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Non-AIDS-defining cancers among HIV-infected people

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Abstract. – The natural history of HIV infection has been greatly changed by the introduction of highly active antiretroviral therapy (HAART). As a consequence of improved immune function, the incidence of AIDS-defining cancers (ADCs), such as Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, has significantly declined. On the contrary, non-AIDS-defining cancers (NADCs), such as hepatocellular carcinoma, anal cancer, lung cancer, colorectal cancer and Hodgkin's lymphoma, have gradually emerged as a major fraction of the overall cancer burden. The reasons are still partially unknown. Some of the increased risk may be explained by a high prevalence of cancer risk factors, such as smoking, alcohol consumption, human papilloma virus (HPV) infection and HCV infection among HIV-infected people. The role of immunosuppression in the development of NADCs is controversial, as several studies have not found a clear-cut evidence of an association between the degree of immunosuppression and the development of NADCs. Analogously, the impact of HAART is still not well defined.

Future research should focus on the etiology of NADCs, in order to shed light on the pathogenesis of cancer and ultimately to work for prevention; moreover, additional studies should evaluate the best therapeutic approaches to NADCs and the impact of cancer screening interventions among HIV-infected people, in an effort to diagnose cancer at an earlier stage.

Key Words:
Anal cancer, Colorectal cancer, HAART, HCC, HIV, Hodgkin's lymphoma, Lung cancer, NADCs.

Introduction

The natural history of HIV infection has been greatly changed by the introduction of highly active antiretroviral therapy (HAART)[1-4]. HIV-infected people have experienced a significant improvement in immunity and increase in life expectancy[5-10]. However, patients taking otherwise effective antiretroviral drugs remain at increased risk of non-AIDS-related mortality and morbidity, including cardiovascular disease, neurocognitive disease, neuroendocrine dysfunctions and cancer[11-14]. Furthermore, HAART cannot eradicate HIV infection[15-20]. Nevertheless, recent advances in our understanding of molecular and cellular mechanisms regulating HIV-host interplay and HIV escape strategies may help finding new therapeutic targets[21-25].

As a consequence of improved immune function, the incidence of AIDS-defining cancers (ADCs), such as Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, has significantly declined[26-29]. On the contrary, non-AIDS-defining cancers (NADCs) have gradually emerged as a major fraction of the overall cancer burden[30]. These NADCs include hepatocellular carcinoma, anal cancer, lung cancer, colorectal cancer and Hodgkin's lymphoma[31-35].

It is known that cancer risk is higher in HIV-infected people compared to the general population[30], but the reasons are still partially unknown. Some of the increased risk may be explained by a high prevalence of cancer risk factors, such as smoking, alcohol consumption, human papilloma virus (HPV) infection and HCV infection among HIV-infected people[36]. The role of immunosuppression in the development of NADCs is controversial: Patel et al[37], for instance, found that the risk of developing colorectal cancer was significantly increased in the presence of a low nadir CD4 cell count; on the contrary, in other papers no association between the degree of immunosuppression and the development of NADCs has been described[38,39]. The use of HAART was associated with lower rates of NADCs in a study by

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Burgi et al[40], whereas the standardized incidence ratio (SIR) for NADCs was reported not to be decreased in the post-HAART era among patients enrolled in the Swiss cohort study[41].

Here we briefly review the epidemiology, risk factors, therapeutic and preventive approach to several NADCs among HIV-infected people.

Lung Cancer

Lung cancer represents the most frequently occurring NADC in HIV-infected people[30,38]. Several studies have shown increased rates of lung cancer in HIV-infected patients as compared with uninfected patients. In a recent meta-analysis of seven studies, globally considering 44,172 people with HIV/AIDS, of whom 1,297 diagnosed with lung cancer, Grulich et al[42] estimated an overall HIV-associated lung cancer risk of 2.7 (95% Confidence Interval (CI) 1.9-3.9). Analogously, the risk for lung cancer associated with HIV infection was estimated to be increased 2.6-fold (95% CI 2.1-3.1) in another meta-analysis of Shields et al[43]. The risk of lung cancer in the setting of HIV infection is elevated for all major lung cancer subtypes (adenocarcinoma, squamous cell carcinoma and small cell carcinoma) and has not been significantly modified by the introduction of HAART: Engels et al[30] reported that the relative risk (RR) of lung cancer occurring during the pre-HAART era (2.5 (95% CI 1.9-3.3)) was similar to that described in the early (3.3 (95% CI 2.9-3.8)) and recent HAART era (2.6 (95% CI 2.1-3.1)).

Considering that smoking is the major etiologic agent of lung cancer, heavier smoking exposure has been considered as the main explanation for higher rates of lung cancer observed in the setting of HIV. In fact, among HIV-infected individuals smoking rates range from 35% to 70%, compared to approximately 20% in the general US population[44,45]. However, HIV infection has been associated with increased lung cancer incidence even after controlling for smoking history data[30,33,46-49]. Several cohort studies were variously affected by important limitations, including lack of complete smoking data, use of estimated smoking rates only, small numbers of lung cancer cases and lack of an uninfected comparison group. In a large, multicenter, cohort study, Sigel et al[48] found that HIV infection was an independent risk factor for lung cancer: the incidence rate of lung cancer was 204/100,000 person-years (95% CI 167-249) in HIV-infected patients and 119/100,000 person-years (95% CI 110-129) among uninfected patients; the incidence rate ratio (IRR) of lung cancer associated with HIV infection remained significant even after multivariable adjustment for major confounders, including smoking and age (IRR 1.7; 95% CI 1.5-1.9).

Although HIV infection is not thought to have a direct role in the promotion of lung cancer[50], it has been hypothesized that HIV-induced inflammation in the lung may predispose to smoking-related lung damage[38]. In addition, lung cancer in HIV-infected people has been associated with a history of AIDS-related pulmonary diseases[49,51]. Sigel et al[48] found that lung cancer was 1.5-fold higher following a diagnosis of bacterial pneumonia, but not following diagnosis of tuberculosis or Pneumocystis *jirovecii* pneumonia.

In some large cohorts of HIV-infected people, an association between declining CD4 cell count and lung cancer risk has been found[37,52,53]. In a French cohort with more than 52,000 HIV-positive individuals[52], a RR of 2.2 (95% CI 1.3-3.6) for lung cancer has been reported in patients with current CD4 cell count between 350 and 500 cells/ l and 8.5 (95% CI 4.3-16.7) in patients with current CD4 counts <50 cells/ l, when compared to HIV-positive patients with current CD4 cell count >500 cells/ l. Nevertheless, other studies have failed to detect any link between CD4 cell count and lung cancer risk[46,48,54,55]. Clifford et al[54]. found that none of the classic markers of HIV-related immunodeficiency, including low CD4 cell count, high HIV viral load, history of AIDS or AIDS-related pulmonary disease, was clearly association with lung cancer in the Swiss HIV Cohort Study, thus ruling out a significant effect of HIV-related immunodeficiency on lung cancer risk in this population.

Surveillance bias might result in a higher rate of lung cancer detected in HIV-infected individuals, who generally tend to have more contact with the healthcare system than uninfected individuals[56]. However, the observation that the majority of HIV patients present with locally advanced or metastatic disease suggests delayed cancer diagnosis, as a possible consequence of low clinical suspicion for malignancy and over-reliance on nondiagnostic chest radiographs[57]. On the basis of these data, even if surgery with curative intent remains the treatment of choice for localized disease, it may be attempted only in a minor part of patients (14% of cases in a study of Brock et al.), being its feasibility conditioned by tumor stage and performance status (PS).

Retrospective studies conducted in the pre- and early HAART era described shorter survival among HIV-positive lung cancer patients as compared with HIV-negative or indeterminate lung cancer ones (24-month survival 10% *vs* 34%)[58], whereas the most recent studies demonstrated similar survival rates[59]. Few data are available on the use of systemic chemotherapy for patients with HIV and lung cancer. Prospective studies are needed to evaluate the interplay between HAART and chemotherapy and to establish if treatment regimens usually employed for HIV negative subjects may represent a safe and effective therapeutic option also for HIV-positive patients with adequate CD4 cell count and suppressed HIV viral load. The Intergroupe Francophone de Cancerologie Thoracique has recently initiated a phase II[60], multicenter, non-randomized, open-label study evaluating the combination of pemetrexed plus carboplatin in HIV-positive patients with lung cancer (NCT01296113).

Given the lack of effective screening options and the improved life expectancy of HIV patients in the HAART era, lung cancer is expected to represent an increasingly important cause of death in the setting of HIV infection. Lung cancer prevention should be based on targeted education for smoking cessation, as the beneficial effects of quitting smoking among HIV-infected people appear comparable to those reported in the general population[61]. In a subgroup of patients belonging to the Swiss HIV cohort study, nicotine replacement therapy and counseling sessions have been associated with a significantly higher rate of self-reported smoking abstinence in comparison with the control group (38% *vs* 7%, odds ratio (OR) 6.2, 95% CI 2.8-14.3)[62]. In an interesting randomized trial, Vidrine et al[63] evaluated the efficacy of a proactive cellular telephone intervention for HIV-positive smokers: 95 active smokers were randomized to receive a "traditional" motivational intervention on smoking cessation (brief physician advice to quit smoking, targeted self-help written materials and nicotine replacement therapy) or a cellular telephone intervention, consisting of eight counseling sessions delivered via telephone, in addition to usual care components. The Authors found that participants who received the phone intervention were 3.6 times (95% CI 1.3-9.9) more likely to quit smoking compared with those receiving usual care; moreover, the point prevalence of abstinence rate was 10% for the usual care group and 37% for the cellular telephone group at 3-month follow up.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the commonest primary cancer of the liver, whose incidence is estimated to be about 500,000-10,000,000 per year worldwide[64]. HCC usually occurs in people with advanced liver disease, which is largely associated with alcohol abuse or coinfection with HCV and/or HBV. In HIV-positive subjects, the risk to develop HCC has been suggested to be six-sevenfold higher than the general population[65]. This may be partially explained by the higher rate of chronic viral hepatitis found among HIV-positive people. As for the impact of HIV itself on liver tumorigenesis, studies performed in mice have reported a potential oncogenic role for HIV Tat gene[66]. However, in humans there is no evidence for a direct role of HIV on HCC development: in a large retrospective study, Giordano et al[67] showed that HCC rates were not higher in HIV mono-infected patients than in general population; in a retrospective cohort study on US veterans, HIV positive people were reported to have a higher risk to develop HCC than HIV negative ones, but HIV status was not independently associated with cancer after adjusting for HCV and alcohol abuse. Anyway, HIV-induced immunosuppression may accelerate liver fibrosis and exacerbate the risk to develop HCC[68]. gp120 may modulate human hepatic stellate cells (HSCs) phenotype in a profibrogenic way and upregulate tumor necrosis factor (TNF)-related pathways, making hepatocytes more susceptible to apoptosis[69]. In contrast with potential indirect effects on HCC risk through improvement in immune reconstitution and survival, HAART is known to have some direct hepatotoxic effects, especially among HIV-infected patients chronically infected with HBV or HCV[70].

In addition to the elevated risk for developing HCC, individuals with HIV infection may have higher HCC-related morbidity and mortality. Some studies have shown that HCC is more aggressive (infiltrating or metastatic) among HIV/HCV coinfected patients and associated with shorter survival time than HIV negative patients[71-74].

In a recent, large, multicenter cohort study, Berretta et al[73] compared 104 HIV-infected and 484 uninfected patients, evaluating HCC tumor characteristics, therapeutic approaches, patient survival time from HCC diagnosis and clinical prognostic predictors. The Authors found that HIV-positive patients were significantly younger than uninfected ones at HCC diagnosis and were coinfected with HBC or HCV in the great major-

ity of cases. CD4 cell count at diagnosis was not independently associated with survival; on the contrary, patients receiving HAART and with undetectable HIV RNA at diagnosis had a better prognosis than untreated subjects or subjects with higher HIV viral load. Of interest, even though in HIV-infected patients HCC was diagnosed mostly at an early stage (66% at Barcelona Clinic Liver Cancer (BCLC) stage A or B) and then amenable for potentially curative approaches, the median survival time was significantly shorter than that observed in the HIV-negative counterpart (35 *vs* 59 months). A more aggressive biological behavior for HCC in the setting of HIV infection may be advocated as a potential explanation, but it should be taken into account that these data may be significantly biased by the difficulty to accurately define when HBV or HCV infection was acquired.

HCC treatment is usually classified as curative or palliative[31]. Curative treatments are represented by surgical resection, orthotopic liver transplantation (OLT) and local ablative therapies, including percutaneous ethanol injection (PEI)/radiofrequency ablation (RFA) and RFA combined with transarterial chemoembolization (TACE)[75-78]. Palliative treatments include systemic chemotherapy and biological drugs (i.e., sorafenib)[79]. In contrast with previous studies[65,67,71,74], showing that HIV-patients with HCC were often untreated or inadequately treated, in the aforementioned study of Berretta et al[73] HCC treatment rates were similar in the HIV-infected and uninfected subgroup, but the overall survival outcome was significantly worse in the HIV-positive cohort. A possible explanation is the less aggressive therapeutic approach at recurrence observed among patients with HIV: in fact, despite the similar rate of recurrence and the better BCLC stage and PS score at diagnosis, HIV-infected patients were retreated in a significant lower number of cases (61 *vs* 86%, $p < 0.001$).

Prevention and early diagnosis are key points for the management of HCC, but, at present, there are no universal guidelines, especially when occurring in HIV-positive patients[31]. Primary prevention should promote alcohol avoidance and HBV vaccination; secondary prevention is based on the use of ultrasonography and alpha-fetoprotein (AFP) measurement every six months. New diagnostic tools, such as transient elastography, may help defining the features of chronic liver disease, even if they require further validation in the setting of chronic hepatitis-HIV coinfection[80-82]. Moreover, the opportunity to treat HCV or HBV coinfection should be adequately evaluated[83-88]. In addition, HCC trials specifically designed for HIV-positive subjects would be worthy to define the best approach to treatment and retreatment of HCC in the specific context of HIV infection.

Colorectal Cancer

Colorectal cancer (CRC) is the third leading cause of cancer death in the general population[89]. Considering that HIV is now a chronic disease, many patients are living long enough to develop CRC; however, few studies have evaluated the incidence of CRC in HIV-positive cohorts and the majority of them have excluded that the risk of CRC is increased among HIV infected people[90-92]. However, a major limitation is the lack of data regarding rates of CRC screening in the HIV population. In fact, Reinhold et al. found that HIV-positive patients were less likely to undergo any CRC screening examination (flexible sigmoidoscopy, fecal occult blood test, air contrast barium enema) than uninfected subjects[93]. As a consequence, reduced screening may have led to an underestimated incidence of CRC in the HIV population-based studies published so far.

Available data suggest that HIV-infected patients with CRC present with more advanced disease and at a younger age than individuals without HIV[91,94-98]. Berretta et al. have compared the clinical presentation and outcome of 27 HIV-positive patients and 54 age- and sex-matched controls with CRC, concluding that HIV-positive patients had a poorer PS, an unfavorable Dukes' stage, a higher grading and shorter survival than uninfected subjects[97]. Bini et al[98] have recently published the results of a screening colonoscopy study evaluating the prevalence of colonic neoplasms in 136 asymptomatic HIV-infected subjects >50 years of age and 272 asymptomatic uninfected controls, matched for age, sex and family history of CRC. Of interest, the authors found that the prevalence of neoplastic lesions was significantly higher in HIV-infected subjects than in control subjects, even after adjusting for potential confounding variables (OR 3 (95% CI 1.83-4.93)). In line with previous studies[91,95-97], HIV-positive subjects with CRC were significantly younger and were more likely to have advanced cancers (stage III or IV) than controls. No association between neoplastic lesions of the colon and either the duration of HIV infection, CD4 cell count or HIV viral load was found. In con-

trast, they reported that the use of HAART was associated with a significantly lower odd of colonic neoplasms. The reasons for these findings are unknown and require further investigation. In addition, the authors showed that among HIV-infected subjects with advanced neoplasms proximal to the splenic flexure, distal neoplastic lesions were absent in 88.9% of individuals in comparison with 33.3% of uninfected controls. These lesions would have been missed by flexible sigmoidoscopy, thus suggesting that colonoscopy may be superior to flexible sigmoidoscopy for CRC screening of subjects with HIV, even if larger prospective studies are needed to confirm these data[99-104].

Considering that CRC is especially amenable to screening, as premalignant adenomas exhibit a slow progression to malignancy and are often visibly identifiable and treatable via colonoscopy, future research should specifically address the issue of screening for HIV-infected subjects, in order to determine the appropriate age to start screening, the frequency of screening and the most cost-effective screening technique for this subgroup of subjects.

Hodgkin's Lymphoma

Hodgkin's lymphoma (HL) is one of the most common NADCs among HIV-infected people[33]; the RR of developing HL is estimated to be 15-fold higher in HIV-positive patients as compared to uninfected people and most HL cases are of the unfavorable mixed cellularity subtype, whereas in the general population the predominant subtype is the nodular sclerosis one[105]. Of note, HL risk has significantly increased during the HAART era[106,107]. Powles et al[107] reported that both the use of HAART (hazard ratio [HR] 1.64 (95% CI 1.13-2.39)) and a nadir CD4 count of less than 200/ L (HR 1.67 (95% CI 1.10-2.54)) were associated with an increased risk for HL. When evaluating the different classes of antiretroviral agents, the authors found that only non-nucleoside reverse transcriptase inhibitors were associated with a significant increase in the incidence of HL (HR 2.20). The relationship between HAART and HL, as well as immunosuppression and HL, is complex and still largely unclear. In HL the malignant cell is the Hodgkin Reed-Sternberg cell (HRS), a transformed B lymphocyte, reported to be almost always EBV positive in immunocompromised subjects[108]. Among HIV-infected subjects, the association between CD4 cell count and HL risk has a non-linear "inverted U" shape[105]. In fact, HL risk has been shown to increase with a decline in CD4 cell count to 225-249 cells/ l but then to fall again as the CD4 cell count declines further. This may be due to the fact that in the setting of severe immunosuppression the alteration of cellular microenvironment (inadequate growth signals, cytokinic responses) may inhibit the development of HL. On the other hand, HAART-induce immune reconstitution may provide a favorable environment for the proliferation of HRS, by increasing CD4 cell count and stimulating B cells, the target cells for EBV[109]. At the time of diagnosis, HIV-infected people present more frequently with extranodal disease (bone marrow, liver and spleen being the most frequent sites) than HIV uninfected individuals; the majority of them have "B" symptoms (i.e. fever, night sweats and/or weight loss of more than 10 % of the normal body weight). Considering that bone marrow involvement may be found in more than 50% of patients, bone marrow biopsy is mandatory for adequate staging[110-112].

The prognostic criteria for HIV-positive subjects are the same currently used for the general population (stage, bone marrow involvement, bulky disease, B symptoms and high erythrocyte sedimentation rate). It has been shown that survival for HL was better among HIV-infected patients responding to HAART, with an age of less than 45 years at the time of diagnosis and a complete remission (CR) status[113]. Similarly, in another study of 104 HIV-positive patients with HL receiving at least one course of chemotherapy, the authors found that the only variable independently associated with overall survival (OS) was the achievement of CR under adequate chemotherapy and HAART[114].

Currently, combined administration of HAART and chemotherapy regimens has significantly increased survival among HIV-infected subjects suffering from HL. In fact, HAART has been shown to reduce the risk of opportunistic infections and relapses. Xicoy et al[115] observed that the combination of HAART with standard ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy was associated with a CR rate of 87%, with a relapse rate of 11% after 6 to 8 cycles, in contrast with a CR rate of 43% observed in the pre-HAART era, when administering ABVD alone[116]. More intensive chemotherapy regimens include BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[117] and Stanford V

(mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone)[118] regimen. Another regimen, including epirubicin, bleomycin, vinorelbine, cyclophosphamide and prednisone (VEBEP), with radiotherapy and HAART, has been proposed by the Italian Cooperative Group on AIDS and Tumors (GICAT) for the treatment of HIV-positive patients with HL[119]. The authors demonstrated that VEBEP in combination with HAART was less toxic than the Stanford V regimen; CR was obtained in 76% of cases and OS at 30 months was 80%. In addition, supportive care (e.g. granulocyte colony-stimulating factor (G-CSF)) and anti-infectious prophylaxis (i.e. prophylaxis for Pneumocystis *jiroveci* and herpes simplex virus) should be associated with chemotherapy and HAART, in order to reduce hematological toxicity and the risk for opportunistic infections[115]. Limited options are available for patients with refractory or relapsed HL[120-123]. The association of high-dose chemotherapy and Autologous Stem-Cell Transplantation (AS-CT) has represented a successful salvage therapy for HIV-positive patients with relapsing or progressing HL[124,125], but future therapeutic trials are needed to establish which regimen may more favorably impact the quality of life and survival of this specific subgroup of patients.

Anal Cancer

Anal squamous cell carcinoma (ASCC) is an uncommon cancer in the general population, whereas it represents an important source of morbidity and mortality in HIV-infected subjects[34,126,127]. Two meta-analysis have established a 30-fold increased risk for anal cancer among HIV-positive people in comparison with the general population[42,43]. ASSC arises from precursor high-grade anal intraepithelial lesions (AIN) within the anal canal[128]. Infection with high-risk types of human papillomavirus (hr-HPV), especially HPV-16, causes more than 80% of cases of anal cancer. Due to sexual transmission of HPV through anal intercourse, the risk is particularly higher in HIV-infected men-who-have-sex-with-men (MSM) (46/100,000 per year *vs* 5/100,000 per year of HIV-negative men)[34].

The role of HIV-related immunosuppression in promoting development of anal cancer has been difficult to establish. On the one hand, low CD4 cell count has been associated with detection of anal HPV infection and precancerous lesions[129-131], possibly as a result of decreased clearance of HPV with immunosuppression. On the other hand, it has been shown that anal cancer incidence has significantly increased during the HAART era[30,37,127,132]. A possible explanation is that HIV-related immunosuppression may play a more important role during the earliest stages of anal carcinogenesis, such as HPV persistence and low-grade AIN, rather than the later progression to invasive cancer[133]. Therefore, if administered after the early steps of tumorigenesis, HAART would not significantly affect the course of disease. In addition, as for other NADCs, increased survival of at risk patients would allow the progression of early-stage neoplastic lesions to invasive cancer.

Screening interventions for anal cancer include anal Pap smear screening and high-resolution anoscopy (HRA), which may help detecting precancerous anal lesions that can be ablated with localized therapies (i.e. imiquimod)[134,135]. A recent study[136] has shown that among HIV-infected MSM, the highest anal cancer risk group, HRA may represent the most cost-effective screening modality, even though it is moderately invasive and it needs an experienced anoscopist to give reliable results. Testing for hr-HPV has a limited role, considering that the presence of hr-HPV has very high sensitivity but low specificity for high-grade AIN, because of high prevalence of hr-HPV carriage in HIV-infected people[137]. Vaccine for hr-HPV has been shown to be highly effective for prevention of anal cancer precursor lesions in women[138]; vaccination of boys or high-risk groups, such as MSM, may potentially be a cost-effective approach to prevent anal cancer, but it needs further evaluation in the setting of HIV[139-141].

Conclusions

In the HAART era, HIV-infected people are living longer and therefore are aging. Considering that the incidence of most malignancies increases with age, they have more opportunities to develop cancer. In addition to prolonged survival, the NADC epidemic may be significantly influenced by behavioral risk factors, such as intravenous drug use and smoking, and HAART.

Unfortunately, many questions regarding the relationship between HIV and NADCs are still left unanswered. Future research should focus on the etiology of NADCs, in order to shed light on the pathogenesis of cancer and ultimately to work for prevention; moreover, additional studies

should evaluate the best therapeutic approaches to NADCs and the impact of cancer screening interventions among HIV-infected people, in an effort to diagnose cancer at an earlier stage.

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