Perspective

Non–AIDS-Defining Malignancies in HIV

During the potent antiretroviral therapy era, the incidence of AIDS-defining cancers has decreased and the incidence of non–AIDS-defining cancers (NADCs) has increased, as has the proportion of mortality associated with NADC in HIV-infected patients. The increase in NADCs is partly associated with increased longevity of the HIV-infected population, but it may also reflect consequences of increased immune activation and decreased immune surveillance as well as direct effects of HIV. The NADCs appear to have earlier onset and worse prognosis in HIV-infected patients than in the general cancer population. Among cancers that have increased in incidence are lung cancer, with its strong association with tobacco use, and skin cancers. Much remains to be learned about risk, risk reduction, optimal treatment, and drug interactions in HIV-infected cancer patients. This article summarizes a presentation on malignancies in HIV infection made by Ronald T. Mitsuyasu, MD, at an International AIDS Society-USA Continuing Medical Education course in San Francisco in May 2008. The original presentation is available as a Webcast at www.iasusa.org.

The incidence of non–AIDS-defining cancers (NADCs) has increased by greater than 3-fold over the past 10 years and has now surpassed that of AIDS-defining cancers (ADCs) in HIV-infected patients. Some of this increase is associated with the longer survival and aging of patients in the potent antiretroviral therapy era, but some also appears to be associated with direct effects of HIV that increase susceptibility to such cancers.

Early reports in the 1980s suggested that malignancies might constitute a second "epidemic" within the AIDS epidemic (Monfardini et al, *AIDS*, 1989). Kaposi sarcoma and non-Hodgkin lymphoma (NHL) initially accounted for the majority of malignancy-associated morbidity and mortality in HIV disease. With the advent of effective antiretroviral therapy, NADC as a cause of death in people with HIV has increased from less than 1% in the pre–potent antiretroviral therapy era to as high as 13% (Stein et al, *Am J Med*, 1992; Bonnet et al, *Cancer*, 2004).

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A report on cancer trends in HIV-infected patients between 1989 and 2002 showed that there has been an overall decline in cancer incidence from 77 cases to 12 cases per 1000 patient-years, reflecting a decline in incidence of ADC. During this period, however, the incidence of NADCs increased from 3.3 to 10.9 cases per 1000 patient-years (relative risk, 3.3; 95% confidence interval [CI], 1.7-6.6) (Bedimo et al, *Clin Infect Dis*, 2004). Among types of malignancies, incidences of Kaposi sarcoma and central nervous system lymphoma have decreased, those of prostate and breast cancer have remained relatively constant, and those of other lymphomas (eg, NHL and Hodgkin disease) and of cervical, anal, and lung cancers have increased (Table 1).

Contributing Factors in NADC

In addition to increased life expectancy and reduction of other causes of death in HIV-infected persons, contributors to the increased prevalence of NADCs include (1) greater prevalence of coinfection with viruses that have etiologic roles in cancer, including human herpesvirus 8 (primary effusion lymphoma, Kaposi sarcoma, Castleman disease), human papilloma virus (HPV; cervical, anal, penile, and possibly head and neck cancers), Epstein-Barr virus (Hodgkin disease, NHL, primary central nervous system lymphoma, pediatric leiomyosarcoma), and hepatitis B and C viruses (hepatomas); (2) behaviors and environmental toxins, including tobacco and alcohol use; and (3) effects of HIV infection, including potential direct effects of the virus and the consequences of long-term immunosuppression.

Potential direct effects of HIV include HIV Tat protein transactivation of cellular genes or proto-oncogenes. Various HIV genes have also been reported to inhibit tumor suppressor genes (eg, *TP53*). The incidence of lung cancers has rapidly increased in HIV-infected individuals, and cell culture studies have shown a 6-fold higher frequency of microsatellite alterations in cells from HIV-infected lung cancer patients than from non–HIV-infected cancer patients; it is suspected that the genetic instability may be a direct effect of HIV. Infection with HIV is believed to also increase the susceptibility of tissues to

Table 1. Changes in Incidence of Cancers Associated with HIV Since the Beginning of the Potent Antiretroviral Therapy Era in 1998

Kaposi sarcoma	↓
Central nervous system lymphoma	↓
Lymphoma (non-Hodgkin)	↑
Lymphoma (Hodgkin disease)	↑
Cervical cancer	↑
Anal cancer	↑
Lung cancer	↑
Prostate	↔
Breast	↔
Hepatoma	↔

Derived from data in Patel et al, *Ann Intern Med,* 2008.

the effects of carcinogens. Endothelial cell abnormalities have also been detected in HIV infection, including elaboration of angiogenic factors, which could serve to facilitate tumor growth.

A recent meta-analysis comparing the incidence of cancers in HIV-infected persons and immunosuppressed transplant recipients has strongly suggested a link between immunosuppression and cancer (Grulich et al, *Lancet*, 2007). Among 444,172 HIV-infected patients and 31,977 transplant patients, both groups had a significantly increased incidence of 20 of 28 cancers examined. For example, standardized incidence ratios for cancers in patients with HIV and AIDS and transplant recipients were 2.7 and 2.2 for lung cancer, 3.2 and 2.4 for leukemia, 1.5 and 6.8 for kidney cancer, 1.6 and 3.1 for esophageal cancer, and 1.9 and 2.0 for stomach cancer, respectively. There was some indication that hematologic malignancies may be more common in HIV-infected patients, with both populations having high frequencies of numerous solid tumors.

NADC Risk in HIV Infection

Data from the HIV Outpatient Study (HOPS) indicate differences in cancer risk among HIV-infected patients and non-HIV-infected cancer patients. In this analysis, age-, race-, smoking-, and sex-adjusted rates of NADCs were compared between 7893 HIV-infected patients in Chicago and Illinois cancer registry patients during the period of 1992 to 2002 (Clifford et al, *J Natl Cancer Inst*, 2005; Long et al, *AIDS*, 2008; Phelps et al, *Int J Cancer*, 2001; Serraino et al, *AIDS*, 2000; Giordano and Kramer, *Clin Infect Dis*, 2005; Patel et al, *Ann Intern Med*, 2008. HIV-infected patients had increased relative risk for Hodgkin disease (77.4), head and neck cancer (10.0), anorectal cancer (5.0), melanoma (4.1), and lung cancer (3.6). No excess risk for breast, colon, or prostate cancer was detected. The excess lung cancer risk was primarily related to tobacco use. Cancers occurred at an earlier age in both men and women with HIV infection than in non–HIV-infected patients.

An HIV natural history study among US military beneficiaries found 133 cases of NADC among 4144 participants during the period of 1988 to 2003, yielding an incidence rate of 980 cases per 100,000 person-years (Burgi et al, *Cancer*, 2005). The most common primary cancer was basal cell skin cancer, accounting for 32.3% of cancer cases, followed by squamous cell skin cancer (12.0%), Hodgkin disease (9.8%), anal cancer (7.5%), melanoma (6.8%), colorectal cancer (6.0%), prostate cancer (4.5%), renal cancer (3.0%), and lung cancer (2.3%); other cancers accounted for 15.8%.

The low rate of lung cancer in this study underscores the notion that rates of particular cancers in HIV disease reflect different risks (eg, behavioral, environmental, and genetic risk factors and prevalence of coinfections) in different populations. Comparison of rates in the study cohort with rates reported in the general population in the US Surveillance Epidemiology and End Results (SEER) database showed that white patients with HIV infection had higher rates of basal and squamous cell skin cancer, melanoma, Hodgkin disease, and anal cancers, whereas black patients with HIV infection had higher rates of lung and colorectal cancers in addition to higher rates of Hodgkin disease and anal cancers. On multivariate analysis in this cohort, predictors of NADC (all $P < .001$) were age greater than 40 years versus less than 24 years (odds ratio [OR], 12.2), white or non-Hispanic ethnicity versus black (OR, 2.1), longer duration of HIV infection (OR, 1.2 for each year), and history of opportunistic infection (OR, 2.5), with antiretroviral therapy being a negative predictor (OR, 0.21). Neither CD4+ cell count at time of diagnosis nor nadir CD4+ cell count was predictive of NADC.

At least 1 analysis also suggests that risk for NADC is not associated with viral load. The Strategies for Management of Antiretroviral (SMART) study, in which 5472 patients with CD4+ counts of 250 cells/μL to 350 cells/μL underwent randomization to either continuous viral suppression or drug-conserving, intermittent antiretroviral therapy, was stopped early because of greater frequency of mortality or other endpoints in the drug-conserving group. The second highest proportion of endpoints was from NADC (36%, with 25% of the 60 events being fatal) after cardiovascular disease (42%; hepatic and renal endpoints accounted for 12% and 10%, respectively) (Silverberg et al, *AIDS*, 2007). Analysis of risk for NADC, according to latest measure of plasma HIV RNA level less than or equal to 400 copies/mL versus greater than 400 copies/mL, did not yield a significant hazard ratio after adjustment for other risk factors (age, sex, prior diagnosis of AIDS, hepatitis B and C virus coinfections, smoking, latest CD4+ count) (Silverberg, *AIDS*, 2007). In this analysis, significantly reduced risk with lower versus higher viral load was observed for all serious non-AIDS-defining events, renal events, cardiovascular events, and other non-AIDS mortality, but not for liver events.

A review of the literature on NADC published in 2003 (Chiao and Krown, *Curr Opin Oncol*, 2003) indicated increased incidence rates in the United States for anal cancer, Hodgkin disease (mixed cellularity and lymphocyte-depleted types), lung cancer (adenocarcinoma, tobacco-related), testicular cancer (mostly seminoma), skin cancers (basal and squamous cell and melanoma), multiple myeloma, leukemia (mostly M4, M5 subtypes), and pediatric leiomyosarcoma (affecting 1 in 5000 and accounting for 8%-14% of pediatric cancers), as well as for lip, head and neck, penile, and conjunctival cancers. As of the time of that review, there had been no obvious increase in breast, colon, or prostate cancers, although it is possible that increased risk will be observed for these malignancies with longer and closer follow-up.

It has been difficult, however, to accurately define risk for cancer overall and for individual malignancies in HIV-infected persons because of several factors. These include absence of relevant or good-quality data in registries and databases, competing risk factors for death, underreporting, variations in screening practices, and underdiagnosis, as well as population

factors including differences in behavior and coinfections. The National Cancer Institute (NCI) has initiated a concerted effort to improve access to information on the incidence of cancer in HIV disease in both HIV cohorts and cancer registries in the United States. This and other efforts will ultimately allow us to better define risks and risk factors.

Issues in Management, Treatment, and Outcome

Available evidence suggests that HIV-infected cancer patients have a worse prognosis than similarly staged non–HIV-infected patients with the same cancer; they are also more likely to have more advanced disease at diagnosis. Data from a retrospective study comparing characteristics of HIV-infected patients and HIV-indeterminate subjects with lung cancer are shown in Table 2 (Brock et al, *JAIDS*, 2006). HIV-infected patients were much younger (median age 46 vs 64 years); were more likely to be black, past or current smokers, and injection drug users; had more advanced disease and a history of fewer pack-years of smoking; were less likely to undergo surgery with curative intent; and had significantly reduced median survival. An earlier study indicated that, as in the non–HIV-infected population, median survival was longer in HIV-infected lung cancer patients able to undergo resection (approximately 17 months) than in those receiving radiotherapy (approximately 7 months) or chemotherapy (approximately 3 months) without surgery, although few patients had resection as an option (4% vs 10% for radiotherapy and 86% for chemotherapy) (Powles et al, *Br J Cancer*, 2003).

Although available evidence also suggests that HIV-infected cancer patients should receive at least the same intensity of cancer therapy as non–HIV-infected patients, much remains to be learned in every facet of treatment and management of patients with NADCs. Unanswered questions and research needed can be categorized generally as follows:

Table 2. Lung Cancer Characteristics in HIV-infected Patients and HIV-indeterminate Patients

	HIV-infected (n = 92)	HIV-indeterminate (n = 4973)	*P* Value
Sex, no. (%)			
Male	62 (67.4)	2860 (57.5)	.06
Female	30 (32.6)	2113 (42.5)	
Age in years, no. (%)			
<40	12 (13.0)	99 (2.0)	
40-60	70 (76.1)	1594 (32.1)	<.001
>60	10 (10.9)	3280 (66.0)	
Age in years, median (IQR)	46 (42-59)	64 (57-71)	
Race, no. (%)			
White	19 (20.7)	3749 (75.4)	<.001
Black	73 (79.4)	1224 (24.6)	
Histology, no. (%)			
Adenocarcinoma	44 (47.8)	1754 (35.3)	
Squamous	16 (17.4)	1225 (24.6)	
NSCLC	14 (15.2)	814 (16.4)	.19
Small cell	8 (8.7)	379 (7.6)	
Large cell	5 (5.4)	432 (8.7)	
Other	5 (5.4)	371 (7.5)	
Stage, no. (%)			
I	6 (6.5)	1150 (23.1)	
II	6 (6.5)	447 (9.0)	<.01
III	17 (18.5)	1059 (21.3)	
IV	63 (68.5)	2317 (46.6)	
Smoking status, no. (%)			
Never	1 (1.1)	510 (11.2)	
Ever	91 (98.9)	4037 (88.8)	
Former	8 (8.7)	1815 (39.9)	<.001
Current	83 (90.2)	2222 (48.8)	
Pack-years, median (IQR)	30 (20-45)	50 (30-75)	
Injection drug use, no. (%)	53 (57.6)	47 (1.0)	<.001
Surgery with curative intent, no. (%)	13 (14.1)	1343 (27)	<.001
Survival, months, median (IQR)	6.3 (2.3-11.4)	9.4 (3.6-24.0)	<.001

IQR indicates interquartile range; NSCLC, non–small-cell lung cancer.
Adapted from Brock et al, *JAIDS,* 2006.

Efficacy

Are standard treatments for each stage of each cancer in non–HIV-infected patients similarly effective in HIV-infected patients? Does the presence of worse prognostic factors in HIV-infected patients require the use of more aggressive cancer therapy? Are molecular and virally targeted therapies more or less appropriate for use in HIV-infected patients?

Adverse Effects and Complications

Do HIV-infected patients experience additional and more severe toxicities from cancer therapies? What are the pharmacokinetic and pharmacodynamic drug interactions of HIV medications with cancer therapies? How can HIV therapies and cancer therapies be adjusted to minimize toxicities? For example, it is already known that the dosage of iri-

notecan, which is metabolized by cytochrome P450 enzymes, needs to be reduced in patients receiving HIV protease inhibitor therapy, and holding antiretroviral therapy may be prudent in some cases in which short-term, high-dose cancer chemotherapy is required that contains agents known to interact with antiretroviral drugs. We still need to determine what degree of toxicities is acceptable and can be managed in patients treated for NADC as well as the overall effect of these toxicities on quality of life. Are standard palliative measures for adverse effects effective in HIV-infected patients? What are the costs and benefits of more aggressive therapy, if such is needed in this population?

Additional Questions

Some evidence indicates that the rate of relapse is higher for anal cancer and Hodgkin disease in HIV-infected patients than in non–HIV-infected patients, and AIDS Malignancy Consortium (AMC) studies are examining the potential role of intensification of cancer therapy in these settings. Is a higher relapse rate characteristic of NADC in HIV-infected patients? Is intensification therapy needed for some or many of these diseases? To what extent is the rate of cancer progression dependent on the degree of HIV replication control or the level of immunodeficiency? Does HIV therapy or therapy for opportunistic conditions influence cancer progression? Which diseases and treatments need to be factored in when planning cancer therapy?

Prevention

Among prevention measures, smoking cessation may be the highest priority. Smoking is associated with several cancers, and lung cancer is clearly increasing rapidly in the HIV-infected population. Use of hepatitis and HPV vaccines should be considered in seronegative individuals; immunogenicity studies currently are being conducted for HPV vaccine in HIV-infected persons. A high index of suspicion for cancer must be maintained in HIV-infected patients. Yearly cervical and anal Papanicolaou testing should be performed, including gynecologic examinations and high-resolution anoscopy. Yearly breast examinations and prostate examinations (including measurement of prostate-specific antigen) should be performed. In patients who are hepatitis B virus- or hepatitis C virus-seropositive, liver function tests and alpha-fetoprotein measurements should be performed periodically. A complete family history of malignancies should be obtained because the results can increase index of suspicion and lead to early detection of disease that might otherwise be missed. Sunscreen use and avoidance of overexposure to sunlight should be stressed, given the observed increase in skin cancers and evidence indicating that endothelial and epithelial cells in HIV-infected individuals may be more susceptible to carcinogenesis.

Resource-limited Settings

Cancers are distributed unevenly throughout the world. As examples, high incidences of head and neck cancers and plasmablastic lymphomas (aggressive Epstein-Barr virus-associated cancers) occur in India, and a high incidence of squamous cell tumors, including conjunctival cancers, occurs in Africa. Challenges include determining which treatments are available locally and which treatments are reasonable to use in locales where high-dose chemotherapy is beyond the reach of most patients and extensive palliative therapy and supportive treatment may not be available. Questions that must be confronted include the following: Can effective treatments that are easier to administer and locally feasible be designed? What are the medical and public health trade-offs that must be faced? What prevention and risk-reduction approaches can be instituted locally?

Current Needs, Future Prospects

Prospective studies are needed both to more accurately assess risk and risk factors for NADC and to determine optimal treatment strategies for NADCs. Efforts aimed at defining optimal treatment and management should have increased focus on pathogenesis-directed treatment and prevention strategies and greater emphasis on use of antiretroviral drugs, prophylactic antibiotics, and other supportive measures. It is crucial that interactions among cancer chemotherapies, antiretroviral drugs, and other drugs routinely used in HIV-infected patients be identified. Ultimately, simpler but effective treatments for both ADCs and NADCs need to be designed, and screening guidelines need to be developed to facilitate earlier recognition of disease and improve treatment options and outcomes.

Conclusion

As patients with HIV disease live longer, morbidity and mortality from NADCs are increasing. Cancers in HIV infection need to be quantified and characterized, particularly given that the types and frequencies of cancers are likely to vary in different populations and locales. Treatment of malignancies in HIV disease should be vigorous and appropriate to the disease and stage of disease. Optimal treatment strategies and strategies for treating and preventing adverse effects associated with antiretroviral therapy and cancer therapy need to be identified. Prevention strategies for viral-associated malignancies need to be investigated, and strategies for reducing or eliminating known risk factors need to be implemented.

For information on AIDS Malignancy Consortium clinical trials, see: http://pub.emmes.com/study/amc/public/index.htm. For information on NCI programs in HIV cancer, see: http://www.cancer.gov/cancertopics/types/AIDS/.

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Suggested Reading

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Correction

An error was made in "Update of the Drug Resistance Mutations in HIV-1: Spring 2008" from the March/April 2008 issue, Volume 16, Issue 1. On page 66 in Footnote 12, the second sentence should have read, "The K103N or Y188L mutation alone prevents the clinical utility of *efavirenz and neviripine* (Antinori et al, *AIDS Res Human Retroviruses,* 2002)." The correction was previously made in the PDF version of the article on our Web site, www.iasusa.org, where updates are posted as they become available.