Malignancies in People with HIV: Successes and Challenges at the Intersection of Virology, Immunology, and Oncology

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In 1981, a cluster of cases of Kaposi sarcoma (KS), a hitherto rare skin tumor, in previously healthy men who have sex with men in the US, often along with *Pneumocystis* pneumonia, heralded the onset of the HIV/AIDS pandemic. The frequent occurrence of KS in people with HIV (PWH) remained a puzzle until 1994 when Yuan Chang, Patrick Moore and colleagues showed that this tumor was caused by a novel gammaherpesvirus, Kaposi sarcoma herpesvirus (KSHV), and epidemiologic studies documented the simultaneous spread of KSHV and HIV among men who had sex with men during the early 1980s. Over the next several years, it became apparent that PWH had a substantially increased risk of certain other tumors, including aggressive B cell lymphomas. We now know that most of the tumors associated with HIV are caused by oncogenic viruses, including Epstein Barr virus (EBV), KSHV, and human papillomavirus (HPV). The subsequent development of anti-retroviral drugs, initially spearheaded by NCI scientists and collaborators, and the widespread use of these drugs converted AIDS from an almost universally lethal disease to a manageable condition. It also resulted in a substantial decline in the incidence of those tumors (such as primary central nervous system lymphoma) associated with very low CD4 counts. However, as PWH lived longer and the population of PWH increased, there was a substantial increase in the number of other tumors (such as anal carcinoma) that occur at higher CD4 counts. Also, we continue to see new cases of KS and other tumors associated with severe immunodeficiency. KS is increasingly a disease of minority communities in the US and its incidence is rising in young Black men in the rural South. Moreover, HIV-associated tumors continue to be a major public health issue in sub-Saharan Africa and other low- and middle-income countries (LMIC). In particular, KS continues to be the most common tumor among men 65 or younger in several countries in sub-Saharan Africa.

Before the development and use of combination anti-retroviral therapy (cART), PWH who developed cancer often could not tolerate full doses of chemotherapy and treatment regimens employing lower doses of chemotherapy drugs were used, usually with relatively low rates of cure. This has changed, and in general cancers in PWH are best treated with standard-dose regimens that would be used in the general population. For some cancers, such as Hodgkin lymphoma and non-small cell lung cancer, data have shown that when PWH are treated with standard chemotherapy regimens, their outcomes are the same as the general population. In the past several years, there has been a revolution in the development and use of immunologic therapy for various cancers, such as anti-PD-(L)1 monoclonal antibodies. However, there has been a reluctance to enroll PWH on clinical trials using immunotherapy approaches because of concern that the agents may not be tolerated or may not be effective because of the CD4 T cell lymphopenia. Two recent trials, one by the Cancer Immunotherapy Trials Network with the NCI Intramural Program (TS Uldrick et al., *JAMA Oncology*, 2019) and one by the AIDS Malignancy Consortium (AMC) (TA Rasmussen et al., *Clin. Infect. Dis.,* 2021) showed that these agents could be administered safely to PWH and can have activity. Anti-PD-

(L)1 agents are generally most effective in tumors with high mutational burden resulting in neoantigens. Virus-induced tumors tend to have low mutational burdens. However, the oncogenic viruses themselves can provide novel antigens for attack, and these tumors are thus potentially attractive targets for such therapies. A problem, however, is that oncogenic viruses have evolved various mechanisms to suppress expression of surface immune markers (such as MHC-1, B7-2/CD86, or ICAM-1), making the tumor cells invisible to the immune system.

Our group recently conducted a clinical trial showing that pomalidomide, a cereblon-binding immunomodulatory drug, was active against KS (MN Polizzotto et al., J. Clin, Oncol. 2016; R. Ramaswami et al., *Clin Cancer Res.,* 2022). Based on this trial, pomalidomide was recently approved by the US Food and Drug Administration for KS. Also, the AMC is studying the feasibility of using pomalidomide against KS in sub-Saharan Africa and other LMIC. In investigating possible mechanisms of its activity, David Davis, Prabha Shrestha et al. in our group found that pomalidomide could reverse or prevent the KSHV-mediated downregulation of surface immune marker expression, at least in lymphoid cells (DA Davis et al, *Oncoimmunology*, 2018; P Shrestha et al., *PLoS Path*, 2021). Surprisingly, this upregulation was not found in KSHV-infected endothelial cells (a model for KS), and it isn't clear if this accounts for the activity of pomalidomide in KS. At the same time, it suggested that this approach might be worth considering in other virus-induced tumors and moreover, that pomalidomide and related drugs might be worth combining with checkpoint inhibition (for example with anti-PD-(L)1 antibodies) in these tumors. We are now testing this in an ongoing study in the NCI HIV and AIDS Malignancy Branch (NCT04902443). In a limited retrospective study, Kathryn Lurain et al. in our group (K Lurain et al., *J. Immunotherapy Cancer*, 2021) have shown that pembrolizumab with pomalidomide can be effective in HIV-associated lymphomas caused by EBV. Also, we have been exploring the use of other agents that can enhance expression of surface immune markers in virus-infected cells. Yi-Quan Wu et al in our group recently showed that the CDK4/6 inhibitor abemaciclib could upregulate surface immune markers in KSHV-infected endothelial cells as well as in lymphoid cells (Y Wu et al., *J. Translational Med*., 2022) and we are now studying this in a clinical trial for KS (NCT04941274).

In addition to KS, KSHV is the cause of several other severe diseases that occur predominantly in PWH, including a form of multicentric Castleman disease (MCD), primary effusion lymphoma (PEL), and KSHV-inflammatory cytokine syndrome (KICS). These diseases often occur together in the same patient. KSHV-MCD and KICS are characterized by severe inflammatory symptoms associated with increased levels of various cytokines, especially human interleukin-6 (IL-6), interleukin-10 (IL-10), and a KSHV-encoded form of IL-6 (vIL-6). Recent studies by our group and others have suggested that a key pathway in these diseases is the induction of human cytokines by vIL-6 and other factors produced by KSHV-infected cells. We are currently exploring mechanisms to specifically target these pathways.

Thus, while we have made substantial progress in the prevention and therapy of HIV-associated malignancies, they continue to pose a major health problem. At the same time, our increasing understanding of the pathogenesis of these tumors is leading to novel approaches to their treatment.

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