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Editorial – Direct-acting antivirals therapy in HCV patients with HCC: lights and shadow

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The introduction of direct acting antivirals (DAA) has changed the clinical history of chronic HCV hepatitis. Viral clearance is almost always achieved in a few weeks and is a prelude to a sustained virological response (SVR) in more than 95% of cases[1]. The eradication of the virus prevents the development of cirrhosis in patients with chronic hepatitis. In the cirrhotic patient, DAA have shown a reduction in complications, such as decompensation, bleeding, encephalopathy[2-5].

The question relating to hepatocellular carcinoma (HCC) appears to be more complex. However, some studies have shown the development of unexpected HCC, even of an aggressive nature, after SVR after 12 weeks[6-8]. Other large series studies have argued that the risk of HCC occurrence appears stable or slightly reduced after viral clearance[9]. Furthermore, this risk seems to gradually decrease with time after SVR[10]. The hypotheses of these events appear manifold. First, the non-reversible cirrhotic state constitutes a state of pre-cancerous potential that persists even with the absence of the inflammatory stimulus of the virus[11]. Second, the epigenetic modifications induced by the HCV virus in the years of chronic infection and the role of some pro-inflammatory cytokines, grow factors or virus coinfection, constitute further carcinogenetic triggers[12-16]. Furthermore, the elimination of the virus could induce a reduction in immunological surveillance as for the cytotoxic effects of natural killer (NK) cells and mucosal-associated invariant T cells toward cancer cells[17].

The evaluation of HCC recurrence and DAA therapy also produced conflicting data. In fact, in these patients an HCC progress can act as an additional risk factor to those specified for HCC occurrence. A recent multicenter study[18] retrospectively assessed risk factors related to late HCC recurrence (after 24 weeks of SVR) in 326 patients with SVR by DAA. Cirrhosis, previous palliative treatments and the number of nodules> 2 were statistically significant risk factors of late HCC recurrence. These results were confirmed by the retrospective study by Ikenaga et al[19] which compared 72 patients undergoing DAA treatment after curative therapy for HCC and 93 patients not receiving DAA. SVR by DAA significantly reduced the risk for tumour progression and liver-related death and the frequency of HCC treatment following curative treatment in Barcelona Clinic Liver Cancer (BCLC) stage 0/A. A recent meta-analysis[20] conducted on 31 studies including 2957 total patients, evaluated the risk of HCC recurrence after DAA treatment in an interval between 4 and 21 months. The data showed a 68% relapse within 6 months and a lower risk of relapse in patients who received DAA treatment compared to patients who received interferon or no antiviral therapy. Based on these data we believe that DAA therapy in patients treated for early HCC in remission can bring more benefits than risks and that there is no interference between DAA and relapse of HCC. The improvement in survival is mainly correlated in these cases by the reduction of decompensation and the evolution towards liver failure[21,22].

The presence of a more advanced HCC (BCLC B-C-D), on the other hand, poses problems that are more difficult to solve. In these cases, advanced oncological disease significantly reduces life expectancy; in addition, the liver failure that often accompanies these clinical pictures makes it difficult to identify the right priorities for the patient[23]. In fact, the positive effect that can induce viral clearance by DAA may have little real benefits as the oncological pathology advances[10]. There are no solid data on this issue precisely because the stage of HCC or advanced cirrhosis excludes the evaluation of DAA in randomized controlled trials. For this reason, only experiences from small groups of patients or retrospective observational studies are available[24].

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Tsai et al[25] evaluated a cohort of 1684 patients with advanced HCC and HCV who had received sorafenib therapy divided into a group who had received therapy with DAA and another DAA without. The statistical analysis performed by a Kaplan – Meier survival analysis and a propensity score matching, found a significantly higher overall survival in the DAA group (mean 20.7 months versus 12.5 months). Similarly, Dang et al[26] evaluated 1676 HCV-related HCC patients matched into two groups (DAA treated with SVR and untreated). Treated patients included about 30% of HCC treated with trans-arterial chemoembolization (TACE) or Sorafenib. The results showed a higher 5-year survival of DAA treated patients compared to untreated.

Two other studies[27,28] have focused on patients awaiting liver transplantation with or without HCC undergoing compensation or decompensation. The results of both studies highlighted the benefits of DAA therapy both in the downstaging of HCC and in the delisting of some patients for the improvement of liver function. The use of DAA in both cases did not cause either an increase in recurrence or an increase in the recurrence rate of HCC after transplantation.

The studies presented lead us to suggest a personalized evaluation of the therapeutic strategy on intermediate-advanced HCC and HCV. We believe that the choice must identify the greatest risk among the damage caused by tumor progression or liver failure cirrhosis induced. The benefits induced by achieving SVR could in fact be minimized by tumor progression with possible worsening of the clinical picture. On the other hand, the success of antiviral therapy can even favor a downstaging, a delisting allowing a therapeutic treatment for HCC that is less invasive and with less risk. In our opinion, it seems necessary to provide adequate information for patients on the risks and benefits of therapeutic options, as well as a multidisciplinary approach between infectious disease specialists, internists and oncologists for identifying the priorities of the individual patient. Furthermore, a further role may be played by the new target therapies which, after sorafenib, are projecting a significant impact on patient survival[29]. In early forms of HCC in remission, where treatment with DAA has shown a more solid advantage, one can rely on close surveillance for possible relapses of HCC. In this context, the role of ultrasound, transient elastography by Fibroscan®[30-33], chromogranin A and alpha-feto protein, has proved to be of great help and can select patients for closer surveillance[18,34,35].

Conflict of Interest

The authors declare that they have no conflict of interests.

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