Chapter

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AIDS-Related Malignancies*

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Malignancies have been detected in approximately 40% of all patients with acquired immunodeficiency syndrome (AIDS) sometime during the course of their illness. These cancers have been both a primary cause of death in some patients and also a source of considerable morbidity. In the current era of protease inhibitors and highly active antiretroviral therapy (HAART), patients infected with the human immunodeficiency virus (HIV) are surviving longer than ever. HAART appears to have substantially reduced the incidence of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) and may enhance the efficacy of treatment for those patients who do develop these tumors. Unfortunately, HAART has not shown a similar effect on the development of other types of neoplasms, and the need to care for patients who develop malignancies in the setting of HIV remains a challenge. Furthermore, HAART is not available universally, with many patients in resource-poor developing countries not having access to antiretroviral drugs.

In a prospective observation study of the causes of death of HIV-infected patients in France in the year 2000, of 964 deaths, 269 (28%) were attributable to malignancies, with 105 of them being non-Hodgkin's lymphoma. Malignant disease was the most common cause of death in this group of HIV-infected adults in the era of highly active antiretroviral therapy (HAART). The increased proportion of solid tumors as the cause of death (> 10% of all deaths) may be due to the decreasing incidence of AIDS-defining malignancies since widespread use of HAART, longer life expectancies of patients with HIV, and the aggressive and poor prognostic nature of these tumors in HIV patients *(Bonnet F Lewden C, May T, et al. Cancer 2004;101:317-24).*

KAPOSI'S SARCOMA

KS has been the most common tumor associated with HIV infection, but it currently develops in < 10% of homosexual men with AIDS in the United States and 1-2% of other HIV-infected persons. The incidence of KS has declined substantially, from 4.8 per 100 person-years in 1990 to 1.5 per 100 person-years in 1997. In 2003, a European study found that the incidence of KS among HIV-infected individuals was less than 10% of the incidence seen a decade earlier in 1994.

EPIDEMIOLOGY

Gender: Among AIDS patients in the United States, the incidence of KS is higher in males than in females. There is also a higher incidence of KS in men than in women in Africa (male-female ratio) despite the equal prevalence of HIV infection among men and women.

Age: The age distribution of AIDS-related KS follows the distribution of HIV infection. As such, AIDS-related KS can occur in all age groups. In American adult males, the most common age of onset of AIDS-related KS is 30-40 years old. No peak age has been reported.

Race: No racial or ethnic differences in the incidence of AIDS-related KS have been observed.

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Geography: In the United States, KS is seen in <10% of homosexual men with AIDS. The proportion of KS among AIDS-defining diagnoses is lower in parts of Europe, where there are proportionately fewer male homosexual AIDS cases (e.g. 6.8% of Italian AIDS patients), and higher in parts of Africa, where KS is endemic in the non-HIV-infected population. Among AIDS cases in the United States, the proportion of patients with KS has declined from the beginning of the AIDS epidemic, possibly as a result of changes in high-risk sexual behavior among homosexual men and the wider use of more effective antiretroviral combination regimens.

ETIOLOGY AND RISK FACTORS

In the United States, the observation that KS occurs predominantly in homosexual men and the epidemiologic evidence that KS has declined among AIDS patients in parallel with the declining incidence of sexually transmitted diseases (STDs) among homosexual men are cited as support for the theory that a sexually transmitted agent may be involved in the development of AIDS-related KS.

Viruses: In 1994, unique viral DNA sequences were identified in tumor tissues from patients with AIDS-related KS, which led to the identification of a new virus called KS-associated herpesvirus (KSHV) or human herpesvirus type 8 (HHV-8). HHV-8 has been found in >90% of AIDS-KS tumors, as well as in classic KS, endemic African KS, and post-organ transplant-related KS. It has also been identified in body cavity-based lymphoma/primary effusion lymphoma, multicentric Castleman's disease, and angio-immunoblastic lymphadenopathy with dysproteinemia (AILD) in HIV-infected patients.

HHV-8 may be transmitted through sexual contact or blood products or during organ transplantation. Seroprevalence of HHV-8 in AIDS-related KS is nearly 100%. HHV-8 has been found in high concentration in saliva in KS patients.

HHV-8 is critical in the pathogenesis of AIDS-related KS. The mechanism by which HHV-8 induces KS in susceptible individuals is the subject of intense current investigations.

Environmental and host factors: Various environmental and host factors, including HIV- and HHV-8-induced cytokines, AIDS-associated infections, the host's hormonal milieu, immunosuppression, and antiretroviral therapy, may induce or suppress the development of KS and alter its growth.

SIGNS AND SYMPTOMS

The manifestations of KS in patients with AIDS are variable and range from small innocuous-looking cutaneous lesions to symptom-producing visceral or oral lesions, which may be quite troublesome and even life-threatening. Just about every internal organ can occasionally be involved with KS. KS is rarely seen in the bone marrow or CNS.

Skin lesions: KS tumors typically begin as flat or raised lesions that may progress to plaque like or nodular tumors. Lesions vary in size and shape but are generally nonpruritic and painless. They range in color from light pink to red to deep purple. KS lesions may be cosmetically disfiguring and may result in social stigmatization that far exceeds any actual physical impairment.

Dermal and lymphatic infiltration with tumor can result in edema of the extremities, periorbital areas, and genitals and may be complicated by skin breakdown and bacterial cellulitis. Edema can be marked and may prevent patients from wearing shoes and/or walking.

Lesions on the feet can cause pain and hamper walking.

Oral lesions are often asymptomatic but can produce pain and swallowing difficulties.

GI tract involvement with KS is seen in up to 50% of patients. Most lesions are asymptomatic; however, obstruction, bleeding, or enteropathy can occur occasionally.

Pulmonary KS usually presents as dyspnea without fever and may become severely debilitating and rapidly fatal if untreated.

SCREENING AND DIAGNOSIS

Currently, there are no screening tests for KS. Although most KS lesions are readily recognized, early lesions may be difficult to diagnose, and the lesions of other diseases (e.g., bacillary angiomatosis) may mimic those of KS. Once clinically suspected, the diagnosis of KS is made by biopsy and histologic examination of skin lesions, an excised lymph node, or other tissue or by presumptive diagnosis based on the bronchoscopic or endoscopic appearance of a visceral lesion.

GI KS has a typical red, raised appearance and is difficult to diagnose by biopsy because of the submucosal location of many lesions.

Pulmonary KS: In patients with pulmonary KS, chest radiographs typically demonstrate diffuse, reticular-nodular infiltrates, mediastinal enlargement, and, sometimes, pleural effusion. Bronchoscopy may reveal

extensive endobronchial involvement with tumor. Definitive diagnosis requires transbronchial or open-lung biopsy. Transbronchial biopsies, however, often yield negative results. A presumptive diagnosis of pulmonary KS may be made, in the absence of fever, based on typical radiographic and endobronchial findings of KS-appearing lesions and after the exclusion of infections.

Thallium and technetium-99m scanning may help differentiate KS from other pulmonary diseases. Patients with KS have been found to have thallium—and technetium-avid scans, whereas pulmonary lymphomas and infections are more typically gallium-avid.

PATHOLOGY

Cutaneous KS is a lesion of the dermis composed of a proliferation of aberrant vascular structures lined by abnormal-appearing, spindle-shaped endothelial cells and with extravasated erythrocytes and leukocytes within the structures. These spindle cells are generally sparse in early stages but become more numerous and "stack up" between the vascular structures as the tumor advances. Infiltration of mononuclear leukocytes, including plasma cells, T cells, and monocytes, is more prominent in earlier lesions. The histologic appearance of KS in AIDS patients is similar to that seen in non-HIV-infected patients.

Cell of origin: The KS tumor cell is believed to be of mesenchymal, endothelial origin. Several endothelial cell markers are positive in KS, including stains for *Ulex europaeus*, CD31, CD34, and EN-4. In addition, the tumor stains with factor VIIIa, CD68, and α-actin but not with PAL-E.

STAGING AND PROGNOSIS

Prognostic factors: Although it is difficult to predict from the initial presentation which patients are most likely to have rapidly progressive tumors, several retrospective studies have shown a correlation of survival with the degree of T-cell immunodeficiency, as reflected in the absolute number of T-helper cells. Prior opportunistic infections or the presence of such symptoms as fevers, night sweats, and weight loss (B symptoms) also portend a poor prognosis. Patients who develop KS or whose tumor growth accelerates after an opportunistic infection often have a more aggressive clinical course. Patients with pulmonary involvement generally have a poor prognosis.

Table 1: Staging classification for AIDS-related KS[a]

Characteristic	*Risk status* *Good risk (0)*	*Poor risk (I)*
	All of the following:	*Any of the following:*
Tumor (T)	Tumor confined to skin and/or lymph nodes and/or minimal oral disease[b]	Tumor-associated edema or ulceration; extensive oral KS; GI KS; KS in other non-nodal viscera
Immune system (I)	CD4 cells ≥ 150/mm^3	CD4 cells < 150/mm^3
Systemic illness (S)	No history of opportunistic infection or thrush; no B symptoms[c]; performance status ≥ 70 (Karnofsky scale)	History of opportunistic infection and/or thrush; B symptoms; performance status <70 (Karnofsky scale); other HIV-related illness (e.g. neurologic disease, lymphoma)

Adapted from Krown SE, Metroka C, Wernz JC:J Clin Oncol 7:1201, 1989, as modified by Krown SE, et al: J Clin Oncol 15:3085, 1997.

[a] Patients are assigned a disease state TXIXSX, where X corresponds to the risk designation (0 or 1) for each risk category

[b] Minimal oral disease is non-nodular KS confined to the palate

[c] B symptoms: unexplained fever, night sweats, > 10% involuntary weight loss, or diarrhea persisting for more than 2 weeks

Staging system: A tumor classification system has been proposed for AIDS-related KS by the oncology committee of the AIDS Clinical Trials Group (ACTG). This system segregates patients into good or poor prognostic groups based on tumor characteristics, immune system function, and systemic illness (the TIS system; see Table 1). A retrospective analysis of 294 patients with AIDS-related KS has shown that the TIS system is a valid predictor for survival.

Gauging response to therapy: Given the heterogeneity and unpredictable growth of this tumor, it is often difficult to gauge objective responses. The peculiarities of this multicentric tumor make some subjectivity almost inevitable in gauging treatment responses.

TREATMENT

The treatment of AIDS-related KS requires an individualized approach, based on the extent and location of the lesions, the wishes and treatment needs of the patient, the presence of tumor-associated symptoms (e.g., pain, bleeding, edema), the presence of other AIDS-associated illness, and the patient's tolerance of medications. Nevertheless, the following general statements can be made:

- Patients with widespread symptomatic disease or life-threatening visceral involvement require prompt, cytoreductive treatment with one or more chemotherapeutic drugs.
- Even in the absence of symptomatic visceral disease, the disfigurement and emotional distress of having these visible reminders of AIDS may mandate treatment for psychological reasons.
- For patients with asymptomatic indolent lesions, aggressive treatment is not mandatory, but these patients may derive substantial benefits from local treatment or investigational therapies that are directed against HIV or HHV-8 or that may interrupt the pathogenesis of KS and/or restore immune competence.

Treatment Options

With the introduction of protease inhibitors and non-nucleoside reverse transcriptase inhibitors for HIV, cases of KS regression with combination antiretroviral therapy have been reported. Because KS seems to be influenced by the state of HIV infection, we believe that all patients with AIDS-related KS should have their HIV infection under optimal control. There is no one best anti-HIV regimen, and oncologists should consult with infectious disease specialists familiar with the treatment of HIV infection. Eventually, even with good anti-HIV therapy, many patients with AIDS-related KS will require some form of treatment for their tumor.

Local treatments, including cryotherapy, topical retinoic acid, intralesional chemotherapy and other sclerosing agents, and local irradiation, can produce good local control of tumors. Interferon-alfa (IFN-α [Intron A, Roferon-A]) and cytotoxic chemotherapy are effective systemic treatments for patients with more extensive or symptomatic disease. Single-agent or combination chemotherapy is effective in controlling tumors, even in patients with extensive disease and severe immune deficiencies (Table 2). The use of hematopoietic growth factors has facilitated the administration of myelosuppressive treatments, such as IFN-α and chemotherapy.

Table 2: Chemotherapy for AIDS-related KS

Regimen	*Dose*	*Response rate[a] (%)*
Vincristine	2 mg/wk IV	20-60
Vinblastine	0.05-0.1 mg/kg/wk IV	25-30
Doxorubicin	20 mg/m^2 IV every other wk	50-60
Etoposide	150 mg/m^2 IV every d × 3 q3-4 wk	75
Vinorelbine	30 mg/m^2 IV q2wk	47
Liposomal daunorubicin	40 mg/m^2 IV q2-4wk	25-70
Liposomal doxorubicin	20 mg/m^2 IV q2-4wk	58-63
Paclitaxel	100-135 mg/m^2 IV over 3 h q2-4 wk	60-72
Vincristine + vinblastine	2 mg IV (vincristine) alternating with 0.1 mg/kg IV (vinblastine) every other wk	45
Vincristine + bleomycin	2 mg IV (vincristine) + 10 mg/m^2 IV (bleomycin) q2wk	23-70
Doxorubicin + bleomycin + vincristine	10 mg/m^2 IV (doxorubicin) + 10 mg/m^2 IV (bleomycin) + 1-2 mg IV (vincristine) q2wk	87

[a] Complete responses plus partial responses

IFN-α

The first treatment licensed for AIDS-related KS was recombinant IFN-α. Tumor responses have been seen in approximately 30% of patients treated with SC interferon given either daily or 3 times weekly. Current practice is to administer IFN-α 3 times weekly by SC injection. Unmaintained response durations in trials of IFN-α monotherapy have ranged from 12 to 24 months in complete responders and from 8 to 12 months in partial responders.

Duration of therapy: The optimal duration of IFN-α treatment is unknown; however, many patients relapse within a few months after discontinuation of therapy. Reinduction of second responses with IFN-α after relapse may be unreliable and often is of short duration. It is therefore generally recommended that treatment with IFN-α be continued for as long as drug tolerance and tumor responses continue.

Dose: The optimal dose of IFN-α also has not been clearly established. IFN-α is generally administered at either 3 or 5 million units SC 3 times weekly together with antiretroviral therapy.

Major dose-limiting toxicities of IFN-α include fever, chills, rigor, and other flu-like symptoms. They are dose related and often observed at the initiation of treatment but lessen somewhat with continued use. Neutropenia, transaminase elevation, depression, peripheral neuropathy, and other neuropsychiatric abnormalities may also occur.

Other side effects include headaches, cognitive impairments, paresthesias, and mild thrombocytopenia. As the subjective side effects of IFN-α are also common in HIV-related or other conditions, care must be taken to avoid ascribing all of these symptoms to drug toxicity

and overlooking treatable infections and other conditions.

Retinoids

Alitretinoin gel 0.1% (9-cis-retinoic acid [Panretin]) has received approval of the US Food and Drug Administration (FDA) for the topical treatment of localized cutaneous KS. This compound inhibits the growth of KS and induces apoptosis of KS cells by binding to retinoic acid receptors on the cell surface.

Phase II clinical trials comparing 3-4 times daily application of alitretinoin vs placebo gel demonstrated a 35% rate of complete and partial responses in the alitretinoin-treated patients, as compared with a rate of 18% in controls.

Median time to response to alitretinoin was 29-34 days, with a median duration of response of 12-16 weeks. Responses were seen in both previously untreated and previously treated KS patients and were not dependent on patients' CD4 cell count.

Local cutaneous adverse reactions to alitretinoin include erythema, skin irritation, skin cracking, flaking, peeling, and desquamation. The severity of these reactions can be mitigated by less frequent dosing, thinner application, or use of topical vitamin E.

Alitretinoin should be reserved for patients who do not require systemic treatment for visceral disease. However, it may be used in conjunction with other treatments for cutaneous disease.

Oral 9-*cis*-retinoic acid has been investigated in patients with AIDS-related KS and found to have a 37% response rate.

Bexarotene (Targretin), an oral retinoid X receptor (RXR)-selective agonist, has been studied in patients with AIDS-related KS, with an overall response rate of 33% in one study.

Chemotherapy

For patients with more widely disseminated, rapidly progressive, or symptomatic disease, systemic chemotherapy is generally warranted. Chemotherapy drugs are included in Table 2.

Antiretroviral drugs: A total of 21 anti-HIV drugs have received FDA approval, and more are in various stages of clinical development. When evaluated by an oncologist, the majority of HIV-infected individuals will be taking some anti-HIV drugs. The interactions between cytotoxic chemotherapy and the various anti-HIV drugs have not been fully studied. Thus, oncologists treating patients with AIDS-related KS should continue to monitor them frequently for side effects. Withholding antiretroviral therapy during chemotherapy and then immediately restarting it after giving the chemotherapy drugs may avoid some toxic effects of drug interactions.

Combination regimens: The two most frequently utilized combination chemotherapy regimens are Adriamycin (doxorubicin), bleomycin, and vincristine (ABV) and bleomycin and vincristine (BV). These regimens were initially reported to yield tumor response rates in excess of 70-90%, with good palliation of symptoms, including decreased edema, decreased pain, and, in patients with pulmonary KS, respiratory improvement and alleviation of obstructive symptoms. A beneficial effect of these combinations on survival has not been clearly demonstrated, however.

Early reports of a high response rate with these combination regimens have not been reproduced by later multicenter trials. A conservative response rate of 50-60% has been reported in more contemporary phase III trials. The discrepancy in response rates most likely stems from differences in the response criteria used.

Liposomal anthracyclines (e.g., liposomal doxorubicin [Doxil] and liposomal daunorubicin [DaunoXome]) are also very effective in inducing tumor regression in KS. Clinical trials have shown that liposomal anthracyclines as single agents can achieve a response rate equal to or better than that obtained with the ABV combination regimen. As such, the liposomal anthracyclines have become the first line chemotherapy for AIDS-related KS.

The dose-limiting toxicity is neutropenia, and many patients will require the use of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) after several cycles of treatment. Other common side effects include nausea, fatigue, anemia, and thrombocytopenia. A palmar-plantar syndrome, characterized by acute painful erythematous swelling of the hands and feet, has been reported with the use of liposomal doxorubicin. Once the symptoms resolved, readministration of liposomal doxorubicin did not necessarily reproduce the syndrome. Neither of the liposomal anthracyclines has been reported to depress left ventricular function.

Paclitaxel has been shown to produce responses in both chemotherapy-naive KS patients and patients with refractory tumors, including those refractory to liposomal anthracyclines. Dosage is typically 100-135 mg/m^2 IV given over 3 hours every 2-4 weeks. This agent is widely considered the primary secondline chemotherapy for KS.

The dose-limiting toxicity is neutropenia. Other reported toxicities include anemia, stomatitis, alopecia,

and fatigue. Neuropathy has not been a major problem with this low-dose approach.

Investigational agents: Other drugs under investigation for the treatment of KS include thalidomide (Thalomid), antiviral drugs, matrix metalloproteinase inhibitors (MMPIs), and several antiangiogenesis compounds. Studies of compounds that may inhibit HHV-8 are also in development or in early clinical testing in KS patients. Cidofovir (Vistide) does not appear to be clinically active.

Radiation Therapy

Although radiation therapy can easily produce sufficient regression of KS to be useful for palliation of symptomatic disease or cosmetic improvement of disfiguring lesions, this practice has become less common as HAART has changed the natural history of AIDS. More than 90% of lesions will respond (complete responses [CRs] and partial responses [PRs]). Local radiation therapy commonly alleviates pain and bleeding, lessens edema, and shrinks obstructing lesions.

Treatment technique: For most superficial lesions, a single, shaped, en face beam of relatively limited penetration (approximately 100 kV) works well. A relatively low-energy electron beam (e.g., 6 MeV) often can be used with shielding as an alternative to superficial X-rays.

Large lesions: For very large lesions, electron beams are used more often, due to the limited penetration of kilovoltage X-ray beams and the limited width of the treatment cones attached to most superficial X-ray units. For patients with more widespread tumors of the legs with edema, parallel opposed megavoltage X-ray beams and overlying bolus material are often used to provide homogeneous irradiation to the entire area.

Dose fractionation regimens: Several dose fractionation regimens have proven effective in AIDS-related KS. As this tumor is radiosensitive, almost any dose of radiation therapy can produce some response. Interestingly, *in vitro* irradiation of KS cell cultures induces the cells to produce interleukin-6 (IL-6) and oncostatin M (OSM), which, in turn, make the cells more sensitive to radiation therapy.

For most cutaneous lesions, a single treatment of 800 cGy will produce a short-term response. For lesions on sensitive structures (e.g. penis, hands, conjunctivae), some radiation oncologists attenuate treatment to a total dose of 2,000 cGy administered in 300 cGy increments (accepting a 50% decrease in CR rate), whereas 3,000 cGy delivered over 2 weeks is more typically used for lesions in general.

Prospectively acquired data clearly demonstrate a dose-response relationship for radiation therapy in AIDS-related KS. A dose of 4,000 cGy delivered in 20 fractions over 4 weeks was significantly more effective than 2,000 cGy in 10 fractions or 800 cGy in 1 fraction, as measured by a higher response rate, longer duration of tumor control, and the absence of residual hyperpigmentation. However, the short and medium-term effects of moderately intense but briefer regimens, such as 3,000 cGy in 10 fractions over 2 weeks, probably are equivalent to those of higher total dose, more protracted regimens, and the moderately intense regimens require only half the time to deliver.

For patients with an anticipated survival of < 3 months, in whom the response duration may be of less overall importance, a single fraction of 800 cGy is likely to provide the same benefit as the more intensive regimens. In contrast, small lesions in patients who are expected to survive for at least 1 year should be treated with fractionated radiation therapy, such as 3,000 cGy in 10 fractions over 2 weeks.

NON-HODGKIN'S LYMPHOMA

The incidence of NHL is 60 times higher in individuals with HIV infection than in the general population. The overall occurrence of lymphoma as a manifestation of AIDS has declined somewhat as treatment of HIV has improved.

Although NHL currently comprises < 5% of all initial AIDS-defining conditions, it accounts for as many as 15% of all AIDS-related deaths. The majority of patients present with advanced-stage, high- or intermediate-grade, B-cell lymphoma and have a high frequency of extranodal involvement. Primary CNS lymphoma occurs in approximately 0.5% of patients with AIDS.

The majority of patients with AIDS-related lymphoma have advanced HIV disease. Median CD4 cell counts in patients with systemic lymphoma range from 100 to 200 cells/mm^3, whereas CD4 cell counts < 50 cells/mm^3 are found in nearly all patients with primary CNS lymphoma.

Epidemiology

At-risk groups: NHL occurs with approximately equal frequency in all population groups infected by HIV, including IV drug users, homosexual-bisexual men, transfusion recipients, and patients with hemophilia.

Gender and race: AIDS-related NHL is seen more frequently in men than in women and occurs more often in whites than in blacks.

Age: The age distribution of AIDS-related NHL follows the distribution of HIV infection. Primary CNS lymphoma occurs with the same frequency in all age groups.

Geography: Current data do not indicate any geographic differences in the incidence of AIDS-related NHL.

Etiology and Risk Factors

AIDS-related NHL is believed to arise as a consequence of continued stimulation of B-cell proliferation as a result of HIV, Epstein-Barr virus (EBV), and other infections, all of which occur in the setting of profound T-cell immuno-deficiency. An association between the polyomavirus, simian virus 40 (SV 40), and diffuse large B-cell and follicle-type lymphoma has been detected. HIV also induces the expression of a number of cytokines (e.g., IL-6 and IL-10) that can further increase B-cell activation.

Small noncleaved lymphomas: Genetic errors are increased in the setting of chronic B-cell proliferation, and a variety of chromosomal translocations resulting in oncogene activation can lead to polyclonal and monoclonal B-cell expression. Other molecular biological abnormalities associated with small noncleaved lymphomas include expression of an abnormal TP53 (alias p53) tumor-suppressor gene and *the c-myc or ras* oncogene.

Immunoblastic lymphoma: The pathogenesis of AIDS-related immunoblastic lymphoma appears to be distinct from that of small noncleaved lymphoma and is more likely related to EBV infection without *c-myc* dysregulation. Clonal integration of EBV within tumor cells, with expression of various latent EBV proteins, has been demonstrated in essentially all cases of AIDS-related primary CNS lymphoma and in as many as two-thirds of systemic lymphomas.

Diffuse large cell lymphoma: The specific molecular aberrations described in patients with AIDS-related diffuse large cell lymphoma appear distinct as well, with recent descriptions of abnormal *bcl-6* expression in approximately 40% of cases.

Body cavity-based lymphoma/primary effusion lymphoma appears to be highly associated with HHV-8 and EBV. The tumor cells stain positive for CD45. The disease appears to occur predominantly in males and may coexist with KS in patients with AIDS.

Signs and Symptoms

B symptoms (i.e., fever, weight loss, and night sweats) are seen in approximately 80% of patients with systemic AIDS-related NHL. In these patients, it is mandatory to exclude the presence of occult opportunistic infections before ascribing B symptoms to the lymphoma itself.

Extranodal involvement: Advanced-stage disease is expected in the majority of patients, with extranodal involvement reported in 60-90% of patients in most series. Common sites of extranodal involvement include the CNS (occurring in approximately 30% of patients), GI tract (25%), and bone marrow (25%). Essentially any other site in the body can also be involved, including the rectum, soft tissue, oral cavity, lungs, and heart.

CNS lymphoma: Patients with primary CNS lymphoma often present with focal neurologic deficits, seizures, and/or altered mental status. Any site in the brain may be involved, and one to four space-occupying lesions are usually seen on MRI or CT scan.

Other sites: Changes in bowel habits, GI bleeding, weight loss, pain, and hepatomegaly are common presenting symptoms in patients with GI involvement. Pancytopenia may indicate bone marrow involvement.

Primary effusion lymphoma: Patients usually present with pleural or pericardial effusion without an identifiable mass. Pain, shortness of breath, and B symptoms are the main initial complaints.

Screening and Diagnosis

Diagnosis of NHL in patients with AIDS requires histologic confirmation by biopsy with immunophenotypic and/or molecular gene rearrangement studies.

A complete staging evaluation should be done. This should include:

- CT or MRI of the head and chest/abdomen/pelvis
- Bone marrow aspiration and biopsy
- Liver function studies
- Spinal fluid analysis

Assessing spinal fluid for EBV The presence of EBV DNA in CSF, as determined by polymerase chain reaction (PCR), appears to have a high specificity and sensitivity for the diagnosis of primary CNS lymphoma. The use of thallium single-photon emission computed tomography (SPECT) may further increase the diagnostic yield.

Pathology

Common tumor types: Over 95% of AIDS-related NHL cases are of B-lymphocyte origin. Most AIDS-related NHL tumors are high-grade types, including the immunoblastic and small noncleaved lymphomas. Diffuse large cell lymphoma constitutes up to 30% of AIDS lymphomas.

Less common tumor types: Although not considered part of the AIDS epidemic, several cases of T-cell lymphoma occurring in HIV-infected patients have been described. In addition, cases of Ki-1 –positive, large cell anaplastic lymphoma have been reported in HIV-infected patients. The clinical and pathologic characteristics of these forms of lymphoma are similar to those seen in non-HIV-infected individuals.

CNS lymphomas are typically of the immunoblastic or large cell type.

GI and oral cavity lymphomas: Large cell or immunoblastic lymphomas are also more likely to involve the GI tract and oral cavity than are small noncleaved lymphomas.

Primary effusion lymphoma The cells are large and pleomorphic with prominent nucleoli and immunoblastic morphology. Clonal immunoglobulin DNA rearrangement demonstrates clonality of the tumor cells but not surface immunoglobulin expression.

Staging and Prognosis

Staging system: Staging of AIDS-related NHL is the same as that for non-AIDS-related NHL. The Ann Arbor classification system for staging of NHL is utilized (see chapter 30), and the staging work-up includes imaging studies, as well as bone marrow and CNS evaluation for lymphomas.

Prognostic factors: Four factors have been shown to correlate most closely with shorter survival in patients with systemic AIDS-related NHL.

- A history of opportunistic infection prior to the lymphoma
- CD4 cell count < 100 cells/mm^3
- Karnofsky performance score < 70
- Stage IV disease, especially if due to bone marrow or meningeal involvement.

In patients without these findings, median survival is typically 11-12 months, as compared with a median survival of approximately 4-5 months in those with one or more of these adverse prognostic features.

Three factors correlate with *better* survival in patients with primary CNS lymphoma:

- Karnofsky performance score > 70
- Age < 35 years
- Adequate dose of radiation therapy.

Types of lymphoma: To date, no major differences have been seen in response or survival among the various pathologic types of systemic AIDS-related NHL. Patients with polyclonal lymphomas appear to have better tumor responses to chemotherapy and better survival. Patients with primary CNS lymphoma have an extremely poor prognosis, with a median survival of only 2-3 months despite therapy; treatment with potent antiretroviral therapy does seem to improve survival. Prognosis for patients with primary effusion lymphoma is also poor, with a median survival of only 5 months.

TREATMENT

Treatment of Systemic NHL

Chemotherapy

The mainstay of treatment for patients with systemic AIDS-related NHL is chemotherapy. As the likelihood of dissemination is great, AIDS patients who develop NHL must be assumed to have widespread disease at presentation and should be treated with systemic chemotherapy, even if dissemination is not confirmed on routine staging evaluation.

Some of the commonly used regimens designed for AIDS-related NHL are listed in Table 3. No regimen appears to be superior to any other, although early findings show that the EPOCH regimen (etoposide, prednisone, Oncovin [vincristine], cyclophosphamide [Cytoxan, Neosar], doxorubicin) gives the best results to date.

CNS prophylaxis with either intrathecal cytarabine (Ara-C; 50 mg) or intrathecal methotrexate (10-12 mg) every week for four treatments has been shown to be effective in reducing the incidence of CNS relapse.

In an Italian study, rituximab (Rituxan), an anti-CD 20 monoclonal antibody, also has been studied in combination with CDE (cyclophosphamide, doxorubicin, etoposide) at lower doses and has been shown to have an overall response rate of 86% and an actuarial 2-year survival rate of 80%.

To determine whether the addition of rituximab to CHOP resulted in better outcomes in patients with AIDS-related NHL, 149 patients were randomized (2:1) to receive CHOP with rituximab (days 1 and 3 of each cycle) or CHOP alone. Three monthly maintenance doses of rituximab were administered to the rituximab group following completion of chemotherapy. CR rates were

Table 3: Chemotherapy for AIDS-related NHL

Regimen	*Drugs and dosage*	*Cycle length*	*CR rate (%)*	*Median survival*
m-BACOD	Methotrexate, 500 mg/m2 IV on day 15, with leucovorin, 25 mg PO q6h × 4, after completion of methotrexate Bleomycin, 4 U/m2 IV on day 1 Adriamycin (doxorubicin), 25 mg/m2 IV on day 1 Cyclophosphamide, 300 mg/m^2 IV on day 1 Oncovin (vincristine), 1.4 mg/m^2 IV on day 1 (maximum, 2 mg) Dexamethasone, 3 mg/m2 PO on days 1-5	q28d	41	35 wk
CDE	Cyclophosphamide, 800 mg/m2/96 h IV Etoposide, 240 mg/m2/96 h IV	q28d	46	8.2 mo
EPOCH	Etoposide, 200 mg/m2/96 h IV Oncovin (vincristine), 1.6 mg/m^2/96 h IV Doxorubicin, 40 mg/m2/96 h IV Cyclophosphamide, 187 mg/m^2 IV on day 5 (if CD4 cell count < 100 cells/mm3) or 375 mg/m^2 IV on day 5 (if CD4 cell count > 100 cells/mm3)* Prednisone, 60 mg/m2 PO on days 1-6	q3-4 wk	79	53 mo+
CEOP	Cyclophosphamide, 750 mg/m^2 IV on day 1 Epirubicin, 50 mg/m2 IV on day 1 Oncovin (vincristine), 2 mg IV on day 1 Prednisone, 100 mg PO on days 1-5	q3-4 wk	47	10 mo
CHOP	Cyclophosphamide, 750 mg/m^2 IV on day 1 Doxorubicin, 50 mg/m2 IV on day 1 Oncovin (vincristine), 1.4 mg/m^2 IV on day 1 (maximum, 2 mg) Prednisone, 60 mg PO on days 1-5	q2ld	63	9 mo

CR = complete response; 8With dose escalation as tolerated with each subsequent cycle, to a maximum of 750 mg/m^2

similar (58 vs 48%), as were median times to response (11.0 vs 10.5 weeks, respectively). More grade 4 neutropenia (61% vs 48%), was seen in the rituximab group. Death due to infection occurred in 14 of 95 (10%) of those in the rituximab group vs 1 of 50 (2%) of those in the CHOP-alone group. No response benefit was seen from the addition of rituximab to CHOP for the initial treatment of AIDS-related NHL, and the high incidence of infections and death raises concern in this population (*Kaplan LD, Lee J, Scadden DT. AIDS Malignancy Consortium [AMC]: Am Soc Hematol [abstract] 1488, 2003*).

Patients with resistant or relapsed AIDS-related non-Hodgkin's lymphoma after first-line chemotherapy underwent peripheral blood stem-cell (PBSC) collection after a course of second-line chemotherapy. Patients with chemosensitive disease received carmustine, etoposide, cytarabine, and melphalan (BEAM) and PBSC transplantation. Highly active antiretroviral therapy (HAART) was maintained throughout treatment. Of 16 patients, 10 (62%) received PBSC transplantation, with prompt engraftment and no opportunistic or other infections. Complete response was achieved in eight of nine patients. Two patients relapsed and died at +10 and +14 months. Six other patients are disease free at a median of 8 months after treatment. High-dose therapy plus PBSC transplantation appears feasible and active in patients with AIDS lymphoma (*Re A, Cattaneo C, Michieli M, et al. J Clin Oncol 21:4423-4427, 2003*).

Dose intensity Standard-dose chemotherapy (e.g., CHOP [cyclophosphamide, doxorubicin, Oncovin,

prednisone]), is generally recommended for most patients with AIDS-related NHL. Results from trials using continuous infusion therapy (e.g., EPOCH or CDE) have shown better CR rates and long disease progression-free and overall survival.

Certain subsets of patients with high CD4 cell counts (> 100 cells/mm^3), no B symptoms, lower disease stage at presentation (stage I or II), and good performance status (0 or 1) may enjoy prolonged survival (> 2 years) when treated with either standard-dose or intensive, high-dose regimens. However, until more data are available to identify these patients subsets, the intensive, high-dose approach is not recommended outside clinical trial settings.

Growth factor support: The major dose-limiting toxic effect of multiagent chemotherapy regimens is myelosuppression. Studies of m-BACOD (methotrexate with leucovorin, bleomycin, Adriamycin [doxorubicin], cyclophosphamide, Oncovin [vincristine], dexamethasone) or CHOP chemotherapy demonstrated that coadministration of myeloid hematopoietic growth factors enhanced patient tolerance of these regimens.

Salvage chemotherapy: Patients in whom initial treatment fails or who relapse after initial remission rarely achieve a prolonged second remission. Studies of various salvage regimens with or without autologous stem-cell support are in progress. Mitoguazone (MGBG), given at a dose of 60 mg/m^2 on days 1 and 8 and then every 2 weeks, achieved a CR in 11.5% of patients with primary refractory or relapsed disease. The median survival for the whole group was 2.6 months, whereas a median survival of 21.5 months was noted in the complete responders.

Second-line chemotherapy (e.g., ESHAP [etoposide, methylprednisolone (SoluMedrol), high-dose Ara-C, Platinol (cisplatin)]) has been shown to have a CR of up to 31% and a PR of 23%, with a median survival of 7.1 months, in patients with refractory or relapsed AIDS-related NHL.

Radiation Therapy

The role of radiotherapy in systemic lymphoma is limited to consolidation of the effects of chemotherapy. Treatment principles are similar to those used for aggressive NHL in the non-HIV setting and typically involve the use of involved or extended fields only.

Lymphomatous meningitis: For patients with lymphomatous meningitis and/or radiographically detectable cerebral deposits, "step-brain" irradiation (including the covering meninges) is administered along with intrathecal chemotherapy to control microscopic spinal disease. Focal radiation therapy may be required for known tumor deposits in the spine. Unfortunately, many such patients develop multiple deposits anywhere along the spinal axis, either synchronously or metachronously.

Fractionated doses of 3,000-4,500 cGy may be used to control local lymphoma deposits in nodal areas. Patients who have lymphomatous meningitis typically have a poor prognosis and are best treated with regimens that do not unduly occupy their time (e.g., 3,000 cGy in 10 fractions over 2 weeks).

Treatment of Primary CNS Lymphoma

A very effective therapy for patients with AIDS-related CNS lymphoma has not yet been found.

Radiation Therapy

The conventional standard of treatment is step-brain irradiation, which can result in response rates of 50% and improve survival, as compared with untreated patients, even when adjusted for antiretroviral therapy, CD4 cell count, and time to diagnosis. Treatment is directed to the entire cranial contents, including the meninges down to C2.

Doses equivalent to 3,900 cGy (or more) delivered at 200 cGy/fraction appear to be associated with increased survival. Better Karnofsky performance scores and younger age at the time of treatment are also associated with longer survival. Mean survival ranges from 2 to 6 months, with death often due to complicating opportunistic infections.

HAART

By itself, HAART appears to have some activity against CNS lymphoma. Observers have reported anecdotal instances of regression of biopsy-proven, AIDS-related CNS lymphoma after institution of HAART along with ganciclovir and IL-2.

Chemotherapy

As HAART has changed the biologic behavior of AIDS, there has been more interest in using high-dose methotrexate in CNS lymphoma based on evidence of activity in non-AIDS-associated disease. Studies to evaluate short courses of combination chemotherapy or the use of less myelosuppressive single agents followed by whole-brain irradiation are currently in progress. Although these approaches appear to be efficacious in

non-HIV-infected patients with primary CNS lymphoma, the available data do not suggest that this approach is superior to CNS irradiation alone in AIDS patients.

A study of 111 patients, reported in 2004, suggests that patients who have HIV-associated CNS lymphoma survive longer if they receive both highly active antiretroviral therapy (HAART) and radiation therapy (at least 30 Gy). J *Newell ME, Hoy JF, Cooper SG, et al. Cancer 100;2627-2636, 2004*).

CERVICAL CARCINOMA

Cervical carcinoma in the setting of HIV infection has been recognized as an AIDS-defining malignancy since 1993. Unfortunately, in some women, cervical carcinoma may be the first indication that they have HIV infection.

Cervical intraepithelial neoplasia (CIN) is also seen in association with HIV infection. These premalignant lesions, also known as squamous intraepithelial lesions (SILs), may foretell a higher incidence of cervical carcinoma among HIV-infected women. SILs have been associated with human papillomavirus (HPV), particularly those subtypes with greater oncogenic potential, such as serotypes 16, 18, 31, 33 and 35.

Epidemiology

Prevalence of HIV infection and cervical abnormalities: The risk of HIV infection in women with an abnormal Pap smear varies with the prevalence of HIV infection in the given population. Screening in clinics in high-prevalence areas has yielded HIV-positivity rates of between 6% and 7% (and up to 10% in parts of Africa). In such high-prevalence areas, among women younger than age 50 with cervical carcinoma, up to 19% of women were found to be HIV positive. HIV-positive women have up to a 10-fold increased risk of abnormal cervical cytology. Several centers have reported abnormal cytology rates of 30-60% in HIV-positive women and Pap smears consistent with cervical dysplasia in 15-40%. The prevalence of cervical dysplasia increases with declining CD4 cell counts in HIV-infected women.

Nationwide, invasive cervical carcinoma was found in 1.3% of women with AIDS. In New York, invasive cervical carcinoma constitutes 4% of AIDS-defining illnesses in women. Recent findings from linkage studies in the US and Italy clearly have shown increased rates of cervical cancer in women with HIV.

Race and geography: The prevalence of invasive cervical carcinoma among American Hispanic and black women is lower than that in white women. However, this difference may stem from a difference in access to health care. The southern and northeastern sections of the United States have a higher reported number of cases of HIV-associated invasive cervical carcinoma.

Etiology and Risk Factors

The severe cellular immunodeficiency associated with advanced HIV infection may allow oncogenic viruses to flourish and may also compromise the body's immunologic defenses that control the development of these tumors.

HPV: There is abundant evidence that HPV infection is related to malignant and premalignant neoplasia in the lower genital tract. HPV serotypes 16, 18, 31, 33 and 35 are the most oncogenic strains and have been associated with invasive cervical carcinoma and progressive dysplasia. The prevalence of cervical SILs among HIV-infected women may be as high as 20-30%, with many having higher cytologic and histologic grade lesions.

Signs and Symptoms

The majority of cervical SILs are detected on routine cytologic evaluation of Pap smears in women with HIV infection.

Advanced invasive disease: Postcoital bleeding with serosanguineous and/or foul-smelling vaginal discharge is usually the first symptom of more advanced invasive disease. Lumbosacral pain or urinary obstructive symptoms may indicate advanced disease.

Screening and Diagnosis

Because the majority of patients with cervical dysplasia or early invasive cancer are asymptomatic, frequent cytologic screening of women at risk for HIV infection must be undertaken.

Screening of HIV-positive women: Current screening recommendations call for women with HIV infection to have pelvic examinations and cytologic screening every 6 months. Pap smears indicating cervical SILs must be taken very seriously, and abnormalities justify immediate colposcopy. Although abnormalities are sometimes missed by relying solely on cytologic screening, recommendations for routine colposcopy have not yet been established.

Screening of women with a history of cervical SILs: For women who have a history of cervical SILs, more frequent re-evaluation and cytologic screening should be undertaken. Since these women are at high risk for

recurrence or development of lesions in other areas of the lower genital tract, post-therapy surveillance with repeat colposcopy also is warranted.

Work-up of women with invasive carcinoma: For women with invasive carcinoma, complete staging should be undertaken; this should include pelvic examination, CT of the pelvis and abdomen, chest X-ray, and screening laboratory tests for hepatic and bone disease. In addition, full evaluation and treatment for HIV and related complications should be initiated.

Pathology

Squamous cell carcinoma: Most cases of cervical carcinoma are of the squamous cell type.

Staging and Prognosis

The staging classification for cervical carcinoma (see chapter 20), as adopted by the International Federation of Gynecology and Obstetrics (FIGO), also applies to AIDS patients.

Cervical dysplasia in HIV-infected women is often of higher cytologic and histologic grade. These women are more likely to have CIN II-III lesions with extensive cervical involvement, multisite (vagina, vulva, and anus) involvement, and endocervical lesions.

HIV-infected women with cervical carcinoma typically present with more advanced disease and appear to have a more aggressive clinical course. Tumors are typically high grade with a higher proportion of lymph node and visceral involvement at presentation. Mean time to recurrence after primary treatment is short, and many patients have persistent disease after primary therapy. Median time to death in one series was 10 months in HIV-infected women, as compared with 23 months in HIV-negative patients.

TREATMENT

Treatment of Preinvasive Disease

Cryotherapy, laser therapy, cone biopsy, and loop electrosurgical excision procedure (LEEP) have all been used to treat preinvasive disease in HIV-infected patients. Short-term recurrence rates of 40-60% have been reported.

Determinants of recurrence: Immune status of the patient seems to be the most important determining factor for recurrence. Close surveillance after initial therapy is critical, and repetitive treatment may be necessary to prevent progression to more invasive disease.

Treatment of Cervical Carcinoma

The same principles that guide oncologic management of the immunocompetent patient with cervical carcinoma (see chapter 20) are utilized in AIDS patients with this cancer.

Surgery can be undertaken for the usual indications, and surgical decisions should be based on oncologic appropriateness and not on HIV status.

Radiation therapy: As most AIDS patients with cervical cancer present with advanced disease, radiation therapy is indicated more often than surgery. If the patient's overall physical condition permits, treatment regimens are identical to those used for the same stage disease in uninfected individuals. It is important to note that the standard of care for advanced carcinoma of the cervix (stages III-IV, without hematogenous dissemination) now includes a combination of irradiation and concurrent cisplatin-based chemotherapy. At present, there is insufficient evidence to suggest that irradiation or other treatments for cervical carcinoma in AIDS patients is any less effective than in similar non-HIV-infected individuals.

Chemotherapy regimens, such as cisplatin (50 mg/m^2) or carboplatin (Paraplatin; 200 mg/m^2), bleomycin (20 U/m^2; maximum, 30 U), and vincristine (1 mg/m^2), have been used in patients with metastatic or recurrent disease. Vigorous management of side effects and complications of these treatments and of AIDS itself must be provided.

ANAL CARCINOMA

Although anal carcinoma is not currently and AIDS-defining illness, the incidence of this tumor is increasing in the population at risk for HIV infection. The incidence of anal carcinoma in homosexual men in a San Francisco study was estimated at between 25-87 cases per 100,000, compared with 0.7 case per 100,000 in the entire male population.

Etiology and Risk Factors

HPV: Precursor lesions of anal intraepithelial neoplasia (AIN), also known as anal SILs, have been found to be associated with HPV infection, typically with oncogenic serotypes, e.g., types 16 and 18. Cytologic abnormalities occur in nearly 40% of patients, especially those with CD4 cell counts <200 cells/mm^3. Abnormal cytology may predict the later development of invasive carcinoma.

Other STDs and sexual practices: Individuals with a history of perianal herpes simplex, and condylomas, or practice of anal-receptive behavior with multiple sexual partners are at greater risk of developing this tumor than those without such a history.

Signs and Symptoms

Rectal pain, bleeding, discharge, and symptoms of obstruction or a mass lesion are the most frequent presenting symptoms.

Screening and Diagnosis

Studies to evaluate the usefulness of anoscopy with frequent anal cytology have been undertaken to determine whether early detection of AIN may result in interventions that would prevent the development of invasive tumors.

Work-up of patients with anal carcinoma: For patients with anal carcinoma, determination of the extent of local disease, as well as full staging for dissemination, should be undertaken.

Pathology

Squamous cell carcinoma: The majority of anal carcinomas are of the squamous cell type.

Histologic grading The grading for AIN is similar to that for CIN, with AIN-1 denoting low-grade dysplasia and AIN-2 and AIN-3, higher grade dysplastic lesions. The gross appearance of lesions on anoscopy does not predict histologic grade. Higher grade dysplastic lesions are seen in patients with lower CD 4 cell counts.

Staging and Prognosis

The staging of squamous cell carcinoma of the anus in HIV-infected individuals is the same as that in non-HIV-infected patients. Patients with severe immunosuppression, i.e., CD4 cell counts <50 cells/mm^3, may present with more advanced, more aggressive disease. The true natural history of this tumor in the AIDS population has yet to be defined, however.

TREATMENT

Treatment of AIN and Carcinoma in situ

Treatment of patients with local AIN is similar to that of women with CIN. Ablative therapy may be used.

Treatment of Invasive Anal Squamous Cell Carcinoma

Anal cancer can be controlled with chemotherapy and radiation therapy despite HIV infection. However, patients who have low CD4 cell counts appear to be more likely to experience severe toxicity and to require colostomy for salvage therapy than those with higher CD4 cell counts. For patients with squamous cell carcinoma of the anus, chemotherapy with mitomycin (Mutamycin; 10 mg/m^2 on day 1) and fluorouracil (5-FU; 1,000 mg/m^2 by continuous infusion on days 1-4) combined with radiation therapy can produce high rates of complete remission.

Concomitant radiation therapy, 5-FU, and mitomycin have been reported to produce a CR in 9 of 11 patients with AIDS-associated invasive anal carcinoma (median CD4 count at diagnosis of 209 cells/mm^3) and a 60% 2-year actuarial survival rate. Two patients remain alive more than 8 years following treatment, but severe toxicity (three grade 3 hematologic, one grade 3 dermatologic, one grade 4 and one grade 5 gastrointestinal toxicity) and one death resulted from treatment.

Recent evidence appears to suggest that 5-FU plus cisplatin may be superior to 5-FU plus mitomycin. Tolerance to treatment seen in patients who have relatively intact immune systems is similar to that seen in HIV-infected patients. However, the appropriate dose of radiation therapy for patients with anal carcinoma in the context of HIV infection remains unsettled. Patients who are unable to tolerate chemoradiation therapy and those in whom treatment fails (defined as a positive biopsy after CR) should be considered for abdominoperineal resection.

OTHER NON-AIDS-DEFINING MALIGNANCIES

Case reports of other malignant tumors occurring in HIV-infected individuals include Hodgkin's lymphoma, nonmelanomatous skin cancers, lung cancer, germ-cell tumors, myeloid or lymphoid leukemias, multiple myeloma, renal cell carcinoma, breast cancer, head and neck cancer, brain tumors, squamous tumor of the conjunctiva, and leiomyosarcoma in pediatric patients. Most of the case reports describe only a few affected individuals, and there are insufficient numbers of patients to confirm an increased risk of developing these malignancies among HIV-infected individuals, with the possible exceptions of Hodgkin's lymphoma, nonmelanomatous skin cancers, lung cancer, seminoma, and pediatric leiomyosarcoma.

Rates of other non-AIDS defining cancers appear to be increasing among HIV-infected individuals. In an Australian cancer database, 196 cases of non-AIDS defining cancers were noted in 13, 067 individuals (1.5%) among 8,351 HIV-infected-only patients and 8,118 patients with AIDS.

As HIV-infected individuals are suviving longer with currently available combination anti-HIV drugs, clinicians should anticipate seeing the development of more tumors in these patients. Greater vigilance for these tumors is warranted.

Hodgkin's lymphoma: Most of the studies showing a possible increased incidence of Hodgkin's disease in HIV-infected individuals are from European countries, especially Italy and Spain. The most common histology is mixed cellularity and lymphocyte-depleted. Male predominance, a higher prevalence of B symptoms, and more extranodal disease on presentation are the main characteristics of Hodgkin's lymphoma in HIV patients.

Chemotherapy is recommended for this group of patients, due to the high proportion of stage III or IV disease. Standard treatments include ABVD (Adriamycin, bleomycin vinblastine, and dacarbazine [DTIC-Dome]) or ABVD alternating with MOPP (mechlorethamine {Mustargen], Oncovin [vincristine], procarbazine [Matulane], and prednisone). More recently, early results with BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone] and the Stanford V regimen look promising.

The Stanford V regimen and concomitant HAART appear to be well tolerated in patients with Hodgkin's lymphoma and HIV infection, producing a 53% CR rate with a median overall survival of 11 months and a 55% 2-year disease-free survival rate in one study. However, patients with high initial prognostic scores (above 2) fare significantly worse than patients with lower initial prognostic scores.

Radiation therapy appears useful in approximately 50% of cases of HIV-associated Hodgkin's lymphoma. Of 14 patients treated at MD Anderson Cancer Center (stage I: 1; stage II: 3; stage III: 4; and stage IV: 6), 1 patient received radiation therapy alone and 7 received both chemotherapy and irradiation. The projected overall 5-year survival (64-month median follow-up) was 54%. A greater proportion of patients died because of other HIV-related causes than because of Hodgkin's lymphoma.

Nonmelanomatous skin cancers: As in the general population, basal cell carcinoma is more common than squamous cell carcinoma in the setting of HIV infection. The risk factors for the development of these tumors are the same as in the general population: namely, fair skin, history of sun exposure, and family history. A study from San Francisco demonstrated that these skin cancers can be treated successfully with standard local therapy, with a recurrence rate indistinguishable from that of the general population (approximately 6%).

Lung cancer: Patients with HIV appear to have a higher relative risk of developing lung cancer than do age-matched controls (RR=4.5,95%; CI=4.2-4.8). These tumors tend to present at later stages than do tumors with similar histologic distribution in the general population.

Pediatric leiomyosarcoma: Cases of aggressive leiomyosarcoma developing in HIV-positive children have been reported. Leiomyosarcoma is a rare tumor, occurring in < 2 cases per 10 million non-HIV-infected children. However, a much higher than expected frequency of leiomyosarcoma has been reported in HIV-infected children. Visceral sites are commonly involved, e.g., the lungs, spleen, and GI tract.

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