



Cancer and AIDS: National Cancer Institute's investment in research

By Ellen G. Feigal, MD, and Jodi B. Black, PhD

Research on AIDS-associated malignancies has focused on the interplay of immunity and viral infections and has increased our understanding of cancer pathogenesis. But what have we learned, and how can we build upon our knowledge to develop improved preventive and therapeutic interventions? This article outlines resources available from the National Cancer Institute (NCI) to stimulate research and to increase our knowledge of the underlying pathophysiology of HIV/AIDS-associated malignancies and the development of more effective interventions.

The role of viruses and immunity

By now, we know that viruses clearly play a major role in the development of cancer in HIV-infected individuals. Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), anogenital dysplasia, and cervical cancer feature specific infectious agents in their etiology. These infectious agents are human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus (HHV-8/KSHV) in Kaposi's sarcoma; Epstein-Barr virus (EBV) in primary central nervous system lymphoma (PCNSL) and a subset of systemic B cell NHL and pediatric leiomyosarcomas; and human papillomavirus (HPV) in anogenital dysplasia and cervical cancer. Immunity has a critical function in the development of cancers, both in HIV-infected individuals as well as in those individuals with depressed immune systems caused by congenital conditions or iatrogenically induced in the transplant setting. Infection with HIV alters the immunologic landscape, most markedly noted in impaired quality and insufficient quantity of CD4 helper T cells, and dysregulated cytokine expression resulting from persistent antigen stimulation.

The changing face of HIV/AIDS and cancer

While the widespread use of highly active antiretroviral therapy (HAART) has led to a rapid decline of incidence in certain cancers (see article on page 5), the types of cancers associated with AIDS have not substantially changed since the beginning of the AIDS epidemic. So why the decrease in some cancers but not others? The dramatic effect of HAART on KS and PCNSL incidence is postulated to result from partial reconstitution of immunity and enhanced responses to viral and other tumor antigens. However, other plausible explanations that are likely to be concomitantly involved include: 1) inhibition of the broad spectrum HIV trans-activating protein Tat, 2) decreased expression of growth factors and cytokines contributing to cancer development and maintenance, 3) direct antitumor effects of protease inhibitors, and 4) direct effects of HAART on HHV-8 or EBV. But how these mechanisms contribute on an individual patient basis and the differences in their effects or apparent lack of effect are not understood.

The longer life expectancy of HIV-positive people with access to HAART may actually increase the cumulative risk of developing cancer. This, coupled with HAART class switching because of HIV drug resistance, may lead to an increase in the incidence of non-AIDS-defining cancers, including Hodgkin's disease (HD) and lung cancer. HD is currently the most frequently diagnosed non-AIDS-defining cancer that is related to immunosuppression. Lung cancer risk is increased in the HIV-positive population, occurring at a younger age and more frequently in the HAART era. The outcome of these patients remains poor despite HAART. In addition, there are

reports of increased risk of several rare malignancies and proliferative lesions, including Merkel cell carcinoma, squamous cell carcinoma of the conjunctiva, and multicentric Castleman's disease. As HAART becomes available in developing countries, the resulting longer life expectancy combined with the endemic viruses associated with cancer portend an increase in AIDS malignancies in these regions.

Current activities towards developing more effective treatment strategies for HIV/AIDS-related malignancies include: 1) targeting molecules in the angiogenesis and apoptotic pathways; 2) fortifying the immune system using immunomodulatory molecules, vaccines designed to increase the cell-mediated immune responses to viral antigens, and monoclonal antibodies to eliminate cancer cells; 3) targeting EBV or KSHV to disrupt the viral life cycle; 4) investigating low morbidity anal lesion ablation techniques, and 5) combining standard chemotherapy regimens with biologic therapies.

Gaps in our knowledge

What is needed is a better understanding of the pathways to cancer development: whether they are similar in HIV-positive versus HIV-negative individuals and whether we can extrapolate treatment modalities used in the immunocompetent population or need to develop new treatment regimens. Also, we need a better understanding of the roles of HIV viral loads and CD4 T cell counts, immune cell function, and HAART in cancer pathogenesis, treatment, and control. The association of viruses with the AIDS-defining malignancies suggests differential involvement of immune function and viral gene expression in tumor development. Additional research into the precise interactions of viral gene expression and impaired or dysregulated immunity in cancer development and maintenance are required.

NCI resources

In cooperation with other divisions at the National Institutes of Health (NIH), NCI developed a multi-component AIDS Malignancy Program to stimulate and facilitate the integration of the biology and epidemiology of AIDS malignancies with the devel-

opment of treatment strategies. The AIDS Malignancy Program was designed to assist the research community in studying the interplay of viruses, immune dysfunction, aberrant growth factor expression, and the development of cancer in AIDS patients, with the goal of creating more effective treatment regimens. A description of the pertinent components follows.

Bringing more effective treatments to the clinic.

The Inter-Institute Program (IIP) for the Development of AIDS-related Therapeutics is a joint effort between the National Institute of Allergy and Infectious Diseases (NIAID) and NCI. The program aims to promote the preclinical development of microbicides as well as therapies for treating HIV disease, AIDS-associated malignancies, and opportunistic infections associated with AIDS including tuberculosis. The program assists investigators from academic institutions, nonprofit research institutions, and biotechnology and small pharmaceutical companies by providing access to NIH contract resources for therapeutics development. Services include high-throughput screening, studies in animal models, formulation, pharmacology and toxicology studies, and bulk substances acquisition. Additional information and application receipt dates can be found at dtp.nci.nih.gov/docs/dart/dart.html

Clinical trials. The AIDS Malignancy Consortium (AMC) was developed in 1995 to expedite the rapid evaluation of hypothesis-driven Phase I, II, and III multicenter clinical trials that utilize the expertise of both NCI- and NIAID-sponsored scientists. Their charge is to identify therapeutic approaches for the treatment of malignancies in AIDS (also see page 30). These approaches include biologic therapy using interleukin (IL)-2, IL-12, interferon-alpha, monoclonal antibodies directed against B cell targets, cytotoxic T lymphocytes directed against viral targets, immune-based therapy, stem cell reconstitution, angiogenesis inhibitors, therapeutic vaccines, and traditional cytotoxic chemotherapy regimens (often in combination with a biologic or immuno-

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logic approach). In addition to assessing potential antitumor activity and drug-drug interactions, the AMC also evaluates the impact of therapy on viral load and underlying immune function. Additional information about the AMC can be obtained at www.amc.uab.edu

Training. The AIDS Oncology Clinical Scientist Training Program was developed in response to the important need for trained AIDS-oncology specialists. The program was developed to exploit research opportunities, conduct patient-oriented research, and provide the clinical management skills necessary for the advancement of this field. A cadre of clinicians was trained with the highly specialized skills necessary to address the clinical and research problems associated with AIDS-related malignancies.

Access to biospecimens. The AIDS and Cancer Specimen Resource (ACSR) is the nation's leading multisite resource for tissues, fluids, and clinical data collected from HIV-positive patients with cancer. The ACSR was established in 1994 to identify and to improve access to well-characterized tissues, fluids, and associated demographic and clinical data collected from HIV-positive patients and HIV-negative controls. The ACSR contains over 100,000 specimens collected from cohort studies, clinical trials, and other research sources (including international research). Information on available specimen types and how to obtain them is available at acsb.ucsf.edu.

Setting the research agenda. The AIDS Malignancies Working Group (AMWG) was established in 1996 and is charged with identifying the major research priorities in AIDS malignancies. This multidisciplinary group includes members from both the intramural and extramural components of NIH, researchers outside of NIH, and community representatives. The group meets yearly to discuss the biomedical research opportunities for AIDS malignancies, the clinical gaps in our knowledge, and mechanisms to move the research

forward and address specific issues. Summaries from recent AMWG meetings are available at deainfo.nci.nih.gov/ADVISORY/pog/other_wg/index.htm.

Fostering scientific exchange and international collaboration. The International Conference on Malignancies in AIDS and Other Immunodeficiencies (ICMAOI) is a forum for the presentation of basic, epidemiologic, and clinical aspects of research on malignancies in HIV-infected and other immunosuppressed individuals. The objective is to facilitate information exchange between investigators from laboratory and clinical settings to decrease the interval between basic discovery and clinical application. The scope of the conference includes basic and clinical research on viral oncology, immunology, genetics, epidemiology, pathogenesis, drug discovery, and early diagnosis of malignant diseases in AIDS and other immunodeficient states including organ transplantation. Additional information about the international conference is available at www3.cancer.gov/dctd/aids/conference/index.html.

NCI investment in AIDS oncology. The *AIDS Oncology Resource Handbook* provides a comprehensive listing of the clinical and laboratory research resources that receive NCI funding. A brief synopsis of the research studies and recent accomplishments is provided, as well as personnel contact information. The Handbook can be viewed in its entirety at ctep.cancer.gov/resources/aids.html.

NCI partners in AIDS oncology research. NCI partners with other National Institutes and Centers to promote epidemiology and natural history studies, infrastructure, training, and international capacity-building for research on cancer in HIV-positive individuals. NCI co-sponsors the Centers for AIDS Research (CFAR) program, which provides administrative and shared research support to synergistically enhance and coordinate high-quality AIDS research projects. CFARs accomplish this through core facilities that provide expertise, resources, and

services not otherwise readily obtained through more traditional funding mechanisms. There are 19 CFAR sites across the US. Additional information about the CFAR program and a site map is available at www.niaid.nih.gov/research/cfar/

NCI participates in the Multicenter AIDS Cohort Study or MACS (statepi.jhsph.edu/macs/macs.html) and the Women's Interagency HIV Study or WIHS (statepiaps.jhsph.edu/wihs). The MACS, which began in 1984, is an ongoing, multicenter, prospective study of the natural and treated histories of HIV infection in homosexual and bisexual men. The WIHS is a multicenter, prospective study established in 1993 to carry out comprehensive investigations of the impact of HIV infection in women. Both cohorts monitor changes in the natural history of HIV and associated conditions occurring as a result of treatment advances and longer survival.

Rates of HIV/AIDS-associated malignancies have increased in developing countries as a result of the HIV epidemic, thus NCI is helping to strengthen research on such malignancies in these geographic areas. For its international research agenda, NCI partners with the Fogarty International Center to build capacity for basic and clinical studies in resource-poor countries with significant HIV/AIDS incidence and prevalence via their AIDS

International Training and Research Program (AITRP) and the International Clinical, Operational, and Health Services Research Training Award (ICOHRTA). Both AITRP and ICOHRTA are training programs designed to enhance basic, clinical, and health services research on AIDS and co-morbid conditions (including cancer) in resource-poor areas. Information about both programs is available at www.fic.nih.gov/programs/aitrp/aitrp.html and www.fic.nih.gov/programs/ICOHRTA-AIDS-TB/ICOHRTA-AIDS-TB.html.

Conclusion

Current advances in research technology allow the identification of complex interactions between viruses, immune dysregulation, and genetic mutations to better understand their roles in cancer etiology and to develop targeted treatment strategies at an accelerated pace. This, coupled with decreased morbidity from cancer therapies in HAART-treated, HIV-positive patients, provides impetus for the development of more targeted or aggressive regimens that will lengthen patient survival. NCI has critical infrastructures and initiatives in place to further our understanding of both HIV/AIDS and cancer and to allow testing of novel therapeutic strategies. These challenges and opportunities will continue to evolve with the worldwide HIV epidemic as well as new advances in technology.

Ellen G. Feigal, MD, is Acting Director of the Division of Cancer Treatment and Diagnosis at NCI. Jodi B. Black, PhD, is Program Director of the AIDS Malignancy Program for the Division of Cancer Treatment and Diagnosis at NCI.
