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overview

The Changing Face of HIV-Associated Malignancies: Advances, Opportunities, and Future Directions

Kathryn Lurain, MD, MPH[1]; Robert Yarchoan, MD[1]; and Ramya Ramaswami, MBBS, MPH[1]

Because of tremendous advances in HIV care, the survival of many people living with HIV (PLWH) now approaches that of the general population. This has led to a shift in the types of malignancies diagnosed among PLWH from AIDS-defining cancers during the height of the HIV epidemic toward more non-AIDS–defining cancers and age-related incidental cancers in the last 2 decades. Despite these trends, positive cancer outcomes still lag behind patients without HIV, and many PLWH never receive appropriate cancer therapy. We explore the reasons for the epidemiologic shift that has been observed, as well as the factors that influence treatment disparities. Furthermore, several studies have demonstrated similar cancer survival rates when PLWH and certain cancers receive the same treatment as those who are HIV-negative. Among possible solutions to improve cancer outcomes include increasing the inclusion of PLWH in clinical trials, using guidelines specific for the treatment of HIV-associated malignancies, and incorporating a multidisciplinary approach to cancer management in PLWH.

HIV and cancer have had a longstanding association. On July 3, 1981, the Centers for Disease Control and Prevention reported the occurrence of 26 cases of an aggressive form of Kaposi sarcoma (KS) that occurred in young homosexual men in New York and California.[1] At that time, the overall incidence of KS was less than two cases in three million people. The description of this group of patients was vastly different from the initial description of this disease by Moritz Kaposi almost a century earlier, because the eponymous condition was primarily seen among older men of Mediterranean heritage. These cases, in the 20th century, were one of the first warning signs of the coming HIV epidemic. Since that time, the field of HIV has adopted many of the practices and research techniques developed in the field of oncology, from clinical trial design to HIV resistance testing.[2] As a result, there has been extraordinary progress in the diagnosis and management of HIV, so much so that we now refer to this group of individuals as people living with HIV (PLWH). In the United States, the life expectancy for most PLWH on antiretroviral therapy (ART) now approaches that of the general population.[3] However, despite decreasing rates of cancer among PLWH in the United States, cancer is now the leading cause of death among this population in high-income countries.[4,5] In this article, we ask why this is the case and how can we improve cancer outcomes in PLWH.

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THE EPIDEMIOLOGY AND SCIENCE OF HIV AND CANCER

In addition to KS, aggressive non-Hodgkin lymphomas, such as diffuse large B-cell lymphoma and Burkitt lymphoma, occur at excessively high rates in severely immunocompromised patients with advanced HIV and low CD4+ T-cell counts. In addition, there is an increased incidence of cervical cancer. These tumors are termed AIDS-defining malignancies (ADCs).[6] It became apparent over time that many other malignancies occur at higher rates in PLWH with lesser degrees of immunosuppression, and these are termed non-AIDS–defining malignancies (NADCs), including Hodgkin lymphoma, oropharyngeal cancer, anal cancer, hepatocellular carcinoma, and non–small cell lung cancer. PLWH are also at risk for the same malignancies that occur at high rates in the general population, although the overall risk of prostate, breast, and colon cancer is not increased.[7-9] Improved immune function associated with the use of ART has led to a shift in the predominant types of cancers that affect PLWH, from AIDS-defining tumors to non-AIDS–defining tumors over the past 2 decades.[7]

Excess cancers occur in PLWH for several reasons (Fig. 1). One is immunosuppression, which permits the development of a number of tumors, especially those caused by oncogenic viruses; there is a higher prevalence of these among PLWH.[10] The areas and risk groups with the highest incidence of KS align closely with the areas of highest prevalence of Kaposi sarcoma herpesvirus (also known as human herpesvirus-8), the causative agent of KS.[11] In addition, a higher percentage of diffuse large B-cell, Hodgkin, and Burkitt lymphomas are associated with Epstein-Barr virus in

PRACTICAL APPLICATIONS

- HIV is an independent risk factor for the development of many cancers.
- A diagnosis of HIV alone should not be used as a reason to offer less aggressive treatment or to forgo cancer therapy.
- When people living with HIV receive the same cancer treatment as those without HIV, cancer outcomes are the same for many cancer subtypes.
- Cancer treatment-related toxicities are often due to anticancer agents rather than the concurrent diagnosis of HIV.
- Cancer care among PLWH should include, when feasible, an oncologist, HIV specialist, oncology pharmacist, and HIV pharmacist to reduce the possibility of drug-drug interactions and treatment-associated complications.

PLWH than in the general population. Together, with transmission of HIV, unprotected sexual contact may lead to transmission of HPV, a causative agent of cervical, anal, and oropharyngeal cancer, as well as hepatitis B virus, one cause of hepatocellular carcinoma. Needles shared to inject drugs may lead to transmission of hepatitis B virus as well as hepatitis C virus, which has also been linked to hepatocellular carcinoma. Unfortunately, the incidence of hepatocellular carcinoma continues to rise among PLWH despite the availability of treatments for hepatitis B virus and hepatitis C virus, which decrease the risk for the development of these cancers.[12] Even when HIV is well-controlled with ART, chronic immune activation and dysregulation persist, leading to alterations in both innate and adaptive immunity required to control carcinogenesis.[8,13] Chronic antigen stimulation from HIV or other viruses leads to T- and B-cell exhaustion, and the loss of effector functions and effective antibody production.[14,15] Immune dysregulation and a higher use of tobacco products among PLWH also increase the risk of lung and oropharyngeal cancers. In addition to these risk factors, an aging immune system may also alter cancer risk in PLWH. Compared with the general population, overall cancer risk is elevated in older PLWH, particularly for NADCs.[16] Because the proportion of PLWH who are age 65 or older is expected to triple by 2030, it is likely to change the proportion of both ADCs and NADCs in this population.[17]

Since the introduction of ART, the distribution and incidence of cancers have changed. In the United States between 1996 and 2012, the incidence rates of ADCs decreased compared with NADCs.[17,18] If these incidence rates remain stable, the projected burden of ADCs will decrease from approximately 30% of the total cancer burden in 2010 to 11% in 2030 among PLWH.[17] The same cancer projection models estimate prostate cancer followed by lung, non-Hodgkin lymphoma, KS, anal, liver, and colon cancers will be the most common cancers in 2030, reflecting an aging population of PLWH.[17] Although these statistics and models offer an optimistic outlook, the cancer mortality among PLWH with NADCs continues to increase, and mortality associated with ADCs outside of clinical trials has not changed over time, despite the introduction of ART.[19,20] Therefore, these tumors remain relevant to oncologists, and it is important for them to understand viral oncogenesis and the association between immunodeficiency and cancer. Furthermore, these statistics do not apply globally, where prevalence of oncogenic viruses is even higher and access to HIV and cancer care may be challenging, varied, and limited. Certain ADCs have a high incidence in sub-Saharan Africa and lead to death in young people diagnosed with HIV.[21] Therefore, finding new ways to diagnose, treat, and improve cancer outcomes in PLWH remains pertinent for oncologists everywhere.

CANCER DIAGNOSIS AND TREATMENT IN PLWH

Cancer mortality in PLWH may be the result of several factors, such as immunosuppression associated with HIV, disparities in access to care and timely diagnosis, and complications related to cancer treatment. Overall, PLWH are diagnosed with cancer at younger ages and with higher stage disease than the general population with the same cancers.[22,23] Within the United States, a recent meta-analyses of cancer screening of NADCs among PLWH provided insight into social factors associated with cancer screening disparities. PLWH who had access to health care were more likely to undergo cancer screening.[24] Particularly in low- and middle-income countries, existing models of HIV health care infrastructure can be used to integrate screening and diagnosis to address noncommunicable diseases such as cancer.[25]

Oncologists unfamiliar with treatment of cancer among PLWH may have concerns about the safety of cancer therapies in this complex population. Unfortunately, some PLWH fail to receive any treatment of their cancer, which contributes to increased cancer mortality.[26,27] Among PLWH, low CD4+ T-cell count, older age, intravenous drug use as the mode of HIV transmission, black race, and metastatic disease have been associated with a lack of cancer treatment.[26] These concerning findings extend to all stages of cancer and to multiple cancer treatment modalities, including chemotherapy, surgery, and radiation.[27,28]

Hesitancy to treat patients within this immunosuppressed population may arise for fear of infectious complications, dose delays caused by treatment-associated toxicities, or a perceived lack of benefit. Other reasons given for

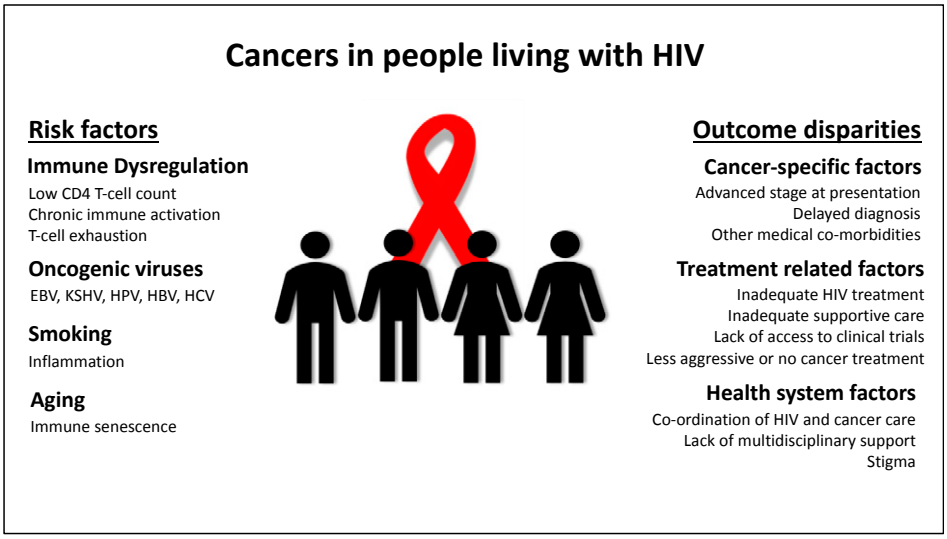

FIGURE 1. Causes of Increased Incidence and Outcome Disparities in People Living With HIV and Cancer

Abbreviations: EBV, Epstein-Barr virus; KSBV, Kaposi sarcoma herpesvirus; HBV, hepatitis B virus; HCV, hepatitis C virus.

disparities in care are the paucity of evidence and previous lack of guidelines for the treatment of cancer in PLWH. However, over time, several studies have demonstrated that administration of standard combination chemotherapy agents for diseases such as Hodgkin lymphoma, lung cancer, and anal cancer, have not resulted in differences in treatment outcomes between patients with and without HIV.[29-31] The management of HIV-associated lymphomas offers particular insight into how oncologists have learned to provide comprehensive cancer care to PLWH during the last few decades. From the pre-ART era to the current age of modern ART, it has become feasible and safe to use full-dose combination immunochemotherapy with opportunistic infection prophylaxis to achieve equal survival outcomes, even in patients with low CD4+ T-cell counts.[32,33] In cases of relapsed or refractory lymphoma, PLWH were initially denied hematopoietic stem cell transplantation. In the late 1990s, retrospective analyses provided encouraging and reassuring safety results, which have been further reinforced by efficacy data from prospective clinical trials in the last 10 years.[34,35] Therefore, it is possible to see the same outcomes, provided that patients with HIV receive timely and appropriate therapy with specialist support.

In 2018, the National Comprehensive Cancer Network published Guidelines for Cancer in People Living with HIV, which was further updated in 2019.[36] Based upon available data, these expert guidelines recommend that most PLWH who develop cancer should be offered the same cancer therapies as HIV-negative individuals. Most importantly, HIV itself is not a reason to offer less aggressive cancer-directed therapy. Ensuring that patients have a careful assessment of concurrent infections before and during treatment are important steps. Furthermore, offering supportive care in the form of opportunistic infection prophylaxis and assessing drug interactions before cancer therapy initiation are ways to reduce treatment-related complications. There is guidance for universal concomitant use of ART throughout cancer therapy and the need for a multidisciplinary approach to cancer care for PLWH.

HOW CAN WE DO BETTER?

The treatment of PLWH and cancer is best undertaken with a multidisciplinary team, which should include an oncologist, HIV specialist, oncology pharmacist, and HIV pharmacist. Specialist centers should also provide nurses, social workers, and outreach staff trained in the care of these complex patients. Many oncology practices in the United States do not have access to these types of specialists, and many PLWH would be best served by receiving treatment at a referral center with experience treating PLWH and cancer. This may lead to improved outcomes, as shown in studies from the United Kingdom.[37] Most importantly, creating an environment free of stigma or prejudice is crucial because many patients encounter these issues within the health care system. PLWH face stigma from health care providers themselves because of their HIV status but also because of race, sexual orientation, and lifestyle.[38] This leads to mistrust of health care professionals, which can adversely affect cancer outcomes.

To close the gap in outcomes between PLWH and cancer and the general population, PLWH need access to the latest advances in cancer care and clinical trials. A review of HIV-related eligibility criteria from National Cancer Institute–sponsored studies by the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group recently found that HIV remains a common exclusion criterion in cancer clinical trials, and, in many cases, these trials do not provide sufficient scientific justification for the exclusion of PLWH.[39] The HIV Working Group addressed how HIV can be incorporated into inclusion criteria for most

early phase clinical trials, while prioritizing the safety of PLWH with cancer.[40] This is key to increasing access to novel therapies for PLWH because lack of data may impair oncologists from offering new cancer treatments to this population of patients. In the case of immunotherapy, data on the safety and efficacy in PLWH are limited to retrospective case reports.[41] This is particularly unfortunate because immunotherapy is increasingly a standard treatment in many cancers that occur at higher rates in PLWH. Although concerns have been raised that these approaches may not be efficacious in PLWH because of immunosuppression, early results suggest that they can be both safe and effective.[41] The usefulness of this class of drugs and other emerging therapies is best assessed prospectively with the inclusion of PLWH in clinical trials.

CONCLUSIONS

Despite the vast improvement in HIV care over the past 3.5 decades, cancer remains one of the most important health concerns facing PLWH today in the United States and throughout the world. Oncologists must be aware of the unique needs of this population because advances in HIV treatment have led to an aging population of PLWH who are increasingly susceptible to cancer. Growing evidence has demonstrated the safety of novel cancer agents in PLWH, and we hope investigators will consider the inclusion of PLWH in clinical trials. Continued efforts by the oncology community as a whole must be made to ensure justice, excellent cancer care, and continued improved outcomes for PLWH.

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AFFILIATION

[1]HIV & AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD

CORRESPONDING AUTHOR

Ramya Ramaswami, MBBS, MPH, 10 Center Drive, Room 6N106, Bethesda, MD 20892; email: ramya.ramaswami@nih.gov

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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