REVIEW PAPER

Non-AIDS defining malignancies among HIV-infected patients

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Abstract

Malignancies are a major cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected patients. With the introduction of an effective combination of antiretroviral therapy, HIV infection has been changed from being a death sentence to a chronic condition. There is renewed clinical interest in the associated morbidities of non-communicable diseases, and most importantly cancers, such as Kaposi's sarcoma and non-Hodgkin's lymphoma, due to prolonged survival on antiretrovirals. Available evidence suggests that there is an increasing frequency of cancers associated with bacterial and viral infections among the HIV-infected population. There is also a concern about the etiology of emergence of cancers, risk factors, and viral infections in HIV-infected individuals. The challenge is for the caregivers to develop and implement effective means to screen, treat, and prevent non-AIDS defining cancers (NADCs) in the HIV-infected patients. There is a need for provision of hepatitis B virus and human papillomavirus vaccines for those who are uninfected and the eligible population. Emphasis should be on these non-AIDS defining cancers during health education, in order to create awareness of the morbidity that may encourage screening uptake, thus resulting in healthy living and reduced mortality rates. This brief review aimed to bring to fore the account of NADCs, risk factors, the role of the microbiota, diagnostic methods, and the need for urgent screening and prevention among people living with HIV/AIDS.

Introduction

Human immunodeficiency virus (HIV) infection and long-term antiretroviral therapy (ART) in aging populations have a tendency to increase the risk for certain types of cancers. Cancer is the main cause of death in HIV-infected patients on ART [1]. The risk for AIDS defining cancers (ADC) such as Kaposi sarcoma (KS), non-Hodgkin's lymphoma (NHL), cervical cancer and non-aids defining cancers (NADCs), namely cancers of the mouth, throat, liver, lung, vulvo-vagina, and anus, Hodgkin's lymphoma (HL) among others, is increasing significantly more in HIV-infected persons than the general population [2, 3]. The role of immunologic status in the development of NADCs is not clear,

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but other factors have been implicated, such as lifestyle and chronic co-infections: hepatitis B and C viruses (HCV, HBV), Epstein-Barr virus (EBV), human papilloma virus (HPV), and *Helicobacter pylori* [1].

In sub-Saharan Africa (SSA), the rate of these cancers is increasing with many deaths already recorded without sufficient data related to the spectrum of NADCs. Therefore, we aimed to describe the epidemiology, risk factors and prevention of NADCs among HIV-infected patients.

Epidemiology of antiretroviral therapy-associated cancers

The use of combination antiretroviral therapy (cART) has significantly improved life expectancy and survival among HIV-infected persons and decreased the incidence of AIDS. Nigeria, among other African countries, has begun the implementation of "test and treat" regardless of the infected individual's CD4 count. As a result of increased access to cART, the coverage gap in most developing countries remains considerably low. People living with HIV/AIDS (PLWHA) have elevated risks of about 2800-fold for KS, 10-fold for NHL, and 3-fold for cervical cancer compared with the general population. The trend of ADC, especially KS, is still high but continues to decline for Kaposi sarcoma (KS −29.3%, 1996-2000; −7.8% 2000-2010), non-Hodgkin lymphoma (NHL −15.7% 1996-2003; −5.5%, 2003-2010), cervical cancer (−11.1%), Hodgkin lymphoma (HL, −4.0%), and lung cancer (−2.8%) [4]. The incidence rates for breast and colorectal cancer have not significantly changed over time. Many studies have suggested links between HIV and malignancies, although without well-described associations [5, 6]. This calls for more definitive regional epidemiologic studies to investigate the ongoing associations between HIV and cancers. There is an increase in the aging population of people living with HIV in the SSA, suggesting that attention must be paid to appropriate cancer screening, prevention strategies and health maintenance measures to curb the menace of HIV-associated malignancies. Despite its success and efficacy in prolonging survival for those infected with HIV, the use of cART does not restore total health, for reasons that remain poorly understood [7]. However, some of these malignancies with associated complications are similar to those among the elderly. This has led to increased concerns that HIV-infected persons suffer from accelerated aging. From studies, cancers are known to be majorly associated with aging [2, 9]. This suggests that the burden of cancer among HIV-infected persons who live longer may increase. Studies of liver, anal, colorectal and lung cancers have observed increased incidence of these cancers after 10-20 years on cART compared to the general population [7, 8]. However, as the HIV-infected individuals continue to age, more cases of NADCs will be expected to occur at older ages [9]. This may be due to a number of mechanisms such as accumulation of inflammatory cells in the liver, microbial translocation and impaired immune responses, improvement in life expectancy with cART, early aging, loss of con-trol of oncogenic infections and high exposure to some other carcinogens (tobacco or alcohol) [10-12].

Viral infections and cancers

There is a higher risk of cancers with a known etiologic cause in HIV-infected persons compared with uninfected persons. Cancers caused by infections represent about 70% of all cancers in HIV-infected persons compared with only 12% in HIV-uninfected persons in developed countries [10, 13], suggesting that the rates could be higher in SSA, where poverty-associated diseases are on the increase. Viral co-infections such as HBV, HCV, HSV-2, EBV and HPV are common in HIV-infected persons [14, 15]. The reason for this high risk of cancers is due to the compromised immune system in HIV-infected persons, which reduces the ability to control oncogenic viral infection [16]. HIV-infected individuals in resource-limited settings still initiate ART with a very low CD4 count, suggesting increasing risk of morbidity and mortality compared to asymptomatic patients with a high CD4 cell count [17]. Many HIV-infected individuals still cannot access cART except by traveling some distance, and this great percentage with the burden has potential to alter the elimination target. Many infection-related cancers occur in this group of individuals where vulnerability to infections is also higher due to poverty and social-related factors. Therefore, infection-related cancers will likely become common even if they are eventually enrolled on cART. Moreover, those who are enrolled at the appropriate recommended salvage time will experience cancer-related complications on aging [12].

Liver cancer (hepatocellular carcinoma)

Patients with HIV coinfections with HBV and HCV have a greater risk for hepatocellular carcinoma (HCC) compared with the general population [18]. Early reported findings on the natural history of HIV and hepatitis co-infections have shown higher incidence rates of cirrhosis, and or liver-related death if the immune system is compromised [14]. Studies have shown that HCC due to HBV and HCV is an emerging complication of chronic liver disease in HIV-infected patients [19]. ART has reduced HCC complications of hepatic decompensation and increased survival of co-infected patients with cirrhosis. However, HIV/HCV-coinfected patients receiving suboptimal ART may have reduced survival time due to end-stage liver disease. HIV/HBV infections hasten the clinical outcome of HBV infection due to cirrhosis and end-stage liver disease and death, particularly at low CD4 counts. It has been speculated that HBV associated with HCC has a stronger impact than that of HCV with HCC [19, 20]. Though the mechanisms by which HIV/HCV co-infection accelerates the liver disease are not well understood, studies have shown that hepatocytes in HIV and HCV co-infected cells expressed higher levels of HCV RNA and HIV RNA than mono-infected cells [12].

In HIV/HBV-co-infected patients, early initiation of ART with tenofovir combination is the preferred choice due to its high potency and high genetic barrier to resistance [21]. However, the combination of efficient drugs for both viruses can be toxic, since hepatocytes are not only infected by viruses, but are also affected by drugs at sites of metabolism, including oxidative stress, being linked to liver injury in HIV/HCV co-infection compared to HIV mono-infection [22]. Therefore, HIV/HBV and/or HIV/HCV co-infected patients on combined therapy should be given special attention for enhanced quality of care. In the HIV/HCV co-infected patients, the progression to liver cirrhosis and HCC may take about 10-20 years and has been demonstrated even in the use of direct-acting antiviral (DAA) treatment. Though HCC development is in most cases reduced by DAA, HIV/HCV co-infected patients with advanced cirrhosis still represent a risk group for HCC progression even in DAA non-responders. Thus, the heterogenicity of these cirrhotic patients is based on various co-morbidities, genetic polymorphism, late treatment initiation and altered response to treatment, which impacts negatively on the end-stage liver disease progression in coinfected patients [23].

Head and neck cancers

Head and neck cancers (HNCs) are the seventh most common type of cancer [24]. Among these cancers, more than 70% of squamous cell carcinoma cases are estimated to be avoidable by reduction of exposure to risk factors such as tobacco smoking and alcohol drinking [24]. There is a paucity of data on HNC prevalence and incidence as many cases go undiagnosed or unreported. HNC is a noncommunicable disease in Africa, and it is becoming an emerging burden like other infectious diseases. It is a disease of ignorance, poverty, and poor health-seeking behavior, which makes Africa vulnerable to the huge cancer burden. The occurrence of HNC is largely due to multiple factors classified as environmental and genetic. Other risk factors for the development of HNC include excessive consumption of salted foods, industrial pollution, medication use, and African race [25, 26]. HNCs represent 5-50% of all cancers globally, and 5-8% of total body cancers in Europe and America [27]. In Nigeria, most studies have reported nasal/paranasal cancers and oral cancers as the most frequently occurring HNC [28, 29]. This suggests that there is a possibility of changes in the patterns of HNCs in the near future. Many studies highlight that risk factors are not only etiological determinants but are also connected with tobacco use and alcohol consumption in addition to HPV [30]. However, pathogenesis and the likelihood of an individual developing HNC have not been well studied. Though the majority of head and neck squamous cell cancers (HNSCC) are attributable to tobacco and alcohol exposure [31], HPV infection has recently been implicated strongly as an important cause of head and neck cancer. High-risk HPV type 16 accounts for the majority (90-95%) of HPV-positive oropharyngeal cancers, and HPV types 18, 33, 35, 45, 59 account for 5-10% of cases [32, 33].

HIV-infected individuals have a 2-4-fold increased risk for HNCs. A recent review showed that the risk of oral cavity and pharynx cancer was 2-4 times higher among HIV patients [34]. Combined ART does not appear to reconstitute HPV-specific immunity. However, some reduction in the risk for oropharyngeal cancer in the post-ART era has been reported [35]. The precise risk factors associated with HNC prevalence and incidence have not been well investigated and reported, except for a few inhomogeneous hospital-based studies. Therefore, there is an urgent need for a national study, and/or the use of a cancer registry to estimate baseline prevalence and associated risk factors.

Hodgkin lymphoma

HIV-infected patients are at increased risk for developing both NHL and HL. While cART has decreased the risk for NHL, NHL remains the most common cancer-related acquired immune deficiency syndrome (AIDS) in both the developed and the developing world. In HIV-negative individuals, HL is one of the commonest malignancies diagnosed in young adults under 45 years of age. The epidemiology of HL is characterized by the age distribution pattern (30-50 years) [36]. In immune suppressed patients, HL occurs more frequently than in the general population of the same age and gender [37]. Studies provide strong evidence that HIV-infected persons have a 10-fold higher risk of developing HL than HIV-negative persons. The risk of HL has remained stable or even increased since the introduction of cART [38]. HL in HIV-infected individuals is more frequent in patients with moderate immune suppression, and this is in sharp contrast with KS and diffuse large B-cell NHL that typically arise in more strongly immunosuppressed individuals [38]. It is, however, not surprising that HIV/AIDS-related immunosuppression would affect the HL risk. This is because persons with genetic conditions associated with T-lymphocyte dysfunction also have a higher risk of HL. Moreover, patients with HL may have underlying unknown abnormalities of T-cell immunity. The relative risk for development of HL is elevated in HIV-infected men and women [9]. At present, the relationship between immunodeficiency, HL development and HL subtypes is poorly understood. Among other risk factors for HL is EBV. EBV DNA has been detected in high proportions of AIDS-associated HLs [39]. It is worth noting that EBV association with HL may be linked to immune dysfunction similar to that of NHL [40].

Anal cancer

Anal cancer is uncommon in the general population. However, its incidence has been rising for the last 3 decades. In both developed and developing countries, it has been rising with the growth of the HIV epidemic. It has been found to be 40-80 times higher in HIV-infected individuals than HIV-uninfected individuals. This therefore has led to

a change in anal cancer demographics. Factors implicated in the etiology of anal cancer in HIV-infected patients include HPV status, sexual habits, and a history of smoking. HPV type 16 infection and anal intercourse have been found to increase the risk of anal cancer by 33% over HPV-negative individuals [41]. In the general population, the rate of anal cancer is approximately 0.9 cases per 100,000 [10]. In patients with a history of anal intercourse, the rate approaches 35 cases per 100,000, which is equivalent to the prevalence of cervical cancer [42]. Smokers are eight times more likely to develop anal cancer [41]. There has not been much discussion about prevention and treatment decisions in HIV-infected patients with anal cancer. In the developed countries, the rates of anal cancer among men who have sex with men (MSM), and immunocompromised men, now exceed the rates of cervical cancer among women [43, 44]. In view of this, anal cancers have become an important cause of morbidity among HIV-infected persons. However, both HIV-infected men and women have been reported to have substantially higher, albeit similar rates of anal cancers than HIV-negative men and women [45]. Due to rising trends of anal intercourse, incidence rates of anal cancer have progressively increased during the HIV epidemic. The relationship between CD4 count and anal cancer was initially unclear, but is now seemingly clarified. Although HIV-infected persons are experiencing longer life expectancies due to ART, ART does not seem to be protective against anal cancer [44]. The most common risk factor for anal cancer is infection with HPV, which is responsible for development of neoplasm in the anal epithelium. Therefore, it is suggested that HIV-infected patients be screened, treated and managed for anal cancer as part of quality of care.

Lung cancer

Lung cancer is the leading cause of cancer death in the US and Asia general population, the most common non-AIDS-defining cancer in people with HIV infection, and the leading cause of cancer-related mortality among HIV-infected individuals [46]. The increased rates of lung cancer in HIV-infected patients are higher compared with HIV-negative individuals [47, 48]. The degree to which the risk is due to tobacco use is poorly understood due to the paucity of data on tobacco use among HIV-infected persons [45, 48]. Previously reported findings showed that HIV-infected individuals had twice the risk of lung cancer in the AIDS [55]. Studies have demonstrated that HIV infection was strongly associated with smoking behaviors that increased lung cancer risk [47]. Despite the reported findings of elevated lung cancer among HIV-infected population, routine prevention remains a challenge. However, health education on smoking cessation remains an important strategy to prevent occurrence of lung cancer in the HIV-infected population. The significance of smoking cessation cannot be overemphasized. However, because of its challenging nature, abstinence periods could be encouraged, while the danger in loss of life in years through tobacco use could be empha-

sized. Lung cancer incidence is increasingly being associated with tobacco use in HIV-infected populations, but specific mortality from lung cancer has not been linked to immunosuppression in the era of effective long-term ART [48].

Microbiota and cancer

Cancer diseases are caused by both genetic and environmental factors. Microbes are becoming an emerging contributor to carcinogenesis, and about 20% of the global cancer burden is linked to infectious pathogens [49], which are known to alter the host cell proliferation, thereby hindering the antitumor immune response and influencing the metabolic barrier of host-produced factors [50]. These barrier hindrances including dysbiosis have been proposed to be responsible for mechanisms driving bacterial initiated carcinogenesis, resulting in increased gut microbiota interactions. This microbiome plays a functional barrier role by suppressing the growth of pathobionts using competitive advantage [50, 51]. More recently, gut alterations by bacterial activity have been linked to the development of colorectal cancer (CRC), and extraintestinal cancers such as liver, breast, and lung cancer [52, 53]. It has become obvious that the evaluation of gut microbiota purposefully will be vital to advancing the research in addressing the knowledge gap about the role of the microbiome in the pathogenesis of cancer and understanding its interactions with possible immunotherapeutic potentials. Though the role of microbiome manipulation for therapeutic purposes is still in its infancy, but rapidly expanding, there are indications that the use of fecal microbiota as a probiotic can be exploited to predict clinical outcomes. Furthermore, gaining research insights into how the microbiota influences HIV disease progression and cancer will be useful in the quest to manipulate the microbiome for therapeutic interventions.

Diagnosis, screening, prevention and control

There are significant interests in HIV/AIDS and associated malignancies in the era of long-term ART, and these malignancies occur disproportionately among those living with HIV. This is why it is very important to screen PLWHA for NAD cancers, particularly in women with individualized risk for type of cancer and to increase life expectancy. The review is not exhaustive, but for a few cancers (liver, lung, anal, neck and colorectal) screening methods have shown to be beneficial in the general population and people living with HIV/AIDS.

Liver cancer (hepatocellular carcinoma)

Globally, one of the main areas for decreasing the burden of HCC is to improve cancer detection, diagnosis and therapy. The use of biomarkers for early detection and in

therapeutic intervention has been very useful for HBV and HCV screening among HIV infected individuals. This has improved survival of those with HBV through therapeutic intervention by the use of tenofovir ART combinations. The recent development in quantifying HBV and HCV by GeneXpert as support from the "Clinton Health Access Initiative" (CHAI) in Africa has increased access to treatment of HCV using direct-acting antivirals (DAAs). The screening for HCC in patients with persistent HBV surface antigenemia could be helpful, but another non-invasive scoring system, the fibrosis-4 (FIB-4) index score calculated from platelet count and liver enzymes (alanine, transaminase, aspartate transaminase) as well as patient's age, is used for predicting severe fibrosis in hepatic fibrosis and cirrhosis. This has increased survival apart from the recommendation of the American Association for the Study of Liver Diseases (AASLD) screening guidelines using ultrasonography every 6 months for individuals at high risk for HCC [54]. However, the recommended method is known to be associated with potential complications such as excess radiation or liver biopsy related issues if an abnormality is detected including reported false-positive tests.

Lung cancer

There is an increasing number of lung cancers among people living with HIV, and this number has doubled over the past 20 years, especially in those over 50 years of age and with tobacco use [55]. The available lung cancer screening in developing countries is the use of chest radiography with or without sputum or cytology. In advanced countries and some tertiary hospitals in less developed countries, the more effective technology of computed tomography (CT) scans has been introduced, providing better details of the tumor in the body and perhaps tracking its growth. However, this method has its pitfalls such as subjective interpretation depending on the training expertise of the operator or physician handling the result. The other effects of CT screening include the cumulative effect of repeated radiation exposure, surgical and medical complications associated over-diagnosis and over-treatment of lung cancer [56]. This, however, may be true for HIV-infected individuals with very low CD4+ cell counts and who are likely to have a false-positive result due to infections that may cause non-specific scarring. Overall, cessation of smoking is still the most valid prevention method to avoid development of lung cancers, since smoking has been found to be a significant risk factor.

Anal, neck and cervical cancer

Anal, neck and cervical cancers are mostly associated with HPV infection. The available anal cancer screening is based on cytological detection of HPV infection induced abnormalities and histological confirmation followed by treatment of the lesions, high-grade anal intraepithelial neoplasia [56]. Other techniques include digital anal rectal exam, anal

Papanicolaou (Pap) smear test, and high-resolution anoscopy. Anal cytology is a fair predictor of AIN with a sensitivity ranging from 61% to 93% [57, 58]. Anal cytology screening for PLWHA was endorsed and supported by the Centers for Disease Control and Prevention (CDC), emphasizing the need for larger studies to address screening and treatment programs [59]. Also, the use of biomarkers such as HPV16/18 genotyping, HPVE6/E7 mRNA expression and p16/Ki-67 cytology has been in use for the screening of these cancers [60, 61]. Similarly, the World Health Organization (WHO) has adopted HPV testing, followed by immediate treatments such as cryotherapy for identified cervical abnormalities among those living with HIV [62]. The drawback of the implementation of this strategy in resource limited countries is the cost barrier, which remains to be further evaluated. Among women living with HIV/AIDS, invasive cervical cancer (ICC) presents about 15 years earlier than in the general female population with higher incidence, which may be a reflection of the limited screening opportunities [63]. However, the management of ICC requires collaborative efforts of the gynecological surgeon, radiation therapist and oncologist, though this could be very challenging in resource-limited countries where fear of cancer and poor infrastructure hinder early diagnosis and treatment efforts.

The use of vaccination (nine-valent HPV vaccine) against HPV infection for prevention and subsequent reduction of HPV-related cancers is also ongoing in some countries, but this opportunity is abysmally underutilized among the target ages of 9 to 26 years for anal cancer and 11 to 26 years for cervical cancer. The vaccination program has capacity to reduce the high incidence of anal cancer in adolescents, adults, and particularly men who have sex with men. The CDC now recommends 2 doses of the HPV vaccine against the previously recommendation of 3 doses in ages 11-26 to protect against HPV infection [64].

Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer worldwide and the cause of death in both genders. The prevalence of colonic adenomas in PLWHA was high compared to the general population [65]. The U.S. Preventive Services Task Force (USPFT) recommends CRC screening for adults aged 50-75 years with high-sensitivity fecal occult blood testing (FOBT), sigmoidoscopy plus FOBT, and/or colonoscopy every 5, 3, 10 years, respectively, including barium enema and CT colonography [66]. New biomarkers such as the fecal immunochemical test (FIT), serum carcinoembryonic antigen (CEA) and fecal calprotectin are also in use for the evaluation of early cases or symptomatic patients. The presence of NADCs represent a significant source of morbidity and mortality in the aging population of PLWHA. However, the decision to screen the HIV-infected population for cancers is somewhat complex and the risk involvement should be carefully considered depending on the type of cancer, including specific benefits in terms of life expectancy and the associated harms from the screening

approaches. Further larger studies are needed to estimate the associated harms and benefits of cancer screening methods in HIV-infected persons.

Conclusions

Non-AIDS-defining cancers are increasingly becoming a major health challenge among HIV-infected patients, and they are increasingly at greater risk compared with HIV-negative individuals. The prevalence is higher with hepatocellular carcinoma, Hodgkin lymphoma, anal cancer, and lung cancer. Co-infections can complicate the treatment and management of HIV infection. Therefore, HIV-infected patients co-infected with oncogenic viruses should seek care from healthcare providers with expertise in the management of both HIV and infection-related cancers. It has become pertinent that prevention efforts in HIV-infected persons should consider an infection-related cancer and ensure that HBV surface antigen-negative individuals be vaccinated. In view of this, anti-hepatitis virus testing should be followed with optimum care and treatment. This has the capacity for better health outcomes by reducing hepatitis-related cancer mortality among persons living with HIV coinfections. The government should, as a matter of urgency, provide the HPV vaccine to uninfected adolescents beginning from age 12 to 19 years. The universal guideline for cancer prevention is screening and early detection, which should be integrated as part of quality of care among HIV-infected patients. Emphasis should be on these non-AIDS defining cancers during the health education to create awareness of the morbidity that may encourage screening uptake, resulting in healthy living and reduced mortality rates. Previous findings have shown that for patients on ART care becomes more complicated as aging sets in due to occurrence of co-morbidities. However, because of the complex nature of required attention in this population, there is a need for a multidisciplinary approach involving teams with hepatologists, gastroenterologists, oncologists, gynecologists, hematologists, and HIV-trained specialists to combat the emerging challenges of our time. This review highlights the epidemiology, challenges, diagnosis and the need for aggressive cancer screening and prevention efforts in the management of HIV-infected patients.

Finally, the use of long-term ART in suppressing the virus alone is insufficient in the management of HIV; therefore, it is also important to evaluate the role of the gut microbiome in HIV-associated pathology, such as bacterial translocation, immune cell activation, and gut inflammation, that may potentially influence therapeutic efficacy. It is also suggested that the use of metagenomic approaches is crucial to bridge the knowledge gap of microbial markers associated with HIV infection and non-AIDS defining cancers.

Conflict of interest

The authors have no conflict of interest.

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