 19 months were reported; only 3.6% of patients had a local recurrence (19). Others have reported 1 year HCC recurrence rates following ablation of 18.6% (20) and resection of 24% (21) which may be due to local recurrence, at the site of treatment, or metachronous disease, at an untreated site.

Why might IFN-free treatment of HCV paradoxically raise the risk of HCC recurrence after viral eradication with DAAs? The authors speculate that very rapid clearance of HCV from hepatocytes and the subsequent loss of virus-induced inflammation might result in diminished immune surveillance for cancer that can allow cancer growth. This might explain why ablation, which specifically targets a visualized cancer, is associated with the highest risk of HCC recurrence; whereas, resection and TACE, which targets larger areas surrounding the visualized cancer, may be lower risk for HCC recurrence. Potentially, there were small foci of cancer cells not visualized on imaging that were allowed to grow after rapid HCV suppression. This argument is like having the cake and eating it too. Ongoing chronic inflammation is thought to increase the risk of HCC through accelerated hepatocyte death and resulting regeneration followed by liver fibrosis. It is not known if in this cohort, leaving HCV untreated would not have led to even higher HCC recurrence risk. Prior studies of HCV immunology have shown very weak HCV-specific immunity in those with chronic HCV infection, especially those with cirrhosis (22). To date, there have been no studies correlating

HCV immunity with HCC immunity. Chronic inflammation from ongoing viral hepatitis is thought to promote immune tolerance of HCC that allows cancer growth (23). Many immune pathways may be involved. For example, programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) are immune checkpoints. Increased checkpoint signaling may lead to HCC immune tolerance and increase tumor aggressiveness (24). Inhibitors of PD-1 and CTLA-4 are currently being investigated for treatment of advanced stage HCC.

It is important to remember that this is a small case series without a control group. Risk of HCC recurrence is dependent on many factors. The authors did not report on factors that might predict HCC recurrence, such as tumor size, AFP at diagnosis (tumor biology), the delta of ALT/AST levels before DAA and on/off treatment (a potential correlation between the degree of hepatic injury/inflammation), the choice of DAA used to treat HCV (is one antiviral more permissive of HCC development). We therefore do not know if the underlying tumor characteristics played a significant role in the elevated recurrences rates as described by this study or if it was due to DAA treatment alone.

Should we stop treating HCV in those with successfully treated HCC? It is unlikely that patients with chronic HCV infection that has led to cirrhosis and then HCC will forego HCV treatment post HCC control. These are perhaps the patients most desperate to have HCV treatment. There is a risk that these two reports represent publication bias where the groups that have successfully treated HCV without HCC recurrence have not reported because this was the expected outcome. With these two reports, we have been reminded that neither HCC “curative” treatment nor HCV treatment can guarantee a cure of HCC. Until these findings can be confirmed with much larger cohorts, more frequent monitoring for HCC recurrence with at least CT or MRI in the first year, before and post HCV treatment, seems reasonable. In this cohort, 17 had HCC imaging within 4 months of starting DAAs and of the 7 with HCC recurrence, all were still re-treatable. If confirmed that DAAs really do raise the risk of HCC recurrence, it would be important to identify factors that predict which patients might benefit from HCV treatment versus those who might have increased risk of HCC recurrence with treatment. Most of these patients are unlikely to tolerate IFN-based therapy given the severity of their cirrhosis and so transplant may be the answer for those with highest risks for HCC recurrence.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Mu-Xing Li, MD (Department of Abdominal Surgical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China).

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.08.06>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Evren S, Wong DK. Tumor recurrence in patients treated with direct-acting antivirals for hepatitis C following curative therapy: a cause for concern? *Transl Cancer Res* 2016;5(S2):S233-S236. doi: 10.21037/tcr.2016.08.06