



Addressing the Challenges of HIV/AIDS-Defining Non-Hodgkin's Lymphomas in Sub-Saharan Africa

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Abstract

Southern Africa has the highest HIV incidence worldwide. Thus far there is no cure; however, the lives of individuals infected with the virus can be prolonged through the use of Highly Active Anti-Retroviral Therapy (HAART). According to the United Nations Programme on HIV and AIDS (UNAIDS) fact sheet for 2015, 2 out of 3 new HIV infections are in the Sub-Saharan African region, with approximately 25.8 million people living with HIV and 1.4 million new infections in 2014. In 2004, South Africa introduced ART (Anti-retroviral Therapy) free of charge in the public healthcare sector, and today South Africa has the largest treatment programme in the world - approximately 2.4 million people have received the life-saving treatment which has significantly increased their life expectancy.

Introduction

With this prolonged lifespan has emerged a new challenge: HIV infected people acquire HIV related co-morbidities, one of which being HIV-defining cancers. Non-Hodgkin's lymphoma (NHL) is one of the most common HIV/AIDS-defining malignancy, with Diffuse Large B Cell Lymphoma (DLBCL) and Burkitt's lymphoma (BL) being the main subtypes affecting HIV infected individuals [1-4]. Both are highly aggressive cancers of the immune system, and have significantly increased incidences among HIV positive people, compared to the general population. Studies show that despite combination antiretroviral therapy (HAART combined with or preceding chemotherapy), the outcome of these lymphomas among HIV infected individuals remains inferior compared to HIV-uninfected patients suffering from the same cancers [5]. Clinical, genetic and molecular observations suggest that these cancers have a unique pathobiology in HIV positive patients and that new and improved treatment options are needed.

The design of new therapeutic strategies should be guided by a thorough understanding of the genetic landscape of DLBCL and BL in HIV positive patients, as well as the molecular mechanism of disease. The pathobiology of HIV-associated cancers is unique and in recent years some HIV-encoded proteins have been shown to have a direct and active oncogenic role in the development and progression of certain HIV-associated malignancies. The most convincing evidence yet is seen in HIV-associated Kaposi sarcoma (KS) in a study by [6]. HIV Nef and the HHV8 protein K1 of the Kaposi's sarcoma-associated herpesvirus (KSHV) were found to synergistically promote cellular proliferation and angiogenesis through the PTEN/AKT/mTOR pathway, which was in turn mediated by miR-718 [5]. Further studies have shown that infection with KSHV alone among HIV infected individuals is not the driving force of KS, but rather it is the complex interactions between KSHV, genetic susceptibility, immune status, and HIV infection that determine the oncogenic outcome [6].

Diffuse Large B Cell Lymphoma (DLBCL) and Burkitt's lymphoma (BL) are both aggressive cancers of B cell origin, and a major cause of mortality among HIV positive individuals. Currently, the pathobiology of HIV-DLBCL and HIV-BL is poorly understood. Gene expression profiling studies (GEP) have identified different subsets of DLBCL and this suggests that DLBCL comprises several disease entities that might ultimately benefit from different therapeutic approaches [7]. Primarily, two genetically distinct groups were identified: the germinal center B-cell-like (GCB) DLBCL and the activated B-cell-like (ABC) DLBCL, with ABC-DLBCL being the more aggressive and refractory subtype. Therefore GEP has been a powerful tool in delineating a group of heterogeneous disease seemingly morphologically identical, but which are molecularly and genetically distinct. This has had profound significance and impact in disease prognosis and management (although not yet in South Africa), and currently a number of clinical trials are underway aimed at evaluating combinations of

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novel targeted agents for these two subtypes [8]. Despite undergoing therapy, about 40% of HIV negative DLBCL patients suffer from relapsed or refractory disease under current the chemotherapeutic regimens (R-CHOP-rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone) [9]. The majority of them succumb to their disease. The poor response is largely attributed to how genetically and molecularly heterogeneous the disease is [10]. Among DLBCL patients who are HIV positive, response to standard therapy is even more heterogeneous. Currently, the genetic causes of HIV-DLBCL are unknown. Additionally, the contribution of Epstein Barr Virus (EBV) co-infection, which is common in HIV-DLBCLs, is also unknown and current studies in our laboratory are focusing on exploring the genetic and molecular subgroups of HIV-DLBCL patients within our population.

While HIV uninfected patients with BL generally respond well to existing therapy, the response in HIV infected patients remains poor, and in some settings, there is report of no improvement at all [11-13]. The pathogenesis of BL is strongly related to the overexpression of c-MYC resulting from translocation of the c-MYC gene to the highly active immunoglobulin (IGH) locus in B cells. The common treatment approach for BL is surgical resection if necessary, followed by chemotherapy. Different combinations of chemotherapeutic agents are used such as cyclophosphamide, Vincristine, doxorubicin and dexamethasone; and in HIV positive patients this is administered after HAART [13,14]. Several case studies have shown that despite combination antiretroviral therapy, the outcome of HIV infected individuals with BL remains inferior compared to HIV-uninfected patients suffering from this cancer. Contrary to what is expected, some reports found that BL incidence among HIV infected individuals has not improved significantly despite the advent of HAART, and that the cancer develops in patients with relatively high CD4 counts [5]. The latter observation points to other enabling factors, aside from an immunocompromised state. Indeed, in recent years, our laboratory as well as others have shown that HIV-encoded proteins can contribute to oncogenesis by activating or enhancing oncogenic pathways in B cells. This is already shown in Kaposi sarcoma where the HIV Tat protein was found to cooperate with the Kaposi sarcoma herpes virus (KSHV) to enhance the development of the cancer [15].

Conclusion

The oncogenic role of HIV in lymphoma is an emerging concept which is rapidly gaining credibility as more reports emerge supporting this. Recent studies indicate that viral proteins, presenting either extracellularly or within B cells, may be directly promoting cancer development and/or progression. For example, a study by Popovic et al. [16] demonstrated that HIV-1 structural proteins p17, p24 and gp120/gp41 continued to persist in the germinal centres of lymph nodes in HIV positive patients undergoing HAART treatment which resulted in the deregulation of B cells. Another study found that the HIV-1 p17 could interact with an unidentified-cell surface receptor, resulting in increased phosphorylation and activation of c-MYC and CREB which in turn switch on genes required for cell proliferation and survival [17]. A very recent study showed that when normal B-cells from healthy donors are incubated with transcriptionally active HIV Tat protein, there is up to 10-fold increase in the MYC gene locus moving closer towards the IGH locus, compared to controls [18]. Moreover, studies in our laboratory have demonstrated that HIV proteins Tat and Nef have the ability to enhance an important driver of c-MYC translocation, namely the DNA modifying enzyme

activation-induced cytidine deaminase (AID) as well as expression of c-MYC itself [19]. This is achieved through various mechanisms including activation of transcription factors, as well as deregulation of microRNAs. Our team uses a multidisciplinary approach; novel and powerful sequencing technologies; as well as molecular tools; to identify genes and molecular pathways contributing to disease in an HIV positive setting with the ultimate goal to develop more effective therapies for our patients.

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