Non-AIDS Defining Cancers

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Reductions in HIV-associated morbidity and mortality in the era of **highly active antiretroviral therapy (HAART)** have been accompanied by increases in the incidence of some malignancies in people with HIV/AIDS. Indeed, malignancy is now one of the most frequent causes of death and leading cause of hospitalizations in HIV-infected people in the HAART era.[1] The **World Health Organization (WHO)** recognizes three malignancies as AIDS-defining cancers: **Kaposi sarcoma (KS), non-Hodgkin Lymphoma (NHL),** and cervical cancer. These neoplasms were called "AIDS-defining" because of their incidence in patients with low CD4 counts; hence, they are thought to be directly related to the degree of immunodeficiency.

In the last decades, in people with HIV/AIDS, **non-AIDS-defining cancers (NADC)** (anal cancer, liver cancer, skin cancer, Hodgkin lymphoma, head and neck cancer, lung cancer, among others) have been increasing. These neoplasms occur with greater frequency in HIV-positive patients than in the general population, but are not thought to be directly associated with the degree of immunosuppression. Some of these malignancies are associated with risk factors thought to be more common in HIV-positive populations (smoking, alcohol consumption and coinfection with oncoviruses), but for others the underlying pathophysiology is less understood.

Epidemiology of NADCs

Studying the epidemiology of malignancies in the pre- and post-HAART eras has proven challenging because most data do not correlate CD4 counts at the time of malignancy diagnosis or during the course of treatment for specific cancers. However, the overall trend has been that incidence of NADCs has increased in excess of what would be expected in a comparable non-HIV infected population.[2,3] A tool for better understanding this phenomenon is the **standardized incidence ratio (SIR)**.

SIRs measure the incident number of cases in an HIV-positive population as compared to what the incidence in this population would be expected to be if all individuals in the population were HIV-negative. Using the example of AIDS-defining cancers, the overall risk of KS and NHL have decreased in the era of HAART, but they still occur much more commonly than would be expected if the members of the population were not infected with HIV. The SIR for KS, NHL and cervical cancer are as high as 3640, 350 and 22, respectively. A recent report shows that the SIR for all NADC in the HAART era is 2.5 while in the pre-HAART era was 0.95.[3] However, the SIRs vary depending on the malignancy;' for example, the SIR for anal cancer have increased to 141 while the SIR for prostate cancer has not increased. The incidence of NADCs and AIDS-defining cancers in Rhode Island from 2004 to 2008 are shown in Table 1.

Clinical Presentation

Overall, HIV positive patients with NADCs present with more advanced disease with overall worse prognosis compared to their HIV negative counterparts. This is true even for malignancies with the same incidence rates in HIV positive and negative populations. The reasons for these differences are not well understood, but likely vary depending on the malignancy and relevant risk factors. Additionally, the overall poorer health of patients with HIV, the greater number of comorbidities in HIV-positive patients, and the presence of other co-infections such as HCV, HPV, and HHV8 may play a role in the presentation and aggressiveness of NADCs.

Lung Cancer

Although the SIR is only between 2 and 4, lung cancer is the most frequent NADC in the HAART era because lung cancer is common in both HIV-positive and negative populations.[4]. Adenocarcinoma is the most common histological subtype seen in HIV/AIDS patients. The higher than expected incidence is likely not directly related to HIV status, but is more likely related to the high prevalence

Table 1. Number of cases of AIDS-defining and non-AIDS-defining cancers in Rhode Island and The Miriam Hospitals from January 2004 to December 2008 (AIDS patients only)

	Rhode Island Hospital	The Miriam Hospital	Number of cases (percentage)
AIDS-defining cancers			
Non-Hodgkin lymphoma	11	24	35 (25%)
Kaposi sarcoma	8	17	25 (18%)
Cervical cancer	1	1	2 (1%)
Subtotal	**20**	**42**	**62 (45%)**
Non-AIDS-defining cancers			
Hodgkin lymphoma	3	6	9 (7%)
Head & neck cancer	5	5	10 (7%)
Liver cancer	1	7	8 (6%)
Lung cancer	2	5	7 (5%)
Anal cancer	0	5	5 (4%)
Gastrointestinal cancers*	2	9	11 (8%)
Genitourinary cancers**	3	6	9 (7%)
Leukemias	2	3	5 (4%)
Other solid malignancies	5	7	12 (9%)
Subtotal	**23**	**53**	**76 (55%)**
Total	**43**	**95**	**138 (100%)**

*Includes esophageal, gastric, pancreatic and colorectal cancers

**Includes renal, prostate, bladder and testicular cancers

of tobacco use in the HIV population. Current recommendations are to stage and treat patients without regard to HIV status.

Hodgkin Lymphoma

HL is another common NADC. HIV-positive patients typically present at more advanced stages relative to their HIV-negative counterparts and extranodal involvement is common.[5] HL in HIV-positive patients tends to be histologically and clinically more aggressive. Of note, almost all cases of HL in HIV patients are EBV positive. There is an increased risk of HL at CD4 counts between 150-275 cells/mm^3, suggesting that the pathophysiology of the disease is modulated by moderate immunosuppression or immune reconstitution.[6] However, HL occurs less frequently at CD4 counts of less than 150 cells/mm^3; hence, one can infer the exact mechanism is not immunosuppression alone. The general treatment approach is initiation of HAART plus chemotherapy (ABVD). The data on radiation therapy in HIV-associated Hodgkin lymphoma are limited.

Head and Neck

The increased incidence of head and neck cancers in HIV-positive patients may be due to a number of factors including tobacco use and co-infection with HPV (particularly in men who have sex with men). Patients present at younger ages and with more advanced disease when compared to their HIV-negative counterparts.[7] Head and neck cancers associated with HPV have a better overall prognosis than those associated with tobacco use. Treatment options are the same as for HIV-negative patients and focus on loco-regional control with surgery and radiation therapy or systemic therapy for metastatic disease. Notably, HIV-positive patients experience more severe and frequent side effects from therapy, which may ultimately prevent or inhibit aggressive approaches. HIV-positive patients often experience more severe xerostomia, oral infections, severe mucositis and secondary significant malnutrition. Clinicians must closely weigh the overall performance status of HIV-positive patients when deciding treatment options of head and neck cancers.

Hepatocellular Carcinoma

Because hepatitis C and HIV have similar routes of transmission, HIV- positive patients are at an increased risk to develop **hepatocellular carcinoma** (HCC). Approximately 30% of HIV-positive patients are co-infected with hepatitis C.[8] The relative efficiency of transmission of both viruses differs by route; thus the co-infection rate varies significantly by risk group: IV drug users have the highest incidence of co-infection while heterosexual partners the least. Additionally, increased rates of alcohol consumption in the HIV-positive population and higher rates of liver disease may also increase the risk for HCC. As with all forms of HCC, treatment options remain limited. Liver transplant may be considered in some patients, but the efficacy of this in an immunosuppressed high-risk population remains unknown.

Overall, HIV positive patients with NADCs present with more advanced disease with overall worse prognosis compared to their HIV negative counterparts.

Anal Cancer

Human papilloma virus (HPV), another co-infector with HIV, is a risk factor for invasive epithelial dysplasia and anal cancer. As such, there is a significantly increased risk of anal cancer in HIV-positive populations, particularly in patients who practice anal-receptive sex.[9] It is unclear if HAART has affected the incidence of this malignancy. Treatment is the same for patients with and without HIV infection. The reported increase incidence may represent a true increase likely secondary to HAART therapy or may represent increased detection with improved screening with anal PAP smears and more frequent clinical evaluations. Routine anal screening for HIV-positive patients who practice anal intercourse is recommended; however, anal cancer can occur in the absence of anal intercourse. The role of HPV vaccines in the prevention of anal cancer in HIV-positive patients remains unknown.

Breast Cancer

Breast cancer occurs at approximately the same incidence in HIV-positive patients as compared to HIV-negative patients. However, when breast cancer occurs in HIV-positive patients, the malignancy tends to be bilateral and poorly differentiated with the early development of metastases.[10] Some researchers speculate the progressive disease may be

Table 2. Standardized Incidence Ratios (SIR) of selected non-AIDS defining cancers from recent large-scale studies* (post-HAART era)

Non-AIDS defining cancer (NADC)	Engels (2006)	Long (2008)	Dal Maso (2009)	Powles (2009)
Anal cancer	19.6	39	44	141
Liver cancer	3.3	16.5	6.4	7
Head/neck cancer	2.1	5.1	1.8	1.5
Lung cancer	2.6	5.5	10.3	1.5
Melanoma	1	4	0.6	2.7
Skin cancer (non-melanoma)	NR	NR	1.8	NR
Prostate cancer	0.5	0.6	NR	0.9
Kidney cancer	1.9	2.9	0.7	NR
Penile cancer	8	24.2	12	NR
Vulvar/vaginal cancer	4.4	NR	24.3	NR
Brain cancer	0.5	NR	3.2	1.6
Colon cancer	1	0.5	1.4	NR
Breast cancer	0.8	0.6	0.6	NR
Hodgkin lymphoma	13.6	9.8	20.7	32
Multiple myeloma	2.2	3	3.9	NR
All NADC	**1.7**	**NR**	**2.2**	**2.5**

NR: not reported

*SIR=Number of cases observed/number of cases expected

secondary to delayed screening or health care intervention for HIV-positive women and poor socioeconomic status. The overall incidence compared to the general population remains controversial with several studies suggesting a decreased overall incidence in HIV-positive populations. Lower average body weight with higher incidence of amenorrhea and decreased hormonal states may contribute to this possible decreased SIR.

Skin Cancer

Skin cancer is one of the most frequent NADC with increased incidence of both **basal cell carcinoma** (**BCC**) and **squamous cell carcinoma** (**SCC**) variants. HIV-positive patients tend to develop skin cancers at younger ages, in non-sun-exposed areas, multiple sites at once and with increased rate of recurrence.[11] BCC are treated using a similar approach as HIV-negative patients; SCC must be approached aggressively with wide-excision margins and local or regional therapies including radiation.

Effect of HAART on NADCs

The direct effect of HAART on NADC is controversial and may be twofold, 1) HAART can affect the overall incidence of a specific NADC, and 2) HAART can affect the prognosis of a specific NADC. The latter could be a double edged sword, since HAART can improve the immune status of HIV/AIDS patients conveying a good prognosis but sometimes can cause interactions with chemotherapy, potentially increasing the rate of adverse events or decreasing the bioavailability of the drugs.[12]

Impact of HAART in the incidence of NADCs

In the HAART era (since 1996), the incidence of AIDS-defining cancers and other opportunistic infections have decreased dramatically; these reductions have been accompanied by a corresponding relative increase in the SIRs for NADCs. Importantly, the absolute incidence of Hodgkin lymphoma has increased significantly in the HAART era.[3] See Table 2 for the SIRs of NADC from several large-scale studies.

Impact of HAART in the prognosis of NADCs

The impact of HAART on the prognosis of ADCs has shown an improved overall survival and decreased incidence for AIDS-defining malignancies in multiple studies. The effect of HAART on the overall prognosis for individual NADCs remains unclear. HAART may help improve local control of some malignancies and improve overall morbidity and performance status of patients potentially allowing earlier and more aggressive treatment options. These benefits of HAART appear to have limited impact on the prognosis of the majority of NADCs.

Potential interactions between HAART and chemotherapy

HAART and chemotherapy can potentially interact due to several mechanisms, which could result in accumulation and toxicity or a decreased efficacy. However, the limited data on this topic are largely presented in case reports. Antiretroviral and chemotherapeutic agents could be substrates or inducers of the cytochrome P450 system. Several case reports have shown increased rate of toxicity with taxanes in patients receiving HAART.[13] Few cases have shown increased rate of peripheral neuropathy with *Vinca* alkaloids in patients treated for HIV-associated lymphoma.[14] Interestingly, anthracyclines do not seem to be affected by HAART.[15] These data suggest that special attention needs to be paid in HIV-positive patients undergoing chemotherapy for the arousal of unexpected and potentially dangerous adverse events.

Conclusions

NADC are emerging malignancies that represent a new challenge for the oncologist. These patients often have aggressive disease and poor performance status, and due to their immunosuppression and ongoing antiretroviral therapy can be substrate for potential life-threatening or disabling interactions. For all these reasons, there is an increasing and unmet need for HIV oncologists familiar not only with the diagnostic but also the therapeutic aspects of the care of HIV-infected patients with malignancies. Furthermore, multi-institutional efforts, such as the NIH-sponsored AIDS Malignancies Consortium, are warranted.

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