**Name of Journal: *World Journal of Hepatology***

**Manuscript NO: 38680**

**Manuscript Type: LETTER TO THE EDITOR**

**Responsibility of hepatitis C virus in the development of hepatocellular carcinoma: From molecular alterations to possible solutions**

Bertino G *et al.* HCV and development of HCC

**Gaetano Bertino, Giulia Malaguarnera, Evelise Frazzetto, Alice Sciuto, Gaetano Inserra, Guido Nicola Zanghì, Michele Malaguarnera**

**Gaetano Bertino, Evelise Frazzetto, Alice Sciuto,** Hepatology Unit, Department of Clinical and Experimental Medicine, University of Catania, Policlinico “G. Rodolico”, Catania 95123, Italy

**Giulia Malaguarnera, Michele Malaguarnera,** Research Center “the Great Senescence”, University of Catania, Catania 95100, Italy

**Giulia Malaguarnera, Michele Malaguarnera,** Department of Biomedical and Biotechnological Science, University of Catania, Catania 95100, Italy

**Gaetano Inserra,** Internal Medicine Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania 95123, Italy

**Guido Nicola Zanghì,** Department of Surgery, Policlinico Vittorio Emanuele University Hospital, University of Catania, Catania 95100, Italy

**ORCID number:** Gaetano Bertino (0000-0002-4557-2649); Giulia Malaguarnera (0000-0003-3655-4307); Evelise Frazzetto (0000-0000-0000-0000); Alice Sciuto (0000-0000-0000-0000); Gaetano Inserra (0000-0002-0986-402X); Guido Nicola Zanghi (0000-0003-3665-8325); Michele Malaguarnera (0000-0002-7145-6377).

**Author contributions:** All authors made equal contribution in the preparation of this manuscript and final approval of the version of it to be published.

**Conflict-of-interest statement:** The authors declare here that there is no conflict of interest related to this study among them.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Gaetano Bertino, MD, Associate Professor,** Hepatology Unit, Department of Clinical and Experimental Medicine, University of Catania, Policlinico “G. Rodolico”, Via S. Sofia n.78, Catania 95123, Italy. gaetanobertinounict@g.mail.com

**Telephone:** +39-9-53781573

**Fax:** +39-9-53781572

**Received:** March 8, 2018

**Peer-review started:** March 8, 2018

**First decision:** March 19, 2018

**Revised:** March 30, 2018

**Accepted:** May 11, 2018

**Article in press:**

**Published online:**

**Abstract**

There are several causes of hepatocellular carcinoma (HCC), but certainly the hepatitis C virus (HCV) is one of the most common. The HCV is able to contribute, both directly and indirectly, to the development of HCC. Determining early HCV clearance before an advanced liver disease develops, is absolutely necessary as this prevents the initiation of the cascade of events induced by HCV that may result in the development of HCC. The early treatment of the infection and the clearance of HCV represents today, in the age of the direct antiviral agents (DAAs), an extraordinary opportunity for true prevention of the development of HCV-related HCC.

**Key words**: Hepatitis C virus; Hepatocellular carcinoma; Inflammation; Fibrosis; Insulin-resistance; Oxidative stress; Direct acting antivirals

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The hepatitis C virus (HCV) is able to contribute, both directly and indirectly, to the development of hepatocellular carcinoma (HCC). The early treatment of the infection and the clearance of HCV represents today, in the age of the direct antiviral agents, an extraordinary opportunity for true prevention of the development of HCV-related HCC.

Bertino G, Malaguarnera G, Frazzetto E, Sciuto A, Inserra G, Zanghì GN, Malaguarnera M. Responsibility of hepatitis C virus in the development of hepatocellular carcinoma: from molecular alterations to possible solutions. *World J Hepatol* 2018; In press

**To the Editor**

I read with great interest the paper by Mohammad Irshad, Priyanka Gupta and Khushboo Irshad, published in *World J Hepatol* on 28 December 2017; 9(36): 1305-1314 titled “Molecular basis of hepatocellular carcinoma (HCC) induced by hepatitis C virus infection”[[1](#_ENREF_1)].

Among all human cancers, the hepatocellular carcinoma (HCC) is one of the most frequent[2-6]. There are several causes of HCC (asian males > 40 years, asian females > 50 years, africans, family history of HCC, hepatitis B chronic infection, non-alcoholic steatohepatitis, occupational exposure to chemicals), but certainly the hepatitis C virus (HCV) is one of the most common[7,8].

In recent years, many efforts have been made to obtain an early diagnosis of HCC, through: (1) the use of serum HCC biomarkers, such as: Alpha fetoprotein (AFP), Lens culinaris agglutinin-reactive AFP (AFP-L3), des-gamma-carboxyl prothrombin (DCP), glypican-3 (GPC-3), osteopontin (OPN), squamous cell carcinoma antigen-immunoglobulin M complex (SCCA-IgM), alpha-1-fucosidase (AFU), chromogranin A (CgA), human hepatocytes growth factor (HGF), insulin-like growth factor (IGF); (2) through the computerized axial tomography (CT); and (3) the nuclear magnetic resonance with hepatospecific contrast agent (MR). The use of these tools, often in combination, allows an early diagnosis of HCC especially in the context of close follow-up protocols[9-[11](#_ENREF_1)].

However, there remains the great problem of understanding the mechanisms that determine the development of HCC in subjects with chronic HCV infection[12,1[3](#_ENREF_1)]. Moreover, even if an exact diagnosis of image and histology of HCC is often obtained, a molecular typing of the alterations that determine HCC is not routinely carried out, also because these are not yet fully known[[6](#_ENREF_1)].

Irshad *et al*[[1](#_ENREF_1)], in a very clear and precise way, show that chronic HCV infection is able to determine a progressive fibrosis with transition to cirrhosis, through the mechanisms of inflammation, the activation of stellate cells and the proliferation of hepatocytes. Hepatic cirrhosis and cell proliferation are risk factors for HCC.

Nevertheless, we should also take into account the alteration of the hepatic microenvironment in a pro-oncogenic sense and of the intestinal microbiome. The HCV also determine insulin resistance, hepatic steatosis, oxidative stress and all these events are associated with genetic instability[13-15].

Furthermore, the HCV, which is an RNA virus and does not integrate into the host genome, also has a direct role in the development of HCC, through the interaction of its proteins (HCV core, E1, E2, NS3 and NS5A) with various cell pathways that produce different effects as preconditions for the induction of HCC[16-18].

The data provided by the manuscript of Irshad *et al*[[1](#_ENREF_1)] are very interesting because they set up a new panorama in chronic HCV infection, underline the role of HCV in the development of HCC and arouse some considerations.

Since the HCV is able to contribute, both directly and indirectly, to the development of HCC, it is now absolutely a priority to treat all subjects with chronic HCV infection, regardless of the degree of liver disease and the presence or absence of any co-morbidities[8,19].

Nowadays, the therapy is based on the use of direct antiviral agents (DAAs) that guarantee the disappearance of the infection, intended as Sustained Virologic Response (SVR), in over 95% of cases, with no significant side effects, which are instead reported during interferon and ribavirin therapy[20-23].

In the scientific community, the paper by Reig *et al*[[24](#_ENREF_1)] published in *Journal of Hepatology* 2016; 65: 719-726, has provoked great concern because the authors concluded that an unexpected and high percentage of HCC recurrence had occurred in their patients after obtaining the clearance of HCV with DAAs therapy. Fortunately, this statement was “reshaped” by subsequent research that demonstrated, in a large cohort of subjects treated with DAAs, the risk of early recurrence from HCC was comparable and not higher than that observed in patients not treated with DAAs. On the other hand, we must not forget that the rate of early recurrence of HCC remains elevated in patients with advanced liver disease despite the HCV clearance, since liver cirrhosis is a itself risk factor for the development and recurrence of HCC[[25](#_ENREF_1)].

The research by Ikeda *et al*[26] in *Digestive Diseases and Sciences* 2017 Oct; 62(10), by Kanwal *et al*[27] in *Gastroenterology* 2017 Oct; 153(4) and of Petta *et al*[28] in *Alimentary Pharmacology and Therapeutics* 2017 Jan; 45 (1), have clearly shown that Direct-Acting Antivirals therapy reduces the frequency of HCC relapse when performed after initial HCC therapy and that obtaining SVR is associated with the reduction of HCC. However, in patients with cirrhosis, even if SVR is obtained, the risk of HCC remains present. In fact, these subjects require continuous surveillance [26-28].

Determining early HCV clearance before an advanced liver disease develops, is absolutely necessary as this prevents the initiation of the cascade of events induced by HCV which may result in the development of HCC.

The emphasis made by Irshad *et al*[1] on the prominent role of HCV in hepatic tumorigenesis is very important, both in order to intercept possible new pathways of HCC development that could be used for the development of drugs against specific molecular targets of HCC, both because it reinforces our idea, shared by other researchers, that the early treatment of the infection and the clearance of HCV represents today, in the age of the DAAs, an extraordinary opportunity for true prevention of the development of HCV-related HCC.

**REFERENCES**

1 **Irshad M**, Gupta P, Irshad K. Molecular basis of hepatocellular carcinoma induced by hepatitis C virus infection. *World J Hepatol* 2017; **9**: 1305-1314 [PMID: 29359013 DOI: 10.4254/wjh.v9.i36.1305]

2 **Vecchio R**, Marchese S, Famoso S, La Corte F, Marletta S, Leanza G, Zanghì G, Leanza V, Intagliata E. Colorectal cancer in aged patients. Toward the routine treatment through laparoscopic surgical approach. *G Chir* 2015; **36**: 9-14 [PMID: 25827663 DOI: 10.11138/gchir/2015.36.1.009]

3 **Zanghì G**, Di Stefano G, Caponnetto A, Vecchio R, Lanaia A, La Terra A, Leanza V, Basile F. Breast cancer and sentinel lymph node micrometastases: indications for lymphadenectomy and literature review. *G Chir* 2014; **35**: 260-265 [PMID: 25644726]

4 **Di Cataldo A**, Astuto M, Rizzo G, Bertuna G, Russo G, Incorpora G. Neurotoxicity during ifosfamide treatment in children. *Med Sci Monit* 2009; **15**: CS22-CS25 [PMID: 19114973]

5 **Del Vecchio GC**, De Santis A, Giordano P, Amendola G, Baronci C, Del Principe D, Nobili B, Jankovic M, Ramenghi U, Russo G, Zecca M, De Mattia D; AIEOP ITP Study Group. Management of acute childhood idiopathic thrombocytopenic purpura according to AIEOP consensus guidelines: assessment of Italian experience. *Acta Haematol* 2008; **119**: 1-7 [PMID: 18176072 DOI: 10.1159/000112837]

6 **Bertino G**, Di Carlo I, Ardiri A, Calvagno GS, Demma S, Malaguarnera G, Bertino N, Malaguarnera M, Toro A, Malaguarnera M. Systemic therapies in hepatocellular carcinoma: present and future. *Future Oncol* 2013; **9**: 1533-1548 [PMID: 24106903 DOI: 10.2217/fon.13.171]

7 **Rapisarda V**, Loreto C, Malaguarnera M, Ardiri A, Proiti M, Rigano G, Frazzetto E, Ruggeri MI, Malaguarnera G, Bertino N, Malaguarnera M, Catania VE, Di Carlo I, Toro A, Bertino E, Mangano D, Bertino G. Hepatocellular carcinoma and the risk of occupational exposure. *World J Hepatol* 2016; **8**: 573-590 [PMID: 27168870 DOI: 10.4254/wjh.v8.i13.573]

8 **Bertino G**, Ardiri A, Proiti M, Rigano G, Frazzetto E, Demma S, Ruggeri MI, Scuderi L, Malaguarnera G, Bertino N, Rapisarda V, Di Carlo I, Toro A, Salomone F, Malaguarnera M, Bertino E, Malaguarnera M. Chronic hepatitis C: This and the new era of treatment. *World J Hepatol* 2016; **8**: 92-106 [PMID: 26807205 DOI: 10.4254/wjh.v8.i2.92]

9 **Bertino G**, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellualar carcinoma serum markers. *Semin Oncol* 2012; **39**: 410-433 [PMID: 22846859 DOI: 10.1053/j.seminoncol.2012.05.001]

10 **Bertino G**, Ardiri AM, Calvagno GS, Bertino N, Boemi PM. Prognostic and diagnostic value of des-γ-carboxy prothrombin in liver cancer. *Drug News Perspect* 2010; **23**: 498-508 [PMID: 21031166 DOI: 10.1358/dnp.2010.23.8.1444236]

11 **Biondi A**, Malaguarnera G, Vacante M, Berretta M, D'Agata V, Malaguarnera M, Basile F, Drago F, Bertino G. Elevated serum levels of Chromogranin A in hepatocellular carcinoma. *BMC Surg* 2012; **12** Suppl 1: S7 [PMID: 23173843 DOI: 10.1186/1471-2482-12-S1-S7]

12 **Bruno CM**, Valenti M, Bertino G, Ardiri A, Consolo M, Mazzarino CM, Amoroso A, Neri S. Altered pattern of circulating matrix metalloproteinases -2,- 9 and tissue inhibitor of metalloproteinase-2 in patients with HCV-related chronic hepatitis. Relationship to histological features. *Panminerva Med* 2009; **51**: 191-196 [PMID: 20195229]

13 **He X**, Guo X, Zhang H, Kong X, Yang F, Zheng C. Mechanism of action and efficacy of LY2109761, a TGF-β receptor inhibitor, targeting tumor microenvironment in liver cancer after TACE. *Oncotarget* 2017; **9**: 1130-1142 [PMID: 29416682 DOI: 10.18632/oncotarget.23193]

14 **Malaguarnera G**, Catania VE, Francaviglia A, Malaguarnera M, Drago F, Motta M, Latteri S. Lipoprotein(a) in patients with hepatocellular carcinoma and portal vein thrombosis. *Aging Clin Exp Res* 2017; **29**: 185-190 [PMID: 27822883 DOI: 10.1007/s40520-016-0653-z]

15 **Malaguarnera G**, Giordano M, Nunnari G, Bertino G, Malaguarnera M. Gut microbiota in alcoholic liver disease: pathogenetic role and therapeutic perspectives. *World J Gastroenterol* 2014; **20**: 16639-16648 [PMID: 25469033 DOI: 10.3748/wjg.v20.i44.16639]

16 **McGivern DR**, Lemon SM. Virus-specific mechanisms of carcinogenesis in hepatitis C virus associated liver cancer. *Oncogene* 2011; **30**: 1969-1983 [PMID: 21258404 DOI: 10.1038/onc.2010.594]

17 **Rusyn I**, Lemon SM. Mechanisms of HCV-induced liver cancer: what did we learn from in vitro and animal studies? *Cancer Lett* 2014; **345**: 210-215 [PMID: 23871966 DOI: 10.1016/j.canlet.2013.06.028]

18 **Mitchell JK**, Lemon SM, McGivern DR. How do persistent infections with hepatitis C virus cause liver cancer? *Curr Opin Virol* 2015; **14**: 101-108 [PMID: 26426687 DOI: 10.1016/j.coviro.2015.09.003]

19 **Mangia A**, Cenderello G, Orlandini A, Piazzolla V, Picciotto A, Zuin M, Ciancio A, Brancaccio G, Forte P, Carretta V, Zignego AL, Minerva N, Brindicci G, Marignani M, Baroni GS, Bertino G, Cuccorese G, Mottola L, Ripoli M, Pirisi M. Individualized treatment of genotype 1 naïve patients: an Italian multicenter field practice experience. *PLoS One* 2014; **9**: e110284 [PMID: 25340799 DOI: 10.1371/journal.pone.0110284]

20 **Ragusa R**, Bertino G, Bruno A, Frazzetto E, Cicciu F, Giorgianni G, Lupo L. Evaluation of health status in patients with hepatitis c treated with and without interferon. *Health Qual Life Outcomes* 2018; **16**: 17 [PMID: 29343250 DOI: 10.1186/s12955-018-0842-x]

21 **Neri S**, Bertino G, Petralia A, Giancarlo C, Rizzotto A, Calvagno GS, Mauceri B, Abate G, Boemi P, Di Pino A, Ignaccolo L, Vadalà G, Misseri M, Maiorca D, Mastrosimone G, Judica A, Palermo F. A multidisciplinary therapeutic approach for reducing the risk of psychiatric side effects in patients with chronic hepatitis C treated with pegylated interferon α and ribavirin. *J Clin Gastroenterol* 2010; **44**: e210-e217 [PMID: 20838237 DOI: 10.1097/MCG.0b013e3181d88af5]

22 **Bertino G**, Ardiri A, Boemi PM, Calvagno GS, Ruggeri IM, Speranza A, Santonocito MM, Ierna D, Bruno CM, Valenti M, Boemi R, Naimo S, Neri S. Epoetin alpha improves the response to antiviral treatment in HCV-related chronic hepatitis. *Eur J Clin Pharmacol* 2010; **66**: 1055-1063 [PMID: 20652232 DOI: 10.1007/s00228-010-0868-4]

23 **Malaguarnera M**, Motta M, Vacante M, Malaguarnera G, Caraci F, Nunnari G, Gagliano C, Greco C, Chisari G, Drago F, Bertino G. Silybin-vitamin E-phospholipids complex reduces liver fibrosis in patients with chronic hepatitis C treated with pegylated interferon α and ribavirin. *Am J Transl Res* 2015; **7**: 2510-2518 [PMID: 26807195]

24 **Reig M**, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, Díaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol* 2016; **65**: 719-726 [PMID: 27084592 DOI: 10.1016/j.jhep.2016.04.008]

25 **Cabibbo G**, Petta S, Calvaruso V, Cacciola I, Cannavò MR, Madonia S, Distefano M, Larocca L, Prestileo T, Tinè F, Bertino G, Giannitrapani L, Benanti F, Licata A, Scalisi I, Mazzola G, Cartabellotta F, Alessi N, Barbàra M, Russello M, Scifo G, Squadrito G, Raimondo G, Craxì A, Di Marco V, Cammà C; Rete Sicilia Selezione Terapia - HCV (RESIST-HCV). Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? A prospective multicentre study. *Aliment Pharmacol Ther* 2017; **46**: 688-695 [PMID: 28791711 DOI: 10.1111/apt.14256]

26 **Ikeda K**, Kawamura Y, Kobayashi M, Kominami Y, Fujiyama S, Sezaki H, Hosaka T, Akuta N, Saitoh S, Suzuki F, Suzuki Y, Arase Y, Kumada H. Direct-Acting Antivirals Decreased Tumor Recurrence After Initial Treatment of Hepatitis C Virus-Related Hepatocellular Carcinoma. *Dig Dis Sci* 2017; **62**: 2932-2942 [PMID: 28884320 DOI: 10.1007/s10620-017-4739-z]

27 **Kanwal F**, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. *Gastroenterology* 2017; **153**: 996-1005.e1 [PMID: 28642197 DOI: 10.1053/j.gastro.2017.06.012]

28 **Petta S**, Cabibbo G, Barbara M, Attardo S, Bucci L, Farinati F, Giannini EG, Tovoli F, Ciccarese F, Rapaccini GL, Di Marco M, Caturelli E, Zoli M, Borzio F, Sacco R, Virdone R, Marra F, Felder M, Morisco F, Benvegnù L, Gasbarrini A, Svegliati-Baroni G, Foschi FG, Olivani A, Masotto A, Nardone G, Colecchia A, Persico M, Boccaccio V, Craxì A, Bruno S, Trevisani F, Cammà C; Italian Liver Cancer (ITA.LI.CA) Group. Hepatocellular carcinoma recurrence in patients with curative resection or ablation: impact of HCV eradication does not depend on the use of interferon. *Aliment Pharmacol Ther* 2017; **45**: 160-168 [PMID: 27790734 DOI: 10.1111/apt.13821]

**P-Reviewer:** Quarleri J, Tarantino G **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Italy

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0