Review Article

Specific issues in the management of hepatocellular carcinoma in Hepatitis B Virus/Hepatitis C Virus-Human Immunodeficiency Virus co-infected patients

ABSTRACT

Hepatocellular carcinoma (HCC) has become in recent years a leading cause of morbidity and mortality in HBV or HCV-HIV co-infected patients. Our aim is to describe the peculiarities of HCC occurring in this highly demanding scenario, covering all topics from diagnosis to treatment. We begin with the epidemiology of co-infection with hepatitis B and C. The following sections deal with suggestions and recommendations about screening, diagnosis and treatment, highlighting the cornerstone role of liver ultrasound imaging and serum alpha-fetoprotein determination in patients at high risk for HCC development. Special consideration has been given to the issues hindering the access of HIV patients with HCC to liver transplantation programmes. We hint to the much awaited availability of highly efficacious Directly Active Antivirals. In fact, the advent of these molecules is likely to produce a deep impact on and a dramatic improvement of the natural history of HIV/HCV co-infections. Nevertheless, large prospective trials are badly needed to assess the optimal management of patients who have cleared HCV but still risk to develop a liver malignancy.

Keywords: hepatocellular carcinoma, Human Immunodeficiency Virus, Hepatitis C Virus, Hepatitis B Virus, liver transplant

1. INTRODUCTION

Human immunodeficiency virus (HIV)-infected patients have benefited from the diffusion of combination antiretroviral therapy (cART) showing an increased survival with a better quality of life [1-3]. This has allowed conditions with a long latency to occur at higher rates [4-6]. In particular, during the last 10-15 years, where cART was easily accessible, end-stage liver disease (ESLD) emerged as a leading cause of morbidity and mortality among HIV-infected subjects co-infected with Hepatitis C Virus (HCV) and/or hepatitis B virus (HBV) [4, 7]. An increased incidence of hepatocellular carcinoma (HCC), a clinical complication which takes places several years after the infection with HBV or HCV, has been observed as well [7-10].

It has never been proved that HIV is an independent risk factor for the development of HCC, although chronic hepatitis progression toward cirrhosis has been shown to be progress more rapidly by coinfection with HIV [8-11].

2. EPIDEMIOLOGY

Hepatitis B virus and HCV infections present different epidemiological and geographical peculiarities because of their way of acquisition. In fact HCV acquisition is usually related with use of injectable illicit drugs in all Europe, USA and Australia, while in developing countries it is due to a mix (i.v. drug use and iatrogenic transmission). The same modes of transmission are shared by HBV, but sexual contact and vertical transmission remain the main route of infection in endemic areas where vaccination has not yet been introduced. Since HIV shares modes of transmission with both HCV and HBV, even geographical and demographic distributions are shared with both hepatic viruses.

Relative proportions of co-infection with HCV and/or HBV show broad variations among HIV-infected populations and sub-groups in the world depending onthe prevalence of different high-risk behaviours in the sub-groups and populations evaluated. In Europe and in the USA, approximately 15–30% of patients infected with HIV are also infected with HCV [12, 13], and, among these patients, the number of deaths due to ESLD is higher than that from acquired immunodeficiency syndrome (AIDS) defining conditions [13, 14].

The highest rates of HCV-HIV co-infection are found among intravenous drug users (IDUs) and prisoners (up to 75–90%) [15-17]. Differently, prevalence of HBV among HIV-infected patients is reported to vary between 5 and 10% in Europe and the USA, while it reaches15% in countries and settings where HBV is endemic [17-20].

Nevertheless, recorded prevalences are likely to be not precise for several reasons. Testing for HCV antibodies detects 20-25% of subjects in excess who have spontaneously cleared the virus and present undetectable HCV RNA. Few studies of prevalence reported testing also for HCV-RNA, thus we can rely only on those searching uniquely for HCV antibodies. There is general agreement that detection of hepatitis B surface antigen (HBsAg) identifies those with HBV infection. Moreover, a small but significant amount of HBsAg negative patients are presenting detectable HBV DNA and positive anti HBc antibodies. This condition is defined as occult HBV infection and it occurs frequently in HIV patients with HCC and no evidence of coinfection with HCV [21-23]. Its clinical relevance is due to the capability of occult hepatitis B to preserve its oncogenic potential even in presence of minimal viral replication. Actually, a recent study evidenced circulating HBV DNA in most (63.5%) patients with HBsAg-negative HCC [24]. Similarly, another study reported that occult HBV infection was present in the vast majority (up to 70%) of patients with HBsAg-negative HCC [25].

Hence, prevalence studies employing RNA and DNA testing would be more accurate in estimating the actual burden of hepatic viral co-infections among HIV-infected subjects [9].

As to co-infections and HCC, a large retrospective US cohort study (14 018 male patients followed for 8 years up to 2004) reported a much higher risk of HCC among those HIV infected, almost exclusively associated to HCV (and to a lesser extent HBV) infection [26]. Incidence of HCC in HIV-HCV co-infected patients belonging to another large retrospective cohort (11 678 subjects) – including both pre-cART and cART eras – was strikingly higher than in the HCV mono-infected population. The difference between the two populations was really striking during the vART era (only 5 HCC cases during the years before the introduction of cART versus 22 after) in the cART era) [11]. Another report on 2383 HIV-infected patients found a higher than expected incidence of HCC in HCV co-infected subjects compared with the average population [27]. Similar results have been reported by small European retrospective studies

The incidence of HCC among HIV infected subjects showed a constant increase increase over time, in parallel with introduction of better antiretroviral regimens, up to a 2009 estimate of 30 per 100 000 individuals in the US AIDS population [9, 10]. Recently, a Spanish study reported the incidence of HCC in a prospective cohort of 371 HIV infected patients enrolled between 2004 and 2005, the majority receiving ART, with liver cirrhosis from different causes. Among them the incidence rate of HCC was 6.72 per 1000 person-years [95% confidence interval (CI): 2.6 to 10.9]. There was a

trend toward a higher cumulative probability of developing HCC at 6 years of follow up (considering death and liver transplant as competing risks) in patients with decompensated versus compensated cirrhosis at baseline (6% vs. 2%, P < 0.06) [28]. Conversely, HCC incidence in the general population is low, e.g. in 2008 it was of 16 cases per 100 000 inhabitants [29]. It ranges from 1.6 per 100 000 inhabitants for North European women up to 35.5 per 100 000 inhabitants for Eastern Asian men [30].

It has to be underscored that studies from the years before cART introduction, or in countries where cART is not universally accessible, have generally reported rates of HCC lower or equal to those observed in the general population [31,32]. The main reason is probably that patients would die of AIDS related conditions long before the prospective development of cirrhosis and subsequently of HCC.

In fact, as recently reported in a studied population where cirrhosis had time to develop, no difference in HCC incidence among cirrhotic HIV-HCV co-infected patients was observed in the pre- and HAART eras [33].

3. DIAGNOSIS

Early diagnosis of HCC is crucial for a better management of the disease in co-infected patients. Thus, regular screening of patients with hepatitis and HIV co-infection is needed to reach this objective.

Current European AIDS Clinical Society guidelines give specific recommendations to perform screening of cirrhotic HBV and/or HCV-HIV co-infected individuals [34]. Such recommendations are similar to those released for HCV or HBV mono-infected patients with established cirrhosis, suggesting screening with ultrasonography and alpha-fetoprotein (AFP) level determinations every 6 months [35]. With a slight different approach, US screening guidelines for HIV and HCV coinfected subjects recommend to employ ultrasonography as the first step in HCC screening [36]. In addition, it is suggested that, only in settings where ultrasonography is not available, AFP determination can be used alone . Nevertheless, screening should be carried out every 6-12 months and should address all those at an increased risk for HCC [37].

To summarize, once the patient is diagnosed with cirrhosis, screening for HCC every 6 months with ultrasonography , coupled or not with AFP, is recommended [30,34-36,38].

Even sustained virological response (SVR) after anti HCV treatment cannot completely arrest the development of HCC in the mid term and long term. It is known that in cirrhotic patients in spite of the absence of the virus after successful eradication with anti-HCV treatment, an increased risk of HCC development persists [39]. Actually, presence or absence of cirrhosis in HIV co-infected patients obtaining SVR after anti HCV treatment is crucial in determining the subsequent risk of HCC occurrence.

Recently, findings from a Spanish study reinforce the need to continue surveillance for HCC with ultrasound examinations in patients with cirrhosis who respond to anti HCV therapy [40]. Indeed, HCC can become manifest even during treatment course, as it has been reported [41]. In particular, the majority of cases in the Spanish series appeared after 1.5 years since the end of anti HCV therapy and the elapsed time for some cases was even longer than 5 years, as it has been also shown in HCV mono-infected patients [42]. Their findings reinforce the current recommendation of clinical guidelines to maintain HCC surveillance indefinitely in patients with cirrhosis, even for those with SVR who cleared HCV with therapy [36].

Liver nodules need to be detected by ultrasonography during the recommended biannual (i.e. every 6 months) follow up visits. Then, second level imaging such as computed tomography (CT) or magnetic resonance (MRI) should be accessible to characterize such nodules at the earliest possible stages [35]. When nodule nature is not determinable by such imaging techniques, biopsies should be performed with the shortest possible delay. The early characterization of

nodules would help in timely addressing the patient to the most appropriate treatment, thus preventing further tumour growth that could make the patient ineligible to curative procedures. Nevertheless, no algorithm has been drawn so far for the HIV-infected population in absence of studies in this specific population [43].

4. RISK FACTORS AND PATHOGENESIS

HCV infection in HIV infected patients frequently causes chronic liver disease potentially leading to cirrhosis and HCC. In the presence of cirrhosis the annual risks of HCC, liver disease progression and death in HCV infected patients are approximatively 1-7%, 5% and 2%, respectively [44]. The principal oncogenic effect of HCV is mediated indirectly through activation of immune-mediated inflammation and its downstream effects on cell proliferation and apoptosis.

HIV–HCV co-infected patients have been shown to develop liver cirrhosis more quickly than HCV mono-infected individuals; in addition, HCC behaviour is more aggressive in these patients [45-49]. Presence of cirrhosis is the essential element for HCC development, in HCV infected subjects; it is observed in 1%-4% of patients per year after cirrhosis occurrence.

The ongoing processes of inflammation and repair in the cirrhotic liver are a significant pathogenic factor for HBV and HCV infections. Specifically for HBV, the degree of viral replication is an additional key factor for HCC development. In fact, patients with active chronic hepatitis B present a 90 fold greater risk of developing HCC than HBV negative (cross matched for age). On the other hand, inactive carriers with low levels of viremia are exposed only to a 9 fold increase. Additionally, the risk of HCC is reported to directly correlate with HBV-DNA levels [50]. The random integration of viral DNA into the host chromosomes (an incidental process not necessary for viral replication) leads to secondary chromosomal rearrangement and genomic instability with oncogenic potential [51].

The quantitative decline of T-cells observed in the immunodeficiency associated with HIV infection is probably the factor behind the impaired viral immune response responsible for acceleration of the course of HCV infection [52].

Specifically, in HIV/HBV co-infected patients, an immune disregulation related with CD4+ decrease may be observed. This seems to be the mechanism that in HIV infected subjects sustains the specificity of chronic hepatitis B in such population, i.e. higher rates of chronic evolution of acute hepatitis B, higher levels of HBV replication, a lower rate of spontaneous hepatitis B e antigen (HBeAg) and HBsAg loss or seroconversion to anti-HBe and anti-HBs. Cases of seroreversion (i.e. loss of HBsAb and reappearance of HBsAg) have also been reported [14].

Moreover, in the context of co-infection of HIV with either HBV or HCV, additional severe liver injuries may occur in consequence of cART efficacy in rapidly restoring immune function and therefore giving place to the so-called ‘immune reconstitution syndrome’. Conversely, ART-related immune restoration can lead to improved cellular immune response to viral hepatitis antigens, thus slowing the progression of chronic liver disease [53].

In addition a weaker antitumor answer (HCC-driven) has been described in HIV infected patients, mainly due to the chronic low T cell counts. Such reduced immune response to HCC may justify the fast growth and the extension in diffusion of the disease observed in co-infected subjects [54].

5. TREATMENT

Unfortunately, access to treatment for those infected with HIV is different from those not infected. This is particularly true for liver transplantation.

In the HIV negative population, presence of solitary HCC nodule (up to 5 cm) is an indication to surgical resection, associated with a 5-year survival of 50%-70% [30,55,56]. Eligibility for surgery is assessed employing the Milan or the University of California, San Francisco (UCSF) criteria [30,57,58]. When patients present with local disease that cannot

be eligible for surgery, they can be offered ethanol injection. Such treatment option is reported to have a ~50% 5-year survival rates [59].

Radiofrequency ablation (RFA) is considered a safe and effective therapy for patients with HCC who cannot undergo resection, or as a bridge to liver transplant; the goal of therapy is to destroy the nodule and 0.5 cm of tissues surrounding it [60,61]. RFA is generally performed percutaneously under US or CT guidance [62]. It is indicated if there is a a single nodule ≤ 5 cm or up to three nodules ≤ 3 cm each [30,63]. Some absolute controindications for RFA include lesions larger than 5 cm, lesions adjacent to vital organs, particularly when adhesions are suspected, or to main biliary ducts; and presence of bilionteric anastomosis [64]. The therapeutic efficacy could be monitored with a combination of imaging investigations (contrast enhances-US or CT scan) and serum assays [60].

A recent systemic evaluation showed superiority of RFA over percutaneous ethanol injection for the treatment of small HCC [65]. Therefore, it is probable that ethanol injection should be reserved for those ineligible for RFA or where RFA is not available. When diagnosed with a more advanced disease, patients are amenable to palliative transarterial chemoembolization (TACE). Nevertheless, so far, no chemotherapy or targeted therapy showing a survival benefit has been identified for these patients.

HIV infected subjects with non AIDS defining cancers, such as head-neck, lung cancers, etc., generally present at diagnosis at a more advanced stage, thus generally receiving curative treatments less frequently than those HIV negative [66]. Specifically for HCC, an Italian study reported 15 HIV-infected patients with disease within the Milan criteria for liver transplantation eligibility [46]. Nevertheless, none was treated with liver transplantation and only two received surgical resection. In addition, this cohort reported a poor outcome for HIV-infected subjects compared to HIV negative subjects (28% 1 year survival for those HIV-infected vs. 57%). Other reports showed poor access to curative treatment for HIV/HCV co-infected patients [46,67]; while others evidenced better access to proven effective therapy, as TACE for those with HIV infection [47].

TACE and RFA have been employed more frequently for HIV infected subjects, while surgical resection has been carried out more often for those HIV uninfected. A single recent study could report equal access to treatment for HCC for HIV positive and HIV negative patients [68]. Nevertheless, even in this latter study, differences still existed in actual delivery of recommended curative treatment with about 30% of HIV-infected subjects not receiving it. In addition, other authors reported that the reason behind lack of improvement in curative management for HCC for those with HIV infection was probably late initiation of interventions [69].

Nevertheless, no large prospective cohort has clearly demonstrated the true reasons behind poor access to effective and curative treatment for HIV-infected patients. They probably include, among others, difficulties in management of decompensated cirrhosis, late referral, advanced stage of HCC at diagnosis, deterioration of general health , poor compliance or greater aggressiveness of the tumour.

5.1.Liver transplant.

The current criteria regarding liver status for eligibility to liver transplantation (OLT) for HIV infected patients do not present differences from those agreed upon for those without HIV infection. On the other side, specific HIV related factors (*i.e.*, post-OLT HAART tolerance and CD4 T cell absolute number) have been reported as predictors of mortality in OLT [70]. A stable (for more than six months) absolute CD4+ cell count > 200/mmc and an undetectable HIV viral load are required if the patient is receiving HAART and has a previous history of opportunistic infections (*i.e.*, adequately treated tuberculosis, invasive candidiasis, toxoplasma encephalitis, pneumocystosis, etc). Exceptions are represented by patients

who have lower absolute CD4+ cell count (*i.e.*, between 100 and 200/mmc, potentially related to hypersplenism), but have no history of opportunistic infections, or patients who cannot receive antiretrovirals due to severe liver impairment. In the latter case, previous documentation of therapeutic efficacy and/or genotypic or phenotypic tests documenting the availability of a potentially effective regimen (able to suppress HIV replication to undetectable HIV RNA) for post transplant administration is required [71].

HIV infected patients suffering a first episode of cirrhotic decompensation should be evaluated for liver transplantation, especially if they are under ART with virological response. In the past HIV infection was considered as an absolute contraindication to liver transplantation, but this assumption is gradually changing. In fact, similar survival rates have been reported in HIV positive recipients, when compared to HIV negative MELD-score matched subjects [33,70-78]. Recently, additional specific data on liver transplants in HIV infected recipients with HCC have been published. Such reports with increasing, although still relatively small, numbers showed results comparable to the HIV negative HCC population [79]. Nevertheless, a higher proportion of HIV infected patients appears to die while on the waiting list with late referral being at least partially responsible for increased mortality [80].

A group proposed monitoring of AFP levels during the waiting list phase of HIV infected patients to identify those with higher risk of serious complications after liver transplantation [43]. In fact, a clear correlation between AFP levels (especially when rapid growth is observed) and a poor clinical outcome has been described [81]. However, HCC recurrence has been observed to occur equally among HIV infected transplanted patients and in those HIV negative. In addition, no impact of immunosuppressive treatment has been described on HIV progression, as formerly expected [82].

Liver transplant in HIV infected patients presents specific post transplant challenges. These latter include in particular faster and more aggressive re-infection with HCV, more issues in drug-drug interactions, more common lamivudine resistance in HBV infection (obviously among those HBV co-infected), and a relatively more frequent occurrence of toxicity of some immunosuppressant, such as tacrolimus [70,83].

In summary, HIV infected patients with HCC should be able fully access the complete evaluation steps leading to liver transplantation, and early detection of HCC is key for better management and outcome.

Screening strategy in case of HBV infection is more complex since it must take into account not only liver histology but also the risk factors for developing HCC in the absence of cirrhosis. Actually, some authors have identified for HIV uninfected patients with hepatitis B potential risk scores for HCC that include: age, gender, the length of untreated hepatitis period, a family history of HCC and cirrhosis [35]. These proposed HCC risk scores could probably be employed also for those co-infected with HBV and HIV [43].

5.2.Targeted therapy (Directly Acting Agents).

The recent introduction of specific treatments for hepatitis C such as sorafenib has offered a new option to improve advanced HCC management [84]. Recent studies among HIV-infected patients with HCC have reported a sorafenib efficacy and safety profile comparable with that observed in HIV uninfected patients [85–87]. Nevertheless, possible drug interactions between antiretroviral drugs and sorafenib at cytochrome P450 level with risk of excessive and more toxic blood levels of the antimitotic agent have been reported [87,88].

More recently, a report about 27 consecutive HIV-infected patients with HCC treated with sorafenib showed an overall survival (12.8 months [1.1–23.5]) comparable to the results obtained by other groups [84, 89]. Nevertheless, as in non HIV infected patients, the main limitation to such treatment remains the presence of cirrhosis associated with liver failure and/or portal hypertension.

6. PREVENTION OF HCC

The first step in trying to prevent HCC in HIV infected subjects is treatment of the hepatic co-infections. Actually, main international guidelines for the management of HIV infection already consider – for those subjects co-infected with HBV – mandatory ART including drugs also active against HBV as tenofovir, lamivudine and emtricitabine [50,90-92].

Treatment of chronic hepatitis in HCV/HIV co-infected patients has proven effective and it is recommended by several international guidelines [34, 93-100]. For many years anti HCV treatment has been based on pegylated interferon (IFN) + ribavirin with inconsistent and still unsatisfactory results [98]. New treatment opportunities are opening now with the availability of directly acting agents (DAAs) and some encouraging experiences already exist [95, 99-101].

Sustained virological response rates (SVR) of 27%-40% have been achieved with IFN and ribavirin therapy in HIV co-infected patients [48]. Not only is the risk of HCC reduced with HCV eradication but the resulting enhanced liver function increases tolerance to antiretroviral agents. Treatment of the HIV/HCV patient presents several challenges [8], but it is surely feasible [95, 98-100].

Several studies have shown that the incidence of HCC is lower in HCV infected patients who achieved SVR with IFN based treatment [6, 100-109].

A relatively small advantage in prevention of HCC by IFN treatment, even without obtaining an SVR, has been reported by several authors [110-117]. HCC risk is mainly related to fibrosis and, since antiviral therapy improves fibrosis, it should reduce the risk of developing HCC as well. On the other hand some authors suggest that the benefits of anti HCV therapy could be due to the antifibrotic and antiproliferative properties of IFN, independently of antiviral effects [118]. Actually, if IFN is successful in achieving a persistently and undetectable HCV-RNA, necrotic inflammation should consistently improve. At the same time, carcinogenesis is believed to be suppressed even in biochemical responders who do not achieve viral clearance [119].

As previously mentioned, several studies conducted in patients with cirrhosis have confirmed that incidence of HCC significantly decreases in patients who achieved SVR, but, since cirrhosis is not eliminated, the risk of HCC is not entirely removed [102, 107-109, 120].

Registration trials of anti HCV treatments have usually been restrictive in patient enrolment, not taking into account patients with advanced liver disease or HCC. Thus, treatment of chronic hepatitis C (CHC) in HCC patients has remained an area of limited knowledge as to efficacy and cost/effectiveness. In any case, safety and efficacy of peg-interferon treatment of CHC in patients previously treated for HCC has been proved [40].

Some reports about the usefulness of interferon and ribavirin in the prevention (primary and of recurrence) of HCC in non HIV infected patients have been published [121, 122]. More recently, Italian anti HCV treatment guidelines considered chronic hepatitis C treatment with peg-interferon + ribavirin as secondary prophylaxis against recurrence of HCC [123] and some experiences to this effect have been published [41].

Prevention of HCC in not exclusively based on treatment of hepatitis B and/or C. Among these patients comorbidities may be present and need to be addressed. They include ART-related toxicity, diabetes, alcohol use, steatosis, and other metabolic disorders [43, 124].

7. CONCLUSIONS

Large international cohort studies show that HCC incidence in persons living with HIV keeps rising in regions of the world where ART is currently available. The increasing availability of ART in developing countries can be expected to have

similar consequences. Nevertheless, timing of such increase is difficult to predict. Lack of detailed epidemiological data on HBV or HCV co-infection makes it challenging to easily identify and quantify the at-risk population. Recent studies on management of HIV/HBV co-infection confirm that monitoring of HBV viral load (HBV-DNA) is often inadequate in co-infected patients despite regular viro-immunological assessment of HIV infection [125 and personal observation]. Current HCC screening strategies developed for HBV or HCV mono-infected patients are employed among those co-infected with HIV. However, they have never been validated in this specific population. After diagnosis of HCC, patients are referred and have access to effective treatments less frequently and usually at a more advanced stage of the disease. Guidelines on management of HBV/HCV-HIV co-infected patients have been developed, but new scenarios keep arising, highlighting advantages (e.g. anti-viral cross-efficacy, etc) and disadvantages (e.g. cross-resistance, drug-drug interactions, etc). In the near future the availability of several highly efficacious DAAs will dramatically change the natural history of HIV/HCV co-infection with its potential to eradicate HCV infection in virtually all patients.

Large prospective trials are still needed to explore in depth the risk factors for developing HCC for those who eradicated HCV and to identify the optimal screening algorithm for an early diagnosis of HCC in the population of co-infected patients.

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