Chapter 10
Malignancies in HIV-Infected and AIDS Patients

Yongjia Ji and Hongzhou Lu

Abstract Currently, HIV infection and AIDS are still one of the most important epidemic diseases around the world. As early in the initial stage of HIV epidemic, the high incidence of ADCs including Kaposi sarcoma and non-Hodgkin's lymphoma was the substantial amount of disease burden of HIV infection and AIDS. With the increasing accessibility of HAART and improving medical care for HIV infection and AIDS, AIDS-related illness including ADCs has dramatically decreased. Meanwhile, the incidence of NADCs rises in PLWH. Compared with the general population, most of cancers are more likely to attack PLWH, and NADCs in PLWH were characterized as earlier onset and more aggressive. However, the understanding for cancer development in PLWH is still dimness. Herein, we reviewed the current knowledge of epidemiology and pathogenesis for malignancies in PLWH summarized from recent studies. On the basis of that, we discussed the special considerations for cancer treatment in PLWH. As those malignancies could be the major issue for HIV infection or AIDS in the future, we expect enhanced investigations, surveillances, and clinical trial for improving the understanding and management for cancers developed in PLWH.

Keywords HIV • AIDS • Cancer • Malignancy

Y. Ji
Department of Infectious Diseases, Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, People's Republic of China

H. Lu (✉)
Department of Infectious Diseases, Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, People's Republic of China

Department of Infectious Diseases, Huashan Hospital Affiliated to Fudan University, Shanghai 200040, People's Republic of China

Department of Internal Medicine, Shanghai Medical College, Fudan University, Shanghai 200032, People's Republic of China
e-mail: luhongzhou@fudan.edu.cn

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10.1 Introduction

Globally, more than 35 million people are living with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) [1]. Compared with the general population, the population of people living with HIV infection (PLWH) was at higher risk for cancer incidence [2–8]. As early at the opening phase of AIDS epidemic, it was found that non-Hodgkin lymphoma (NHL), cervical premalignant lesions, and Kaposi sarcoma (KS) were strongly associated with immune suppression induced by HIV infection [9]. As a consequence, the US Centers for Disease Control (CDC) has defined KS, certain non-Hodgkin lymphomas, and cervical cancer as AIDS-defining cancers (ADCs) since the 1990s [10].

Over the years with the increasing accessibility to highly active antiretroviral therapy (HAART) and improving medical care for HIV infection and AIDS, the outcome for PLWH has substantially improved, which is largely benefited from the decreasing incidence and mortality rate of AIDS-related illness including opportunistic infections (OI) and ADCs [11]. While with the extension of life span during the HAART era, the spectrum of malignancies occurred in PLWH has significantly transformed [12]. Compared with the general population or people without HIV infection, several non-AIDS-defining cancers (NADCs) such as lung cancer, hepatocellular carcinoma (HCC), and classical Hodgkin lymphoma were found attacking PLWH more frequently [1, 13]. And especially in developed country, malignancy has gradually become the leading cause of deaths in PLWH, and NADCs have replaced ADCs as the major malignancies burden in HIV-infected population [1, 12, 14, 15].

In recent years, the focal interest for malignancies in PLWH was growing, and a large amount of studies in this field were published. In this review, we will discuss the latest advances of epidemiology, pathogenesis, and special consideration for treatment in this field.

10.2 Epidemiology

10.2.1 AIDS-Defining Cancers

ADCs were identified by comparing the risk (standard incidence ratio, SIR) of cancer incidence in PLWH with that in the general population [16]. According to the definition of US Centers for Disease Control (CDC), Kaposi sarcoma, cervical cancer, and specific non-Hodgkin lymphoma (NHL) including primary central nervous system lymphoma (PCNSL), Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), plasmablastic lymphoma (PL), and primary effusion lymphoma (PEL) were categorized as ADCs [10].

For ADCs, several large-scale epidemiology studies have revealed that the SIR in PLWH population is significantly higher than that in general population in both the

pre-HAART and HAART eras [1, 7, 17–19]. Kaposi sarcoma and NHL contributed to most cases of ADCs in the pre-HAART era [20]. As reported in the United States, in early phase of HIV epidemic, the risk for Kaposi sarcoma and cervical cancer was about 50,000-fold and eightfold higher in PLWH compared with the general population [20]. And for NHL in pre-HAART era, the most common pathological type of NHL occurred in PLWH was DLBCL and PCNSL took the second place [21]. Compared with the general population, the risk of DLBCL and PCNSL for AIDS patients significantly increased 5000 and 98-fold in the pre-HAART era [20].

After entering into the HAART era, the incidences of ADCs in PLWH have decreased and the outcome got substantial improvement [19, 22]. As studies reported in western country, with the introduction of HAART, Kaposi sarcoma and NHL cases declined by more than 80% and 50%, respectively [1, 20]. However even under such circumstances, ADCs still possess as an important issue in the HAART era, several recent studies indicated that the risks of ADCs are still higher in PLWH than that in the general population [5, 7, 18–20].

Several studies found that HIV infection inducing immune suppression indicated by CD4+ T-cell count is the most important risk factor for ADCs development [7, 23, 24]. As retrospectively analyzed, compared with CD4+ T-cell count less than 100 cells/ml, the SIR for NHL and KS in PLWHA decreased from 145 to 35.8 and 571 to 76 per 100,000 person-years separately when CD4+ T-cell count was more than 500 cells/ml [20]. On the contrary, with the CD4+ T-cell count increased from less than 50 to greater than 250 cells/ml, the incidence of Burkitt's lymphoma increased from 9.6 to 30.7 per 100,000 person-years, which could be correlated with immune reconstitution [25]. As a consequence, Burkitt's lymphoma has replaced PCNSL as the second most common NHL in PLWH during the HAART era [18].

10.2.2 Non-AIDS-Defining Cancers

During the HAART era, NADCs incidences among PLWH increase rapidly. As reported in developed country, NADCs have contributed to more than half of all HIV malignancies, while the number in pre-HAART era was less than 40% [1–3]. Similar with other age-associated diseases, the risk for NADCs is higher in PLWH [26]. And also, the prognosis of HIV-infected patients with NADCs is independently worse than those without HIV infection [27].

There have been numerous studies for exploring risk factors of NADCs in PLWH. Previous studies have identified older age and the longer duration time living with HIV infection as the most important risk factors related with NADC incidence in PLWH [7, 28]. While comparing with people without HIV infection, NADCs occurred at similar ages in PLWH [26]. Previously, several studies have found that HAART administration could be a possible contributor for malignancy development [28–30]. However, there is the view that the lifetime extension benefited by HAART other than its direct effective could be the factor related with

Table 10.1 Oncogenic virus infection associated with malignancy development in PLWH

Virus	Malignancies
HHV-8	KS, NHL (PEL, PL)
EBV	NHL (PCNSL, BL, DLBCL PEL), HL, head and neck carcinoma
HPV	Cervical and anal cancer, head and neck carcinoma
Chronic hepatitis virus (HBV/HCV)	Liver cancer

HHV human herpes virus, *HPV* human papillomavirus, *EBV* Epstein–Barr virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *KS* Kaposi sarcoma, *NHL* non-Hodgkin lymphoma, *PEL* primary effusion lymphoma, *PL* plasmablastic lymphoma, *BL* Burkitt's lymphoma, *DLBCL* diffuse large B-cell lymphoma, *PCNSL* primary central nervous system lymphoma

increasing incidence of NADCs [31]. Moreover, the latest epidemiology studies revealed that the early initiation of HAART could diminish the cancer risk and slow the progression of cancer development [32, 33]. The correlation between CD4+ T-cell count and NADCs incidence is controversial depending on different kind of malignancies. For anal cancer, in the setting of patients with CD4+ T-cell count less than 200 cells/ml for more than 5 years, the SIR would rise up [34]. On the contrary, the SIR for Hodgkin lymphoma increases when CD4+ T-cell count rises from 50 to 200 cells/ml [1, 35, 36]. While the incidence of lung cancer is higher among PLWH compared with that in the general population, the CD4+ T-cell count has not been identified as a risk factor [37, 38]. The other risk factors for NADCs development in PLWH included smoking and oncogenic virus infection [39].

10.3 Pathogenesis

10.3.1 Viral Infection

Most cancers including ADCs and NADCs with excess risk among PLWH are associated with oncogenic virus infection (Table 10.1) [39]. Compared with that only less than 5% malignancies in the general population were associated with virus infection, the number in PLWH was reported as up to 40% [40]. This disparity could be attributed to the shared transmission routes of HIV with several oncogenic viruses and immunosuppression induced by HIV infection, which resulted in higher prevalence in PLWH than that in the general population [41–43].

The carcinogenesis of these viruses involves multiple ways, which include regulation of apoptosis and cell life cycle and disturbance of host's tumor-associated genes [44]. And in recent studies, it was suggested that several miRNAs expressed by these oncogenic viruses could be the important promoter for cancer development [45–47]. As for EBV infection, which is highly correlated with various types of lymphoma development in HIV/AIDS setting, the virus expressing MiR-BHRF1-1 and miR-BART1 could involve oncogenesis by inhibiting the tumor suppressor

gene p53 and depressing apoptosis by activating antiapoptotic protein BCL-2 [46–48].

Besides, there is growing evidence that HIV could directly participate in the development of malignancies. Tat, the HIV-expressing transactivator protein, is responsible for the activation of viral and cellular genes. In several studies, Tat demonstrated oncogenic effects in vitro and in vivo. After being excreted from cells infected by HIV and accumulated in tissues, tat could induce malignant transformation by interruption of cell proliferation, DNA reparation, and apoptosis [49]. Further, there is evidence suggesting that tat could enhance malignant capacity of other oncogenic viruses such as HPV [42, 50]. Otherwise, it was found that HIV matrix protein (P17) persists in germinal centers even after efficient HAART [51]. And further, several specific variants of HIV P17 were associated with aberrant proliferation of B cell, which may contribute to the development of B-cell lymphoma [52].

10.3.2 Immunosuppression and Inflammation

Host's immunological function impaired by HIV infection has been recognized as an important risk factor for cancer development, which leads to the attenuation of tumor surveillance. An inverse association between CD4+ T-cell count and ADCs risk has been demonstrated by several studies conducted in pre- and early-HAART era [53–55]. As for NADCs, the inverse relationship between CD4 count and cancer risk for NADCs has been reported in recent studies [56, 57]. Nevertheless, the relationship between immunosuppression induced by HIV infection and cancer risk is controversial [58]. Even in patients with virus suppression, low CD4 count is still an important risk factor for cancer incidences [57]. Otherwise, HIV-infected patients with immune reconstitution (CD4+ T-cell counts >500/ml) are still at elevated risks for HL and liver cancer [56]. Similarly, during the HAART era, the incidence of anal cancer was observed as rising in HIV-infected population [34, 59]. These results suggested that early HIV infection inducing immunosuppression-associated carcinogenesis could not be reversed by immunologic function restoration, or the CD4+ T-cell count could not indicate the alterations of host's immune system related with susceptible to malignancy.

Recently, it is found that chronic inflammation could greatly contribute to carcinogenesis in HIV-infected patients. HIV infection could induce a series of immune activation, as B-cell hyperactivation could be induced by HIV replication [60], and CD4+ T-cell exhaustion in mucosal layer of the intestine could evoke host inflammatory response [61]. In clinical observation, even with long-term virological suppression, inflammatory biomarkers remain at high levels in HIV-infected people [59]. And also, the role of inflammation biomarkers for predicting oncogenesis in PLWHA has been confirmed by cohort study [62].

10.4 Treatment

After entering into the HAART era, more HIV-infected patients with malignancies have accepted chemotherapy which is contradicted to immunocompromised patients. Benefiting from efficient HAART and the advancement of anticancer therapy, the outcome for HIV-infected patients with cancers has been improved significantly. Compared with pre-HAART era, the overall survival rate at 5 years for HIV-infected patients with HL and DLBCL has increased to more than 50% [63–66]. And for anal cancer, the prognosis is comparable between PLWH and general population [67]. Considering the drug interaction and special physical condition, the treatment for HIV-infected patients with cancer would be more complicated. We will discuss around the special points of cancer treatment for PLWH, which needs attention of physician and other medical care providers.

10.4.1 Combination of HIV Treatment and Chemotherapy

Currently, it is suggested that all HIV-infected patients with malignancies should continue HAART during chemotherapy [31], and early HAART could diminish the risk for cancer development. However, similar with chemotherapy agents, many drugs for HIV treatment were metabolized by the liver through cytochrome P450 enzyme system, which could interfere the pharmacokinetic of chemotherapy agents and further influence therapeutic efficacy [68, 69]. Ritonavir, the inhibitor of HIV protease, also could exert potential inhibition effective for CYP34A and defer the clearance of specific chemotherapy agents such as vinca alkaloids, taxanes, and alkylating agents [68, 69]. Therefore, the combination of ritonavir and vincristine or vinblastine-based chemotherapy would increase the incidences of chemotherapy-related toxicity such as neuropathy and neutropenia. Similarly, fluconazole is also the inhibitor for CYP3A4 system, which should be avoided in combining with the vinca alkaloid-based chemotherapy [70]. Otherwise, several ART drugs cause overlapping side effect with chemotherapy agents, such as renal and hepatic toxicity, myelosuppression, and peripheral neuropathy [68, 69].

Considering the complex conditions as described above, all these interaction factors should be carefully evaluated before prescribing combination of HAART and chemotherapy. The optimized therapeutic regimen for HIV-infected patients with malignancies should be made by the consensus between the specialists of infectious disease, oncologists, and pharmacists.

10.4.2 HAART Discontinuation During Chemotherapy

As described above, the excessive adverse effects caused by the combination of HAART and chemotherapy could lead to treatment discontinuation. For AIDS patients with lymphoma, there have been investigations evaluating the outcome for discontinuation of HAART during chemotherapy period [65, 71]. During the course of chemotherapy without HAART ranging from 4 to 6 months, the patients' serum HIV viral load rose with the falling of CD4+T-cell count. However, HAART was resumed when chemotherapy is completed; both HIV viral load and CD4+ T-cell count would restore in 6–12 months. And further, the 5-year OS was comparable with that reported by other studies conducted in AIDS patients with lymphoma co-administrated with HAART and chemotherapy [65, 71]. As the lack of studies directly comparing the outcome for chemotherapy with or without HAART, the optimal choice is still in dispute.

10.4.3 Immunological Suppression Associated with Chemotherapy

As for NHL treatment, even co-administrated with HAART, the patients' CD4+ T-cell counts would decline more than half in most cases after taking chemotherapy [72]. Commonly, with the end of chemotherapy, CD4+ T-cell counts will increase to the level before treatment in about 6 months to 1 year [72]. In conditions with radiation therapy, the immunosuppression would be more serious, which might not recover after treatment [73]. This situation might be caused by myelosuppression related with radiation. Pelvic radiation could induce the most severe immunosuppression, and the intestine as the important gathering place of CD4+ T cell could be also affected by abdominal radiation [74]. For this immunosuppression effect of antitumor therapy, it was recommended that the prophylaxis for *Pneumocystis jiroveci* and other opportunistic infections should be administrated in HIV-infected patients with malignancies when initiating chemotherapy or radiotherapy, regardless of CD4+ T-cell count [73]. Meanwhile, for minimizing the risk of opportunistic infections, granulocyte colony-stimulating agents could be administrated on the basis of risk assessments [71, 72, 75].

10.4.4 Immunotherapy

Besides chemotherapy, treatment targeting the modulation of host immune system has emerged as promising options for tumor treatment. So far, FDA has approved CTLA-4 inhibitor and PD-1 inhibitor for specific cancer treatment, respectively, and the IL-2 stimulation has also been in late clinical development [76, 77]. Of note,

PD-1 inhibitor and IL-2 stimulation demonstrate the effectiveness of CD8+ T-cell restoration. Considering the important role of CD8+ T-cell dysfunction in both HIV infection and malignancies, the immunotherapy for AIDS patients with malignancies would be deserved for anticipating [78].

10.5 Conclusion

It has been more than 50 years after the first case of HIV infection was identified, while HIV infection and AIDS are still one of the most important epidemic diseases around the world [79]. In early phase of HIV epidemic, the high incidence of NHL and KS in PLWH was noted, which was recognized relating with specific virus infection. With the improving medical care for AIDS, AIDS-related illness including ADCs has decreased sharply, and NADCs rise in PLWH. Compared with patients without HIV infection or AIDS, NADCs were characterized as earlier onset and more aggressive in PLWH [80].

Until now, the understanding of pathogenesis for cancer especially NADC development in HIV-infected patients is still unclear. Because those patients with HIV/AIDS have not regularly enrolled in clinical trial for cancer treatment, the optimized therapy for PLWH with cancer is controversial [81]. In the future, the enchantment of foundation and clinical research in this field should be expected. Current epidemiology studies indicated that PLWH seems to be more susceptible for most cancers [82]. Considering that, PLWH should be closely monitored for both ADCs and NADCs. And for treatment, multidisciplinary cooperation including specialists of infectious disease, oncologist, and clinical pharmacist is strongly recommended.

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