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Hepatitis C-related hepatocellular carcinoma: diagnostic and therapeutic management in HIV-patients

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Abstract. – The efficacy of the current HIV therapy has led to increased survival and prolongation of the average life expectancy of people living with HIV (PLWH), as well as the emergence of comorbidities and non-AIDS related cancer. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Current evidence suggests that HCC is an important cause of morbidity and mortality in HIV infected patients. In fact, HCC prevalence rate is indeed higher with respect to the general population average. In this paper, we review the diagnostic and therapeutic management of Hepatitis C-related hepatocellular carcinoma in HCV-HIV co-infected patients. Several therapeutic options are available depending on several factors as HCC stage, liver functions, comorbidities and they have been divided into three groups: potentially curative, proven effective but not curative, and unproven or ineffective therapy. In HIV-infected patients, surgical options are preferred compared to non-surgical therapies. Further studies, especially multicenter ones, are needed in order to define the most appropriate, evidence-based therapeutic approach to PLWH suffering from HCC. It also appears necessary to develop appropriate care guidelines for PLWH.

Key Words:
Hepatitis C virus, HCV, Hepatocellular carcinoma, HCC, HIV.

Introduction

Due to the improvement in current HIV therapy effectiveness, the scientific community has nowadays to deal with problems related to ageing and prolongation of the average life expectancy of people living with HIV (PLWH)[1-9,10]. Hepatitis C virus (HCV) and hepatitis B virus (HBV) infections are more frequent in PLWH than they are in general population, and with a more aggressive development. It appears that hepatocellular carcinoma (HCC) is becoming a huge problem for HIV-positive patients[11-18]. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. With more than 740,000 new cases/year, it is the sixth most common cancer worldwide[19-21] and the second most common cause of cancer-related death. Only in the United States during the last two decades the incidence of HCC has doubled, causing the death of more than 16,000 men and 8,000 women[21]. Although we assisted to an increased incidence of the HCC in the developed world, the majority of cases occur in Asia and Africa. Chronic viral hepatitis B and C are the most common causes of chronic hepatitis in the world potentially leading to cirrhosis and HCC[21,22]. Thus, the differences in the incidence of HCC linked to geography

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are related to the different prevalence of its major risk factors: chronic viral hepatitis B (HBV) and C (HCV), HIV co-infection, alcohol consumption and abuse, smoke and diabetes, higher testosterone levels, aflatoxin produced by *Aspergillus* species, metabolic and genetic diseases such as hemochromatosis, Wilson's disease, α-1 antitrypsin disease, glycogen-storage disease, and porphyria[22]. As for HCV-infection, which is estimated to affect more than 150 million people globally, six major genotypes have been identified worldwide[21,23,24]. Current evidence suggests that HCC is an important cause of morbidity and mortality in HIV infected patients: the HCC prevalence rate in HIV positive patients is indeed higher with respect to the general population average[17,25].

In 2017 FDA and EMA agreed that every single person infected with HCV needs to be treated with Direct-Acting Antivirals (DAAs), and it was considered a huge step forward in the direction of the eradication of HCV infection. However, later in this same year we had the first reports about HCCs appearance after completion of a treatment with DAAs. Therefore, it is still discussed if DAAs and the achievement of sustained virologic response (SVR) are enough to stop the development of HCC[16,26-30].

In this report, we review the diagnostic and therapeutic management of hepatitis C-related hepatocellular carcinoma in HCV-HIV co-infected patients.

Diagnosis

Carcinogenesis

The development of a neoplasm is a stepwise process that involves at least two or more genetic events cumulating in unrestrained cell growth, tissue invasion, and metastasis. Aberrant expression of cancer-related genes is one of the hallmarks of cancer cells and plays a role in carcinogenesis. These genetic changes are more often acquired from a combination of chemical, physical or biological agent. HCC displays numerous genetic abnormalities combined to activate upregulators of cell proliferation and inactivate downregulators [18,22,31]. HCV related carcinogenesis is mediated by host-induced immunologic response[32]. Viral replication does not lead to cellular death: the virus tends to harbor in the endoplasmic reticulum of the hepatocytes where it induces synthesis of the viral proteins, such as NS5A. The NS5A protein inhibits the p53 pathway, ending in the upregulation of cell cycles and cellular proliferation[22,31,33]. An increased cellular replication conducts to dysplastic nodule (DN), normal-appearing hepatocytes with only foci of cellular atypia, and HCC, characterized by an excess of mediator factors produced by tumor cells, which contribute to create an abnormal vascular network within the nodule, ending in hypovascularized regions which, in turn, become necrotic[31,34-36].

Noninvasive Techniques

The atypical vascular profile of HCC and hepatic nodules (HN) can be detected with the ultrasounds (US) or with other noninvasive techniques such as magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CT)[37,38].

US are less expensive, radiation-free, techniques. Abdominal US are recommended at 6-month intervals in cirrhotic patients[39,40]. However, the diagnosis of the smaller HCC nodules it might be often difficult to differentiate benign from malignant lesions in the context of the smaller HCC nodules. Moreover, abdominal US have limited sensitivity and they are not only operator- but also patient-dependent[41,42]. MRI allows the differentiation between tumor and normal liver parenchyma using magnetic fields. The sensitivity and specificity (90% and 95%) of standard MRI with contrast media are high for the detection of HCC bigger than 2 cm in diameter[19,43,44]. HCC classically appears as a hyper-attenuated lesion in the arterial phase in a CT scan. This technique is largely used to make that the radiological diagnosis of HCC after a liver nodule is detected on US and has high specificity but low sensitivity for detecting HCC[19,45,46].

Biomarker

Routinely tested biomarkers could be used for diagnosis and prognostic evaluations. Several studies and guidelines suggest that combining US and A-fetoprotein (AFP), lecithin bound AFP to total AFP ratio (AFP-L3), and des-gamma-carboxy-prothrombin (DCP), is a sufficient surveillance[47]. A-fetoprotein (AFP) has been used for several decades as a serum marker for the detection of HCC[48]. Sensitivity and specificity of AFP have been evaluated with variable results[44,49]. However, AFP levels can be falsely raised in patients who have active hepatitis but no evidence of HCC. Moreover, only a proportion of patients with HCC have elevated AFP serum levels[50]. Serum liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl-trans-

ferase (GGT), have been extensively evaluated in association with liver damage. Hie-Won et al[48] report that the elevation of serum GGT level could potentially be used as a prospective biomarker of the long-term risk of developing HCC. Serum IL-17 and osteopontin levels have been reported to be elevated in HCC patients; however, the diagnostic accuracy for either marker was lower or similar than AFP. Due to the sensibility or specificity limitation of AFP and other markers, new biomarkers are in development. Several authors reported about noninvasive and molecular methods to detect and monitor tumors. A cluster of three circulating (serum or plasmatic) long non-coding RNA – lncRNAs (LINC00152, RP11-160H22.5, XLOC014172), determined by qRT-PCR, may act as novel biomarkers for acting as fingerprint in HCC[51]. De Mattia et al[52] identified some genetic biomarkers, like five polymorphisms that may interact, contributing to predict the risk of developing a HCC. MicroRNAs (miRNAs) received particular attention as potential biomarkers. Differences in miRNA expression patterns have been found in several malignant conditions like HCC, but also inflammatory conditions might influence the miRNA levels[53-55]. Several authors[51,56-59] reported a broad spectrum of changes in microRNAome. Other microRNAs, such as miR454, could be even used as prognostic factors[60]. Circulating tumor DNA (ctDNA) consists in extracellular nucleic acid fragments released into plasma by tumor cells for an active and passive release of DNA. DNA methylation is an epigenetic regulator that usually results in gene silencing; however, there is an increase of this process early in some human tumors[61,62]. HCC-specific methylation markers showed a high correlation among the methylation profiles of HCC and DNA circulating tumor DNA (ctDNA). Xu et al[61] used ctDNA samples from a large cohort of 1,098 HCC patients to build a diagnostic prediction model that showed its high diagnostic specificity and sensitivity, which was highly correlated with tumor burden, treatment response, and stage. Further studies are required to establish the capability of these biomarkers to discriminate between inflammation liver diseases and cancer.

Staging

There are a lot of staging systems for HHC (Okuda classification), French classification, Cancer of the Liver Italian Program (CLIP) score and Barcelona Clinic Liver Cancer (BCLC) system, CUPI score, Japan Integrated Staging (JIS) and TNM, but none of them is universally accepted[63]. However, the most widely endorsed staging is the BCLC system, characterized by several parameters as tumor burden, functional status, and liver function. Moreover, in contrast with other staging systems, BCLC relates the stage of the disease to a specific treatment strategy[64,65]. The BCLC divided patients into four groups: stage 0 corresponds to early HCC, and the optimal treatment is surgery. Stage A is early HCC, a condition where radical therapies like resection, liver transplantation or percutaneous treatments are at their maximum effectiveness. Stage B is intermediate HCC. Patient with this condition may benefit from chemoembolization. Stage C is advanced HCC, when optimal treatment is represented by new chemical agents, while stage D is end-stage disease, when no other treatment than symptomatic therapy is suggested[63,66,67].

HCC in HIV Infected

HCC prevalence rate in HIV positive patients is higher than the general population and current evidence suggests that in HIV-infected patients a six-fold higher development risk of HCC has been reported[17,25].

In 2017 FDA and EMA agreed that every single person infected with HCV needs to be treated with Direct-Acting Antivirals (DAAs), and it was considered a huge step forward in the direction of the eradication of the HCV infection. However, later in this same year we had the first reports about HCCs appearance after completion of a treatment with DAAs. Therefore, it is still discussed if DAAs and the achievement of sustained virologic response (SVR) are enough to stop the development of HCC[16,26-30].

Moreover, people living with HIV (PLWH) may have higher HCC-related morbidity and mortality, with a younger onset age and a worse prognosis[17,68]. The role of HIV on cancer has long been investigated and HIV infection is involved in progression from liver cirrhosis to HCC not only through immunosuppression, but also with a direct effect of HIV on hepatic stellate cells. These cells may play an important role in the progression of liver fibrosis[20]. Furthermore, HIV replication may induce miR-122 synthesis, which is essential for HCV replication[63]. Some investigations highlight that HIV acts with a direct liver toxicity through the predominant $CD8^+$ cell response, mainly mediated by pro-inflammatory cytokines, which also stimulate fibrosis; moreover, HIV also cause an indirect liver damage because of its ther-

apy. As a matter of fact, some antiretroviral drugs have an intrinsic hepatotoxicity.

Treatment

A high number of HIV-infected patients received treatment for HCC. Different therapeutic options are available depending on several factors such as HCC stage, liver functions, comorbidities and they have been divided into three groups: potentially curative, proven effective but not curative, and unproven or ineffective therapy. In HIV-infected patients, surgical options are preferred compared to non-surgical therapies. However, a multidisciplinary team is necessary for a correct management.

Surgical Treatment

The evaluation of liver functional reserve is an essential step before liver surgery. In addition, Makuuchi's selection criteria – presence of ascites, serum bilirubin and ICG retention rate at 15 min (ICGR15) – must be considered[69-72]. Poor resection significantly increases the risk of early recurrence of cancer, so it is imperative to make the right choice. Trans-arterial chemoembolization (TACE) should be offered to patients with preserved function and no vascular invasion or extra-hepatic spread (BCLC tumor stage 0)[73]. HCC usually develops in patients with chronic hepatitis (HCV or HBV related) or cirrhosis, who are at risk of hepatic failure in case of insufficient liver remnant volume after liver surgery; in these patients, the portal vein embolization (PE) technique may prevent hepatic failure and improve survival[74]. Surgical resection is the treatment of choice in solitary tumors ≤5 cm up to three nodules ≤3 cm, without vascular invasion or extrahepatic spread, with preserved hepatic function and absence of portal hypertension. In patients with portal venous invasion, the area supplied by the portal vein branches should be removed. Survival of patients with early HCC amounts to 41-74% at 5 years after resection, while vascular invasion is a poor indicator of long-term survival[19,75-78]. Major perioperative complications may include hemorrhage and intra-abdominal abscesses, while postoperative complications could be mainly hepatic failure and disseminated intravascular coagulation[79,80].

Liver Transplantation

Liver transplantation offers an even better rate of long-term survival after 5 years for many patients with HCC. PLWH often present HCC in an advanced stage, reducing the available therapeutic choices[19,25]. Moreover, just a few years ago, HIV infection was considered an exclusion criterion for liver transplantation, exactly because PLWH only show symptoms of disease in an advanced stage[81]. In recent years, liver transplantation has been performed on patients with HIV infection and HCC[13,25,75,82]. Mazzaferro et al[83] defined in 1996 the Milan's criteria for eligibility for transplantation in HIV-free patients[83-85]. However, the current criteria for liver transplantation in PLWH do not differ from those indicated for HIV-negative individuals, except for an undetectable HIV viral load and a $CD4^+$ cell count higher than 150 cells/ml, the baseline criteria for liver transplantation in HIV-positive people[25,84,86,87].

Medical Treatment

ART, when correctly taken, significantly reduces the rate of hepatic failure events by 28-41%, so cART should be administered to HIV/HCV-coinfected patients to lower the risk of end-stage liver disease[88]. To date, advanced HCC in compensated patients are treated with Sorafenib, the only systemic therapy with a documented improvement in overall survival[73,89-91]. Sorafenib is a tyrosine kinase inhibitor which use in advanced HCC was approved in 2008, based on two multicenter trials: SHARP and Asia-Pacific. Recent studies[11,86] have described the use of Sorafenib for HCC in PLWH and found a comparable efficacy and reasonable safety profile when compared HIV-negative patients. Molecule-targeted therapies represent a new promising field in advanced HCC therapies and tyrosine kinase inhibitors and monoclonal antibodies represent currently established treatments. Ras/Raf/MEK/ERK (MAPK), Wnt/catenin and Phospho-inositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathways are the most evaluated molecular intracellular targets[73]. The development of immune inhibitors for advanced HCC patients is an interesting area of study. Only two drugs are currently being tested in phase 3 trials: lenvatinib, an anti-angiogenic molecule acting as a multi-kinase inhibitor, and nivolumab, an immune checkpoint inhibitor with an overall response rate of 15% and a promising favorable survival data in a small cohort of patients affected with HCC[92]. Unfortunately, no HIV patients were included in the trials.

Conclusions

HCC is a major worldwide public health problem due to its rising incidence and high morta-

lity in both developing and developed countries. This is especially true in PLWH co-infected with HCV, whose cancers present in advanced stage. Early diagnosis is crucial, so PLWH at risk of developing HCC should be regularly checked to find the cancer in an early stage. When an HCC is detected at an early stage, curative treatments as surgery or liver transplantation are possible. A pharmacological approach in advanced stage cancers is possible with the new experimental drugs. Unfortunately, knowledge is limited and comes from case reports and retrospective studies. Further studies, especially multicenter ones, are needed in order to define the most appropriate, evidence-based therapeutic approach to PLWH suffering from HCC. It also appears necessary to develop appropriate care guidelines for PLWH that differ from those applicable to non-HIV infected patients, because of their cancers being more aggressive.

Conflict of interest

The authors declare no conflicts of interest.

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