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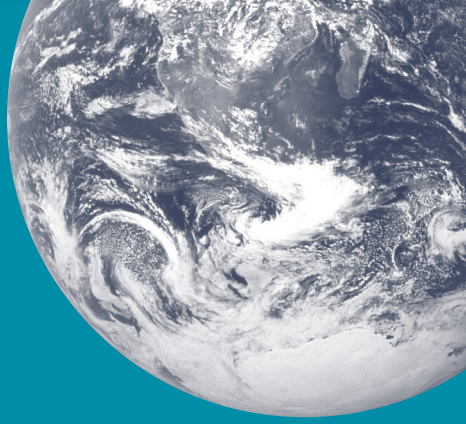

NEW ENTITIES IN THE TREATMENT OF HEPATOCELLULAR CARCINOMA: HIV-POSITIVE AND ELDERLY PATIENTS

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Absract – *The hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and, according to the WHO report, the fourth commonest cause of death. The incidence of HCC has been rising in developed western countries in the last two decades, along with the emergence of hepatitis C virus infection and to the rise of immigration rates from HBV-endemic countries. In addition, even though the incidence of HCC reaches its highest peak among persons over 65 years, an increased incidence among younger individuals has been noted in the last two decades both in USA and Europe. In the last decades two kinds of HCC patients are more interesting, for clinical characteristics, than typical patients with HCC: elderly and HIV-positive patients. In fact due to the increase of the life expectancy in many countries, HCC represents a new challenge in this particular setting of patients.*

KEY WORDS: *Hepatocellular carcinoma, Treatment, Elderly, HIV, Patients.*

INTRODUCTION

The hepatocellular carcinoma (HCC) is the most common primary cancer of the liver[1] and, according to the WHO report[2], the fourth commonest cause of death. The estimated incidence of new cases worldwide is about 500,000-1,000,000 per year, causing 600,000 deaths globally per year[3]. Although there are large areas of the world where the incidence of HCC is still unknown[4-6], several countries like East Asia and some Sub-Saharan African regions result to be affected by a very high prevalence of HCC (over 20 cases/100,000 population)[7]. Areas with moderately high risk (11-20 cases/100,000 population) include Italy, Spain and Latin America; conversely France, Germany and the United Kingdom have an intermediate risk (5-10 cases/ 100,000 population). A relatively low prevalence (less than 5 cases/100,000 population) is found in United States, Canada and Scandinavia.

The incidence of HCC has been rising in developed western countries in the last two decades[1-8], along with the emergence of hepatitis C virus infection and to the rise of immigration rates from HBV-endemic countries. In addition, even though the incidence of HCC reaches its highest peak among persons over 65 years[9], an increased incidence among younger individuals has been noted in the last two decades both in USA and Europe.

In the last decades two kinds of HCC patients are more interesting, for clinical characteristics, than typical patients with HCC: elderly and HIV-positive patients. In fact due to the increase of the life expectancy in many countries, HCC represents a new challenge in this particular setting of patients.

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HCC IN HIV-POSITIVE PATIENTS

The survival rates of patients with human immunodeficiency virus (HIV) have been dramatically improved after the advent of highly active antiretroviral treatment (HAART), and HIV related morbidity and mortality have been remarkably decreased[10,11]. At the same time, the morbidity and mortality related to many different non-HIV-related diseases, such as chronic liver diseases (CLDs) has shown a significant increase[12,13]. In fact, up to 50% of deaths among people with HIV infection now accounts for end-stage liver diseases (ESLDs), which are primarily related to complications of chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) co infection, as well as hepatotoxicity associated with antiretroviral therapy and alcohol use[14-16]. Mortality associated with HCV infection is expected to continue to increase over the next 25 years[17,18]. In a national survey on deaths among HIV-infected patients, liver diseases represented the third most frequent underlying cause of death[18].

HIV-infected patients have a sevenfold higher risk for HCC than the general population[19,20]. Since the introduction of HAART, no decrease in the incidence of HCC has been observed, unlike for other HIV-associated cancers[20-22].

In the general population, HCC occurs several decades after the initial infection with HCV or HBV[21,23,24]. Large retrospective cohort studies also excluded that HIV infection alone may be a risk factor for HCC[22]; the HIV coinfection with HCV or HBV is common and a significantly higher risk for developing HCC as a result of chronic viral hepatitis is well documented. Little is known about the HIV and HBV and/or HCV interaction over the long term. HIV coinfection seems to accelerate disease progression and to reduce the efficacy of anti-HCV and anti-HBV treatments. Conversely, it is uncertain whether HIV infection directly increases the likelihood of HCC in patients with viral hepatitis[25-28]. HAART, besides its potential indirect effects on HCC risk through improvements in immune reconstitution and survival, is known to have some direct hepatotoxic effects, especially among HIV-infected patients with chronic HBV or HCV infections[16,29]. A large retrospective cohort study on US veterans demonstrated that HIV positive persons had a higher risk to develop HCC than HIV negative ones but, after adjusting for HCV and alcohol abuse, HIV status was not independently associated with cancer[30]. Also the 2001 French Mortavic study[31], a prospective 1-year cohort study involving 25,178 HIV positive patients (enrolled between 1995 to 1997), showed a significant increase in death from ESLD and HCC. Death due to ESLD rose from 1,5% to 14.3% whereas HCC-related mortality rose 5-fold, from 4.7% to 25%; interestingly, all HCC deaths were in patients HCV co-infection. Throughout the same period, AIDS-related mortality rate fell from 91.6% (in 1995) to 48.7%, suggesting that the increased HCC rate in the 2001 cohort could be due to the increased longevity of patients in the HAART era. In a prospectively followed cohort of HIV-infected individuals, HCC deaths related to HCV infection raised from 10% in 2000 to 25% in 2005[32]. In contrast, the incidence of HCC development and related deaths among HIV-HBV co-infected individuals seemed to be stable[32]. A retrospective study[33] conducted between 1991 and 2000 on a cohort of US veterans with hepatitis C showed that the incidence of HCC did not differ between HIV/HCV co-infected and HCV mono-infected patients in the HAART era, whereas it was significantly lower among HIV/HCV co-infected individuals previously to HAART introduction, demonstrating that, in the pre-HAART-era, HIV patients' deaths occurred before the development of HCC. Furthermore, in countries where HAART is largely unavailable, other retrospective studies confirmed the incidence of HCC to be lower or equal to that of the average population[34,35]. In 2004, the Italian Cooperative Group on AIDS and Tumors (GICAT)[36], identified a total of 41 consecutive patients with HCC (from a joint Italian and Spanish database) and retrospectively investigated their main epidemiological characteristics comparing them with those of 384 HIV negative controls, diagnosed over the same period. The GICAT study emphasized the younger age of HIV positive patients at the diagnosis of HCC (age 40-46 *vs.* 60-70 in HIV negatives). In most studies HCV infection was the main risk factor for HCC development in both HIV positive and negative subjects. The median time to develop HCC after HCV infection was found to be around 22 years in HIV positive patients: 10 years shorter than that reported among HIV negative patients that acquired HCV infection with transfusion[37]. Alcohol abuse (a risk behavior often associated with HIV) and insulin resistance (which causes non alcoholic fatty liver disease and frequentlyoccurs in HIV-infected individuals submitted to protease inhibitors) are other potential risk factors for HCC development among the HIV-positive population[38,39].

HIV-HBV and HIV-HCV Co-Infection: Prevalence and Significance of a Complex Interaction

HIV-infected persons are often HCV and/or HBV co-infected, because of shared routes of transmission. The prevalence of co-infection differs according to the demographic characteristics of

infected patients and their geographic origin[40]. In the Western countries around 25% of patients are HIV-HCV co-infected[41]; in Europe, for instance, the prevalence of HIV/HCV co-infection ranges from 33% to 75% when considering intravenous drug users (IVDUs) according to the European SIDA cohort data on 3,048 HIV positive patients[42]. Also in the USA, the highest rates of HIV/HCV co-infection can be seen among IVDUs[43]. In Europe, up to 9% of HIV positive patients are also HBsAg positive[44,45]; e.g., in Italy, between 3% and 4% of HIV positive individuals carry HBsAg[46]. The data might be inaccurate, due to a large number of occult HBV infections, associated to detectable HBV DNA on quantitative polymerase chain reaction (PCR)[47,48].

HCV typically develops in HCC through the stage of cirrhosis, occurring in about 28-30 years[49,50]. Cirrhosis leads to the development of HCV-related HCC. HCV do not integrate into the host genome and probably hepatocarcinogenesis in patients with HCV relate to the immune-mediated inflammation and hepatocellular damage. HBV chronic infection represents another major cause for HCC[51] but, unlikely HCV, it may occur in HBsAg carriers without cirrhosis, because the direct involvement of many viral-related factors such as viral proteins, BCP mutation in the viral genome, and Pre-S deletion mutants[52,53]. Furthermore, HBV can integrate its DNA into the host genome, with several mutagenic consequences, including large inverted duplications, deletions, amplifications and traslocation, resulting in chromosomal instability[53-55]. As expected, patients with both HCV-HBV infections are more likely to develope HCC than those mono-infected, therefore, HBV vaccination should be highly recommended to all patients with chronic hepatitis C[56]. The role of HIV on cancer has been long investigated. Murine models in vivo studies have revealed a possible role of the HIV Tat gene in liver tumorigenesis[53-55]. A higher incidence of HCC and other extra-hepatic malignancies has been found in transgenic mice expressing this gene emphasizing that the oncogenic effect of Tat gene is not potentially liver-specific. Tat gene seems to be able to stimulate cell proliferation, because of its anti-apoptotic activity[57,58], angiogenic functions[59,60] and ability to induce expression of growth factors[61], cytokines[62,63] and transcription factors[64]. This experimental datum contrasts with many epidemiological studies that deny any particular role of HIV itself on HCC development. In large retrospective study by Giordano et al[27], it has been shown that HCC rate among HIV mono-infected patients is similar to that in the general population.

Despite the missing demonstration tha HIV itself might be the cause for HCC, it has been demonstratated that the progression of HCV- and HBV-liver disease to cirrhosis and HCC could be accelerate by HIV. In fact, the co-infection with HIV alters the natural history of HCV increasing the probability of chronicity (over 90%) because the significant lack of CD4+ T-cell responses against HCV[65,66]. Moreover, in the HIV setting, when the chronic HCV infection is established, the liver disease progression results more rapid, ensuing a higher incidence of cirrhosis and its complications, than in patients with only HCV infection[67-70]. The molecular mechanisms of accelerated fibrosis in co-infected patients are yet to be understood. Bruno et al[71], studied the HIV-gp120 capability to exert multiple effects on human hepatic stellate cells (HSCs), modulating their phenotype in a profibrogenic way. Incubation of HSCs with gp120 significantly increased HSCs migration and expression of proinflammatory cytokines, as well as monocyte chemoattractant protein-1 (MCP-1) and type 1 procollagen. Recent data suggest that HIV gp-120 binding to CXCR4 receptor, expressed on the surface of hepatocytes and HSCs, is able to upregulate tumor necrosis factor (TNF)-related apoptosis, inducing ligand (TRAIL) R2 expression. Results indicated that HIV infection makes hepatocytes more susceptible to liver injury[72]. During HIV co-infection, the hepatotoxicity of antiretroviral drugs and immune reconstitution syndrome may also indirectly increase the liver damage[32].

Further prospective studies are recommended to further evaluate the role of HIV in co-infected subjects with HCC. It would be necessary to avoid common bias, quite frequent in some of the quoted retrospective cohort studies. For example, the prevalence of HCV-HBV-HIV co-infections could be underestimated because not all HCV-HBV patients have been tested for HIV. Furthermore, time of viral hepatitis infection is often unknown, making it difficult to correlate HCC rates to mono- or co-infection. In fact, patients with isolated HCV or HBV may just have acquired infection earlier than co-infected patients and this different period of exposure to viral insult may obviously influence HCC incidence. Considering these evaluations, an ideal prospective study should include cross-testing for co-infections before individual allocation to groups, standardized screening for HCC and regular evaluation of HIV viral load in the co-infected cohort, in order to evaluate the potential effect of HAART-induced viral suppression on HCC pathogenesis.

Clinical characteristics

HCC is generally asymptomatic during its initial stage, then, in more advanced phases, hepatomegaly, jaundice and abdominal pain may appear. However, HCC clinical presentation and prognosis vary considerably according to the number and size of tumoral lesions.

Liver cancer may appear either as a single nodular or infiltrating lesion with an eccentric growth or as a multinodular widespread tumor *abinitio*. In some patients HCC lesions have a slow growth rate, with a two-fold increase in 20 months, in other cases it could double in less than one month[73-75]. Multinodular HCC is more common in patients with more than one risk factor[76] and is classified in primitive multicentric HCC or metastatic cancer from a primitive HCC. This distinction has important clinical implications because primitive multicentric HCC are less aggressive and recur less frequently after ablation than metastatic cancers from a primitive HCC[77,78]. Among HIV positive patients cumulative clinical data suggest a more aggressive course of HCC[79-81]. Data from the HIV-HCC Italo-Spanish Group[82] showed a more advanced and infiltrating HCC (also with extranodal metastases), a more advanced stage of cirrhosis at presentation and a reduced survival rate in HIV-positive patients compared with the general population. A 2007 US-Canadian multicenter retrospective study[83] identified 63 HIV-infected patients affected by HCC from 1992 to 2005 and compared them to 226 HIV-negative HCC controls. The HIV positive group was younger and more frequently symptomatic than controls and showed higher median alfa-fetoprotein levels. In contrast with other studies, in this case tumor staging and survival were similar between cases and controls. In untreated HCC cases, the presence of undetectable HIV-RNA was an independent predictor of a better survival. In a recent, large, multicenter, observational study, Berretta et al[84] confirmed HIV-positive HCC subjects to be younger and to have a shorter survival time after treatment than HIV-negative patients.

HCC: Treatment options

The curative therapeutic strategies' for HCC in patients with HIV are often compromised because the advanced stage at presentation. Until a few years ago, HIV infection was an exclusion criteria for liver transplantation. The main concerns were the risk of HIV progression after orthoptic liver transplantation (OLT), a poor post-transplantation prognosis and eventually a waste of graft[85]. In 2003, Ettorre et al[86] demonstrated that about 50% of HIV-positive patients with HCC were not suitable for surgical treatment and only 28% of these patients were more likely to receive a successful surgical treatment.

Later, the GICAT cohort reported on a series of 41 HIV positive patients affected by HCC, 15 (35%) of whom fulfilled the Milan criteria and could potentially be treated with OLT as a curative intent. Despite these results, none of them received liver transplantation and only two underwent surgical resection resulting in a 2-year survival of 41% in treated patients and 0% in untreated cases[36].

The introduction of HAART has significantly changed the outcome of HIV infection, increasing patients' long-term survival. Liver transplantation should then be taken in consideration in the treatment of HCC. Many studies have proved that the majority of HIV positive transplanted patients have a good long-term survival[85,87]. A 2008 report of Di Benedetto et al[85] has shown a series of 7 HIV positive patients with HCC and fulfilling the Milan criteria, who have received OLT. After a mean follow up of 232 days, the overall survival rate was 85.7%; only one patient died of a myocardial infarction with a functioning graft and no HCC recurrence. Radecke et al[88] reported that out of 5 cases of OLT in HIV-infected cirrhotic subjects. In this study, 2 patients achieved stable liver function and non-progressive HIV infection under HAART, 61 and 23 months after OLT, respectively; unfortunately, three out of five patients died because of graft failure.

The liver post-transplant clinical management in the HIV-positive setting is definitely more complex than in the general population. These patients report an earlier and more aggressive HCV recurrence (about 33% of patients)[89], fast occurrence of hepatic fibrosis, a higher rate of rejection (from 33% to 38%)[85,87-90] and a greater incidence of tacrolimus toxicity[91].

The outcome of HIV-positive liver recipients depends on the immunological status of the patient at the time of OLT[92]. A full virological control of the underlying HIV infection before OLT is considered necessary; in fact, the clinical course of HIV-positive patients transplanted patients with higher CD4+ cell count and undetectable HIV viral load is similar to that of HIV negative recipients. Di Benedetto et al proposed some criteria to select HIV positive patients with HCC eligible to OLT: the completely fulfill of the Milan criteria is mandatory, patients should also have an undetectable HIV viral load (< 50 copies/mL) and a CD4+ cell count greater than 200/mmc. After OLT, HAART needs to be reinstituted as soon as clinically possible according to the opinion of a multidisciplinary transplant team (surgeons, infectivologists and oncologists) with great experience in the management of pharmacologic interactions between HAART and immunosuppressive agents (see also Table I). In conclusion, OLT

Table 1. Criteria for considering liver transplantation in HIV-patients (according to Di Benedetto 2008 and O'Grady 2005).

Liver disease criteria
- Child-Turcotte-Pugh socre ≥B7; MELD score ≥14

*Milan criteria:**
- No more than 3 tumor nodules
- No nodule greater than 5 cm in diameter
- Absence of macroscopi portal vein invasion
- Absence in recognizable extrahepatic disease

HIV infection criteria

Immunological criteria
- None of AIDS-defining opportunistic infections in the previous year
- CD4 cell count >200 cells/μL or >100/μL in case of therapy intolerance

Virological criteria
- Undetectable HIV viral load (<50 copies/mL) in the last 12 months or effective therapeutic options for HIV infection during the post-transplant period

General criteria
- Favourable psychiatric evaluation
- Social stability
- N alcohol abuse for at least six months
- No drug consumption for at least two years (patients who are on stable methadone maintenance programmes can be included and can continue on the maintenance programmes after the procedure)
- No extrahepatic malignancy
- No pregnancy

**Patients with HCC who are being considered for liver transplantation should no have a needle biopsy due to the significant rate of needle-track seeding leading to post-transplant recurrence.*

should be considered as an opportunity for patients with HIV and HCC: even if accurate selection protocols are mandatory, with regards to HIV status and HCC stage, now the key question is not "if" but "who" should be referred to liver transplantation.

Medical treatment

Two large phase III trials, although restricted to patients with well-preserved liver function (Child-Pugh class A/B) and with no HIV infection, have shown the effectiveness of orally active multikinase inhibitor sorafenib in improving the median OS and TTP in patients with unresectable HCC[93,94]. Sorafenib has considerably changed the treatment and prognosis of unresectable HCC, offering a therapeutic opportunity for some patients, for whom no effective treatment had been available. Despite the emerging role of HCC as a major cause of morbidity and mortality in HIV-infected patients, no large pivotal trials have been reported the safety and efficacy of sorafenib in this particular setting, which is often discriminated against in clinical trials or for standard oncologic treatment, solely because of their HIV infection.

In the past few years, four case reports have described the safety and efficacy of sorafenib in HIV-infected patients, but they are merely anecdotal[95-98]. The Italian Cooperative Group on AIDS and Tumors (GICAT) has reported on the safety and efficacy of sorafenib in HIV-infected patients with unresectable HCC. In this study, the patient population included patients with Child-Pugh class A-C cirrhosis, BCLC tumor stage B-D, and receiving HAART concomitantly. Despite this study being the first of its kind, and therefore potentially useful, its retrospective nature is a limiting factor, which should be considered if outcomes are to be compared with the prospective trials above mentioned[93,94]. The analysis of the intention-to-treat group showed a median OS of 12.8 months. A subgroup analysis with respect to Child-Pugh class, BCLC stage, and CDC stage showed a tendency toward improved survival only according to the BCLC stage (Figures 1-3). Indeed, for patients with BCLC stage A-B or C-D, the median TTP were 8.7 and 2.1 months, respectively, and the median OS were 14.7 and 5.6 months, respectively. These data suggest that in sorefenib-treated patients with unresectable HCC, HIV infection, and a good viroimmunological profile, survival outcomes depend on the BCLC tumor stage, which is also the determining factor for survival in the general patient population. The evidence supports the suggestion that, to date, because of the use of HAART and its beneficial effects on viroimmunological profile, HIV-positive patients with HCC should be considered

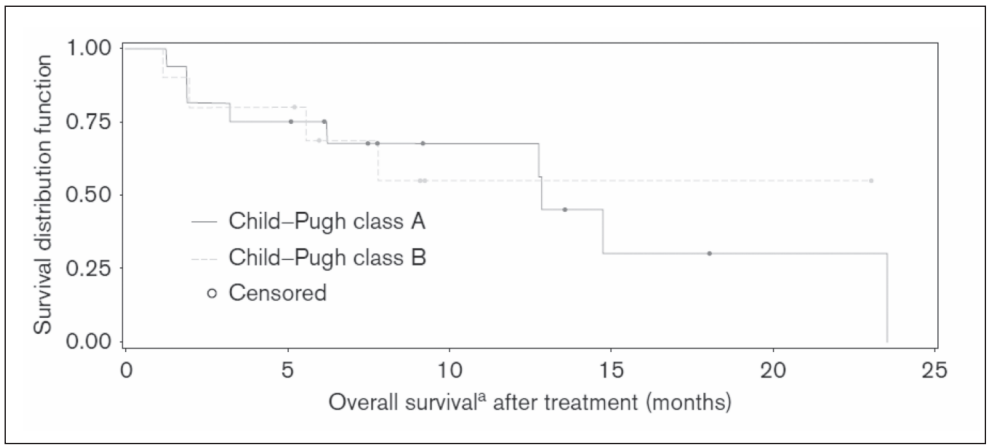

Figure 1. Kaplan-Meier curves representing overall survival after the start of treatment according to the Child-Pugh classification [A (N=16) and B (N=10)]. [a]Wilcoxon's test indicates no significant difference between groups.

similar to the general population. In fact, no significant differences in TTP and OS were found between patient groups with different severities of liver dysfunction (according to the Child-Pugh classification) or between patient groups with different severities of HIV infection (according to the CDC staging of the disease).

Conclusions

The management of HCC in HIV-positive patients lack of universally approved guidelines[23,24,39,99]. Recent data have demonstrated that there are no differences in the outcome of HIV-infected and HIV-uninfected patients in terms of HCC response to the available therapy; different therapeutic strategies for HCC in the HIV setting should be advocated in order to integrate HIV and HCC treatments. HCC therapeutic trials specifically designed for HIV-infected patients are also necessary. Early diagnosis of HCC and retreatment for HCC recurrence have a key role in the survival of patients, therefore, regular screening programs for HCC should be extended to HIV-infected patients according to proposed guidelines[23,39,99-102], together with a greater proclivity for treatment and retreatment options in cases of an HCC diagnosis or recurrence. This may be an important and needed breakthrough for this rising problem.

HCC IN ELDERLY PATIENTS

Management of malignant disease in the elderly has become a global clinical issue, due to the increase of life expectancy in many countries[103]. In the past years, many elderly patients have been

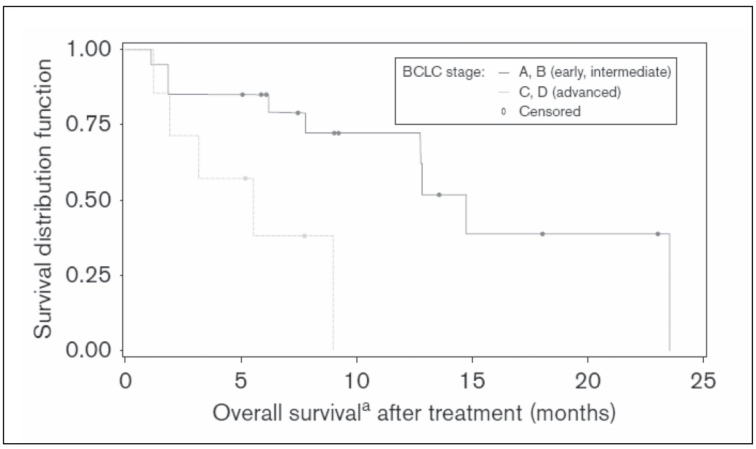

Figure 2. Kaplan-Meier curves representing survival after the start of treatment according to Barcelona Liver Clinic Cancer (BCLC) staging [A or B (N=20) and C or D (N=7)]. [a]Wilcoxon's test (p=0.04) indicates a significant difference between groups.

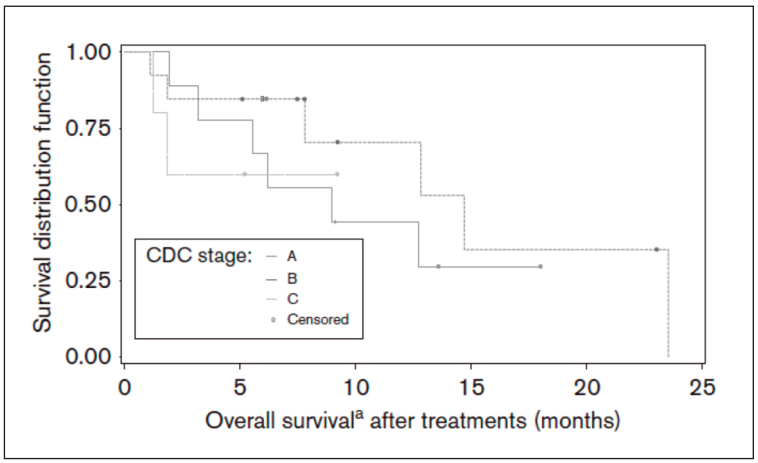

Figure 3. Kaplan-Meier curves representing survival after the start of treatment for Centers for Disease Control and Prevention (CDC) staging of HIV infection [A (N=9), B (N=13), and C (N=5)]. [a]Wilcoxon's test indicates no significant difference between groups.

considered less effectively responsive to treatments compared to younger patients, due to their lifetime addition of different illnesses[104-106]. This hypothesis has been reviewed by some studies and the need for a careful selection of patients has been strengthened, thus implying the possibility to offer elderly patients the same treatment options than younger ones with acceptable results[107-110]. Accordingly, OLT in the old age has now been reconsidered by some authors, even if it was once banned to elderly patients because of ethical reasons and for lack of available organs, rising different debates if consider it as a therapeutic option for elderly patients[111-113]. Of great importance is to define who is old. A person chronological age is scarcely correlated to physiological age, but it may be used as a frame of reference. The age of 70 years is the threshold for this analysis; in fact, many studies have described the 70 years of age landmark as the lower limit after which physiological senescence, the incidence of organ dysfunction and the development of co-morbidities begin to increase[114,115]. Co-morbidities should be assesed when describing elderly patients; however, there is some controversy about how to define it and to stratify the risk of death secondary to the number and the severity of associated conditions[116,117]. The World Health Organization-Eastern Cooperative Oncology Group Performance Status (PS)[118,119], the Charlson's scale[120], and the Cumulative Illness Rating Scale-Geriatrics (CIRS-G)[121], are some of the co-morbidity scales that have been proposed in order to achieve a co-morbidity index to quantify the risk of death in each case.

Several reports have outlined significant differences in the cohort of aged patients with HCC. Elderly patients are less frequently HBsAg positive and more often anti-HCV positive[114,122-124]. Some authors suggest a changing pattern of male/female ratio, reporting a high frequency of old female patients with HCC[114,124,125], and it is recognized that the peak age for women is postponed by 5 years compared to men[121]. However, there is some disagreement among authors[122,123]. This could be explained in younger males with an earlier viral infection due to behavioral risk factors; alcohol abuse may increase the incidence of HCC in males earlier than in females[114,125]. It is also important to mention the impact of non-alcoholic steatohepatitis (NASH) as a risk for HCC onset in elderly patients. The phenomenon of hepatic steatosis and non-alcoholic fatty liver disease (NAFLD) has been recognized as a part of the metabolic syndrome. It is associated with obesity, dyslipidemia, hypertension, sleep apnea, and diabetes mellitus type 2[126-129]. The visceral fat accumulation recurrent in patients with NAFLD/NASH is cause of insulin resistance and hyperinsulinemia that can accelerate hepatocarcinogenesis[130,131]. This event can have an import role in patients as they get older. Elderly NAFLD patients, especially with diabetes, should be therefore monitored carefully during follow-up screening for HCC[132].

Liver Resection

A debate on the safety use of hepatic resection for the treatment of HCC in the elderly patients has been raised in the past decades. Several authors[133,134] reported high morbidity and mortality rates especially after major hepatic resection in elderly patients compared to younger patients, discouraging the use of this procedure for these

patients. Instead, other authors described this treatment as safe and effective in both elderly and younger patients[104,135-137]. There is, therefore, a common misconception that all elderly patients are at high surgical risk only due to their advanced age, consequently a curative treatment has often been denied to them. Nowadays, the vast majority of authors do not consider age itself as a contraindication to surgical treatment anymore and a different approach has been developed in the management of these patients. The patient is considered in toto, with all his/her comorbidities, performance status and functional reserve. Thus both well-selected elderly patients and younger patients are often offered the same treatment options.

Huang et al[122] reported in 2009 the long-term outcomes and prognostic factors of elderly patients with HCC undergoing hepatectomy. The authors evaluated 67 HCC patients older than 70 years of age, compared with 268 younger patients as controls. More preoperative comorbidities ($p<0.001$) were found in the elderly, but no significant difference in the incidence of postoperative complications ($p=0.220$). In their experience the OS rates after hepatectomy at 1-, 3-, and 5-years were 83.3%, 54.6%, and 43.2% in the elderly group and 71.6%, 39.9%, and 31.4% in the control group, respectively. The disease-free survival (DFS) rates after hepatectomy at 1, 3, and 5 years were 66.8%, 57.7%, and 47.0% in the elderly group, and 65.2%, 40.8%, and 36.2% in the control group, respectively. The survival of the elderly group appeared to be better than that of the control group, but the difference was not significant ($p=0.157$). They also found, even if not statistically significant, a lower recurrence rate in the elderly group (55.3% *vs.* 63.5%); Interestingly, no differences were found in the kind of treatment after the recurrence in both groups (repeated hepatic resection, TACE, RFA, PEI, percutaneous microwave coagulation therapy, systemic chemotherapy, radiotherapy). Elderly patients were, in fact, fully included in a comprehensive approach for the treatment of HCC, regardless of their age. pTNM staging was the only independent prognostic factor for the postoperative survival of the elderly patients with HCC. Huang et al concluded that liver resection for HCC is safe in elderly patients without preoperative comorbidities or with well-controlled preoperative comorbidities.

In 2009 Kaibori et al[108] compared the results of hepatectomy for HCC in patients older than 70 years with the results of younger patients. These authors, as well as the previous ones, evidenced a higher incidence of associated diseases, but, in contrast, in their analysis the older group showed a better preoperative liver function. They also found no significant differences in DSF and OS between the younger and elderly groups. Interestingly in this study, alcohol abuse was identified as one of the independent prognostic indicators for DFS and OS in patients older than 70 years. In fact, the recurrence rate for elderly patients with a high alcohol intake was significantly higher than that of younger patients with alcohol abuse. Therefore, they concluded that, in particular for elderly patients with HCC, it is fundamental to stop drinking because preoperative alcohol abuse was a factor indicating a poor prognosis for DSF and OS after resection. They also reported a higher incidence of postoperative delirium in the elderly group. Some papers previously reported older age as a risk factor for postoperative delirium[137-139]. This may be due to a higher frailty and a reduced capacity of self-regulation in response to stresses like those imposed by surgery and anesthesia; furthermore, age related changes of pharmacodynamics and pharmacokinetics increase the side effects of drugs that can lead to postoperative delirium. The same data is deduced by Cho et al[140] who reported only confusion as an age-specific postoperative complication that was far more common in the elderly than the young. They investigated whether advanced age was associated with a higher rate and severity of postoperative complications after hepatic resection for primary and secondary liver malignancies, through a paired matched analysis. A total of 75 patients aged less than 70 years were compared to 75 patients older than 70 years. They found that advanced age led to longer hospital stay and more frequent discharge to a rehabilitation institution. Thus it can be assumed that elderly patients need a more intense monitoring and greater nursing care and physical therapy, but that they can benefit from liver resection as much as younger individuals. It is important to inform elderly patients of the possibilities of their postoperative hospital course and prepare them for possible rehabilitation required after major liver resection. Nanashima et al[141] recently examined the features and survival of 188 HCC patients who underwent hepatectomy. They divided the patients into four groups according to age: young patients <50 years of age, patients between 50-69 years, patients between 70-79 and finally patients aged more than 80 years, thus giving an insight also of extremely old patients. The physiologic ability and surgical stress (E-PASS) score, including preoperative risk score (PRS), surgical stress score (SSS), and comprehensive risk score (CRS) were assessed[142]. They found a higher frequency of preoperative systemic complications in the elderly patients, particularly in the group of patients aged more

than 80 years of age. PS and American Society of anesthesiologists (ASA) score were also significantly increased in the elderly patients ($p<0.05$). The tumor recurrence and DFS rates were similar among the four groups. In line with the other studies they reported that comorbidity and lower general status were significantly higher in the elderly patients. They also found a higher rate of systemic postoperative complications in the elderly patients, in agreement with previous papers, even though the duration of hospitalization did not differ among the four groups. Thus they recorded age >70 and PRS >0.32 as significantly associated with post-operative complications; therefore they concluded that accurate follow-up and proper decision on treatment modality upon assessment of PRS are fundamental for these patients.

In 2009 Oishi et al analyzed 502 patients aged less than 75 versus 64 patients aged more than 75 undergoing hepatic resection. The incidence of cirrhosis in the older group was 31%, whereas that in the younger group was 52% ($p=0.03$). Preoperative laboratory tests also showed that the older group had better liver function than the younger group. On the other hand pathological features showed that the older group was characterized by a higher tumor burden in terms of size ($p=0.057$) and microscopic vascular invasion ($p=0.04$) compared to the younger group. Different studies have reported that elderly patients with HCC have a preserved liver function and a lower rate on liver cirrhosis[124,143]. It may be due to the precocious death of patients with cirrhosis and HCC before reaching the age of 70 years and that those who survive have a good hepatic function. In accordance with other authors they assert that hepatectomy in patients with good liver function is feasible, and that the prognosis after surgery for elderly patients is comparable to that for younger patients.

Similar results in terms of post-operative complications, DFS and OS were previously reported by Ferrero et al[107] and Kondo et al[144] respectively in 2005 and 2008. Both groups suggest that hepatic resection is justified for HCC in selected patients aged 70 years or older.

De Benedetto et al[145], from the Hepato-Biliary-Pancreatic Surgery and Liver Transplantation Unit, Italy, have evaluated 198 HCC patients between January 2001 and November 2010. The 68.2% (135/198) of patients has been younger than 70 years of age and 63 (31.8%) patients have been 70 years of age or older. The 42.9% of the younger group of patients (85 patients) have undergone liver resection compare to the 48 (24.5%) of the elderly group. On a pair-matched basis 48 patients aged over 70 have been compared to 48 younger ones, according to sex, etiology and stage of liver disease, tumor burden and infiltration of cut margin. OS and DFS in the two groups have been similar. The survival rates in the younger group have resulted, at 1, 3- and 5-years, 83.3%, 61.1% and 26.1%, respectively, in comparison with the 78%, 62.2% and 45.6% of the elderly group ($p=0.48$). DFS rates at 1-, 3- and 5-years have been 69.9%, 43.6% and 30.6%, respectively, in the younger group and 71%, 44.1% and 24.5% in the elderly group ($p=0.74$). The incidence of post-operative complications has been similar in both groups (37.5% vs 50%, $p=0.3$). As concerns Dindo's classification[146], similar minor procedures (grade 3) have been required by both groups. Furthermore, a significant reduction in performance status calculated using the classification of Karnofsky[147] has been found in the senior patients' group, compared to the younger group (respectively 71±8% *vs.* 74±7% $p=0.013$). In the elderly group, the ECOG PS score appeared worse than the younger group, although not statistically significant. These data have confirmed that well selected older-patients can safely undergo hepatic resection with satisfactory results[148].

Ablative Treatments

The differences in features and outcomes after ablative treatments between elderly and young patientshave been treated in few papers[149-155], and most of them are mainly focused on radiofrequency ablation (RFA).

RFA presents excellent results in tumors ≤2cm (90-100% complete necrosis)[156], but for bigger nodules the probability of achieving a complete necrosis is higher when combined or repeated treatments are performed. Currently, RFA is considered the best loco-regional treatment, but it has some limitations. Some contraindications may arise when considering the possible procedure-related damage when tumors are located close to other organs (kidney, colon, or gallbladder). Moreover, the treatment may also not been effective when the lesions are nearby large vessels thus they may not be completely ablated due to the heatsink effect[157].

Two studies evaluated the efficacy, the safety and the results of RFA in the elderly HCC population[148,151]. Different results were seen; while no difference in terms of cumulative OS and RFS after RFA comparing 107 patients older than 75 to 354 younger patients have been recorded by Takahashi et al suggesting that RFA should be used for elderly patients even in cases of comorbidity, Kao et al did not present encouraging results in the group of

elderly patients (158 *vs.* 100 patients aged more or less than 65). Noteworthy, Kao et al have found that, particularly for patients with very early stage of disease (tumor size of 2 cm or less or in BCLC stage 0), the younger group presented a significantly higher OS than the elder one due to their better liver functional reserve. If considering the low cut-off age (65 years) of this study, these findings are in contrast with other studies, maybe because the higher tumoral burden found in the elderly group.

Tateishi et al[149] have not shown any difference in the 3-year survival rate between patients aged over 68 years (76%) and under 68 years (79.2%) in 1,000 patients treated with RFA, even though a detailed analysis of specific risk factors on age has not been performed. The only paper describing the effect of age on the outcome after trans-arterial chemoembolization (TACE) is by Thornton RH et al[153] The authors have analyzed 200 patients aged more than 70 versus 168 younger patients undergoing TACE. The distribution and severity of complications have resulted similar between the two groups. Similarly to other reports, the elderly group had significantly more cardiovascular and cardiopulmonary comorbidities at baseline. Of great interest is that when these data have been adjusted for the presence of cardiovascular comorbidity, the association between age and the likelihood of a cardiopulmonary complication has lost significance, meaning that older patients without a cardiovascular comorbidity have had the same probabilities than younger patients to have from cardiopulmonary complication, whereas an older patient with such a comorbidity has been more likely to suffer a cardiopulmonary complication. In this series, other measurements of morbidity, including severity of complications, need for intensive care unit admission, and length of hospitalization, have been not different between the younger and older groups.

Liver Transplantation

An interesting matter of debate is whether elderly HCC patients deserve OLT, and the current shortage of available organs makes the question even harder to solve. This is, however, nowadays more an ethical issue, it regards a very small percentage in the worldwide casuistry. Schwartz et al[110] in 2012 examined the post-transplant overall survival of elderly HCC patients (aged 70 years or old) versus younger patients. In this study 6,320 liver transplants were analyzed, 143 were 70 years old or older (42% of whom were affected by HCC). Thus, as also noted by Perkins[111], this issue concerns a very small percentage of patients, only 0.91% of the population in Schwartz's study. All the same time these results cannot be underestimated and some considerations are also needed. As reported by Schwartz et al, in the group of older recipients, a decreased OS after OLT has been observed, with an actuarial survival rate of 54.5%. Therefore, even though the OS rates in elderly patients with HCC are fare more poorly after OLT in comparison with younger patients, the results have been comparable to the rates associated with other indications for transplantation in this age group, regardless of the HCC diagnosis. In particular, the difference in survival appeared after 18 months and became accentuated 5 years after OLT when the difference between the older and younger groups was almost 15%. They sadly concluded that OLT in older patients should not be supported, even though the presence of HCC does not affect the post-OLT outcome as compared to OLT for other indications. It is of interest to reflect on the elegant comment of Perkins [111] on this matter, he asserts that patients with adequate functional liver reserve (mainly Child-Pugh status A or even B patients), with a resectable tumor, should undergo liver surgery or otherwise ablative treatments sparing the patients from the possibility of early mortality, pain, discomfort and various liver transplant complications, with an extreme gap in terms of cost-effectiveness and sparing of organs. An open debate concerns decompensated cirrhotic patients with HCC who are amenable to neither resection nor locoregional treatments. In a particular age when disparity between demand and available organs keeps on growing, it is important to wonder how to streamline the actual resources.

Targeted Treatments

Generally, elderly patients with HCC are less intensively investigated and more conservatively treated despite similar tumor stages at diagnosis, leading to significantly worse survival outcomes[158]. On the other hand, HCC in elderly patients may have a more favorable tumor biology than in younger patients. A study on hepatitis C infection-related HCC patients demonstrated that, overall, elderly patients presented with more favorable tumor characteristics and had better overall prognosis[159]. In the literature, data on the optima management of HCC in elderly patients is rare. In fact, Although age did not seem to influence treatment options or preclude patients from treatment[160,161], most studies included heterogeneous cohorts with variable underlying liver function and tumor stages. Most of these studies were also performed prior to the era of sorafenib, which is now the recommended treatment for advanced HCC[162].

Sorafenib, a bi-aryl urea[163], is a small molecular inhibitor of several Tyrosine protein kinases (VEGFR and PDGFR) and Raf kinases (more avidly C-Raf than B-Raf)[164,165]. It inhibits tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models[166].

Protein kinases are overactive in many of the molecular pathways that cause cells to become cancerous. These pathways include Raf kinase, PDGF (platelet-derived growth factor), VEGF receptor 2 and 3 kinases and c Kit the receptor for Stem cell factor.

Cellular signaling that is mediated by Raf-1 and vascular endothelial growth factor (VEGF) pathways has been implicated in the molecular pathogenesis of HCC[165-168], providing a rationale for investigating sorafenib for this indication. In the phase III registrative SHARP trial[93], the median age of treated patients was 64.9 years and thus it is difficult to draw further considerations on this treatment in elderly patients.

The first report on the outcome and safety of the use of sorafenib in elderly patients affected by advanced HCC is by Wong et al[161] Analysing the 35 older patients treated with sorafenib they concluded that the "the survival benefits and overall treatment-related adverse events of sorafenib are comparable in elderly and younger advanced HCC patients".

This was the first paper reporting, even if within a limited series of data, the feasibility of this approach in elderly patients.

Conclusions

A multidisciplinary approach shoud be taken when assessing elderly patients with HCC; stage of HCC and liver disease should be taken into account and regardless of the chronological age, the best treatment should be offered. Comorbidities have to be clearly defined, and when possible, the functional reserve of the patient should be known.

Liver resection and ablative treatments should never be denied to these patients only because of their advanced age, and curative procedures should be performed in tertiary hepato-biliarypancreatic Centers.

Each elderly HCC patient has to be evaluated singularly, stratifying each time the risk for the procedure so as to determine which is the best treatment, analyzing all the possibilities that can be offered. This similar approach showed a good efficacy and safety in another "frail" patients category with HCC and HIVinfection[84,85,87,90,92,94,169-171].

A consideration can be made from this review of the literature, the vast majority of the patients studied in the papers analyzed derive from a group of already selected patients, thus no clear data can be obtained about those patients considered not eligible for curative treatment because of their comorbidities or medical unfit status; in the forthcoming years physicians should aim to understand which are the critical points and the boundaries beyond which the risk of an operative procedure becomes too high for these patients. Furthermore, the applicability, the safety and the outcome after aggressive treatments in patients with advanced HCC, such as portal vein embolization, prior extended hepatectomies, combined locoregional treatments and/or chemotherapy protocols, should be assessed; in a constantly aging society it appears to be necessary.

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