

HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE HIV-ASSOCIATED MALIGNANCIES

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INTRODUCTION

Three malignancies are considered as AIDS-defining conditions : Kaposi's sarcoma (KS) ; intermediate or high-grade B-cell non-Hodgkin's lymphoma (NHL) ; invasive cervical cancer (ICC).

In addition, Hodgkin's disease (HD) has been increasingly described in HIV setting [1], and possible increases in anal, head and neck, lung and testicular carcinoma, melanoma and plasma cell myeloma have also been reported [2].

In this review, we will describe the epidemiology, pathology, clinical features and treatment of the cancers most commonly observed in patients with HIV-1 infection.

KAPOSI'S SARCOMA

Introduction

KS has long been the most common malignancy observed in patients with HIV-1 infection. This tumor was first described by the Hungarian dermatologist Moritz Kaposi in 1872. The classical form of KS is rare and affects elderly patients of predominantly Mediterranean or Jewish origin living in the United States and Europe. The lesions usually start with a reddish nodule on a lower extremity with a clinically indolent outcome. In the fifties an endemic, relatively frequent (3%-9% of all cancers) equatorial African variant was described ; this variant is usually more aggressive than the classic KS, with multiple localizations. KS in HIV-positive Caucasian patients develops predominantly in homosexual men, whereas in African patients it is only somewhat higher in men than in women.

Incidence and epidemiology

In Western countries, KS was, at the peak of the AIDS epidemics, over two thousand times more common in HIV-1-infected individuals than in the general popula-

tion. Among people with newly diagnosed AIDS in the United States and Europe the prevalence of KS ranged from 1% in men with hemophilia to 21% in homosexual men [3]. Two important changes have occurred over time : a steep decline in the incidence of KS as index diagnosis for AIDS (from 30%-40% in 1982 to 9%-15% in 1990), KS being now more often diagnosed as a late manifestation of AIDS, and a 30%-50% reduction of incidence (in both the US and Europe) [4] following the availability of protease inhibitors and the start of highly active antiretroviral therapy (HAART) in 1996.

KS may remain asymptomatic for a long time, but a number of patients develop rapidly progressive disease with the multifocal appearance of lesions over the skin and mucosal cavities. The median survival of AIDS patients with KS where HAART is not available is 18-24 months.

Etiology and pathogenesis

A recently identified human herpes-virus termed human herpes-virus 8 (HHV-8) is etiologically linked to the development of KS [5]. HHV-8 is sexually transmissible, particularly through oral-anal contacts, and has been detected in biopsy samples of more than 90% of KS lesions, regardless of age, sex, race, geographic distribution and HIV status. HHV-8 DNA sequences have also been found in peripheral blood mononuclear cells of more than 50% of KS patients.

A high rate of HHV-8-specific antibody seroconversion among homosexual men infected with HIV in whom KS subsequently developed, compared with a low rate of seroconversion in homosexual men infected with HIV in whom KS did not develop, has been showed [6]. However, only a small proportion of HHV-8-infected people ever develop KS, and these do so after a long latency period. Hence, in addition to HHV-8, other factors must play a role. The activation of cytokines such as interleukin-1, interleukin-6, basic fibroblastic growth factor, tumor necrosis factor- and oncostatin-M, in particular, results in the proliferation of the mesenchymal progenitor cell and affects the rate of growth of KS lesions. HIV-1 itself, through expression of the tat protein, could also increase the growth of KS cells. The full pathogenesis of epidemic KS may thus involve a complex interplay of genetic factors, immune defects, HHV-8 and HIV-tat protein.

Pathology

The cell of origin of spindle cells, which are the hallmark of KS, is probably a progenitor cell of either endothelial or monocyte-macrophage lineage. Histo-

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logically, the tumor is characterized by a proliferation of vascular structures, often with large malignant-appearing endothelial cells, set against a background of bland proliferation of spindle-shaped cells, inflammatory mononuclear cells and extravasated erythrocytes [7]. The histological description of the initial lesion (patch or plaque stage) shows only minor changes such as an increasing number of dilated vascular spaces lined with endothelial cells and irregular vessels. In the dermis there is a perivascular mononuclear cell infiltrate of lymphocytes and plasma cells. In the most advanced lesions (nodular) the endothelial component is reduced and compressed by bundles of spindle-shaped cells [7]. Irregular vascular spaces have been described. Inflammatory cells are absent at this point. The lymph nodes involved contain multiple small foci of KS tumors in the capsular and sinus regions, and the disseminated KS lesions in the visceral organs are associated with organ vessels.

Clinical manifestations

Cutaneous KS lesions are usually macular or papular at the beginning, occurring sometimes in clusters, progress to plaque or nodular lesions with dimensions ranging from a few millimeters to several centimeters. The color of the lesions ranges from blue-purple to red-brown. Lesions may spontaneously disappear as other lesions appear [8]. KS has been observed in every site of the body. Common extracutaneous sites include lymph nodes, lungs or gastrointestinal tract.

Pulmonary KS usually occurs in advanced disease and is the most dangerous and life-threatening form of KS. It can be associated with mediastinal or hilar adenopathies and may have an appearance of interstitial pneumonia. Clinically it presents with fever, shortness of breath, cough, hemoptysis and chest pain [8]. Radiographic findings include nodular, interstitial and alveolar infiltrates, pleural effusion, hilar and mediastinal adenopathy, and even an isolated pulmonary nodule. The pleural effusions of KS are typically serosanguineous in nature and are associated with KS lesions on the visceral pleura.

Systemic manifestations may be present simultaneously or even precede the appearance of the skin lesion for several months and include persistent and unexplained weight loss, diarrhea, malaise and fatigue.

Over 50% of patients with skin disease have gastrointestinal lesions. Any segment of the gastrointestinal tract may be involved, although the stomach and the duodenum are the most commonly affected. Gastrointestinal KS is seldom symptomatic, but may cause bowel malabsorption or obstruction, and, albeit rarely, bleeding [8]. Oral-cavity KS occurs in approximately 35% of patients and can be the initial site of disease in about 15% of patients. Intraoral lesions most commonly affect the palate and gingiva, and may interfere with nutrition and speech.

Patients with AIDS-associated KS often have modestly enlarged lymph nodes. Routine lymph node biopsy often reveals focal KS involvement, although this finding appears to have little clinical consequence. Thus,

routine biopsy of small lymph nodes is not recommended for the purpose of diagnosing nodal KS. Occasionally, however, massive nodal enlargement may occur, and lymph nodes may be replaced by KS. This presentation may occur in the absence of KS elsewhere, and may be associated with edema. Because the causes of massive or asymmetric nodal enlargement include lymphoma or various HIV-associated infections, diagnostic biopsy is warranted in such cases.

Lymphedema is a frequent complication of AIDS-associated KS, and its severity may be disproportionate to the extent of cutaneous KS. The edema is generally non-pitting. The feet and legs are most commonly affected, but other common sites include the groin, external genitalia, and the periorbital tissues. Less commonly, edema may involve the upper extremities and trunk. CT scans to investigate proximal lymphatic obstruction as a cause of lower extremity edema generally fail to show dramatic enlargement of inguinal or pelvic nodes. The cause of KS-associated edema is not entirely clear, but it may result from tumor involvement of dermal lymphatics or, perhaps, from the production by KS cells of cytokines that increase vascular permeability. Severe edema, particularly of the legs, may be complicated by reduced mobility, contractures, diffuse serous drainage with protein loss, skin ulceration, and cellulitis.

Staging

The initial evaluation of a patient with KS includes a physical examination with special attention to those areas more frequently affected by the disease, such as the lower extremities, face, oral mucosa, genitalia. Lesions in the gastrointestinal tract are often easily recognized on endoscopy; however, because the lesions tend to be submucosal, biopsies may not demonstrate the disease. A chest roentgenogram is an excellent way to screen for pulmonary lesions. Bronchoscopy can be reserved for those with an abnormal X-ray and persistent respiratory symptoms, when no other cause is found. Gallium-thallium scanning may also be helpful in the evaluation of lung disease: KS is usually thallium-avid and gallium-negative, whereas infections are usually gallium-avid and thallium-negative.

Various staging classifications for epidemic KS have been proposed. In areas of the world where HAART is not available, the most applicable staging classification is that proposed by Krown et al. [9] based on the extent of the tumor (T), immune status (I), and the severity of systemic illness (S). This classification identifies two different risk categories: a good risk (T0I0S0) with skin \pm lung \pm oral disease, CD4 > 150/ μ L, no opportunistic infection (OI)/B (unexplained fever, night sweats, > 10% involuntary weight loss, or diarrhoea persisting for more than two weeks) symptoms and performance status (PS) > 70, and a poor risk (T1I1S1) with edema or ulcerations or extensive oral KS and visceral involvement, CD4 < 150/ μ L, OI and/or B symptoms and PS < 70. Where HAART is used, the combination of poor tumor stage

(T1) and poor systemic disease (S1) risk identifies patients with unfavorable prognosis, whereas the CD4 count seems not important.

Therapy

The treatment of HIV-associated KS is primarily dependent on the extent of disease. In general, delivery of effective anti-KS treatment and maintenance of adequate control of HIV-1 are essential.

Local therapy

Localized KS cutaneous tumors have been successfully treated with surgical excision, laser therapy or liquid nitrogen cryotherapy (response rate 85%), and radiotherapy (RT). RT has become the most important therapy in the local treatment of KS; however, post-radiation hyperpigmentation remained in 20% of lesions and 10% of cases showed local recurrence. In addition, patients with HIV infection tend to have more radiation-related complications for any given dose than non-HIV-infected patients. Late complications of RT include tissue fibrosis, ulceration and superinfections [10].

Intralesional injection of vinblastine, vincristine, bleomycin or interferon- α have also been reported to be effective treatments (response rates 80-90%), with the only side effect of local pain and skin irritation. Finally, 9-cis-retinoid acid (alitretinoin) 0.1% gel is also active in the treatment of small, thin cutaneous lesions of KS, with a response rate of 37% within 2-12 weeks [11].

Systemic therapy

HAART

This should be the first therapeutic option for patients with Kaposi sarcoma, is associated with response rates of 60-90%, even in advanced disease, and has also been associated with significantly longer responses after chemotherapy. The effectiveness of HAART in treating Kaposi's sarcoma may result from improvements in host immunity, although protease inhibitors also have direct antiangiogenesis activity [12].

Immune-response modifiers

Recombinant α -interferon was the first drug specifically approved for the treatment of KS [13]. When given as a single agent, high doses are required for effective treatment of KS, and response rates were 18%-46%. Interestingly, interferon- α has subsequently shown to have anti-angiogenic and anti-HHV-8 activities.

The combination of α -interferon with anti-HIV therapy (zidovudine in particular) showed a response rate ranging from 40% to 50% [14].

Chemotherapy

In general, systemic chemotherapy is reserved for patients with widespread, symptomatic disease, in particular when visceral disease is present.

Several single-agent therapies were initially reported to be active in epidemic KS including the vinca alkaloids (vincristine, vinblastine and vinorelbine), anthracyclines (adriamycin and epirubicin), epipodophylotoxins (eto-

poside and teniposide), and bleomycin. The overall response rate ranged from 10% to 76%, although most were partial responses. Combination chemotherapy regimens included doxorubicin, bleomycin, vincristine and vinblastine producing responses in approximately 70%-80% [15] of patients.

The use of liposomal anthracyclines is the modern approach for the treatment of advanced KS. Daunoxome is a liposomal preparation of daunorubicin in which the anthracycline has been entrapped in small unilamellar vesicles and has been formulated to maximize the selectivity of daunorubicin for solid tumors in situ. This selectivity-increased drug delivery to the tumor translates into a significant improvement in therapeutic efficacy with no increase in toxicity. Similarly, doxorubicin incorporated in the polyethylene glycol PEG-coated liposomal formulation is also effective in advanced stages of KS. Both drugs have been shown to have the same activity as polychemotherapy regimens but less toxicity in randomized studies [16-17].

Hence, liposomal anthracyclines should be considered the standard treatment for patients with advanced stages of AIDS-related KS. Concomitant use of both HAART and hematological growth factors is needed, with the aim of reducing opportunistic infections and myelotoxicity.

Finally, paclitaxel is used in patients who have failed first-line chemotherapy. A response rate of 71% was reported with doses of 135 mg/m² every three weeks [18].

NON-HODGKIN'S LYMPHOMA

Incidence and epidemiology

The relative risk of NHL in people with AIDS ranges between 15 for low-grade and T-cell NHL and 400 for high-grade NHL. NHL occurs among all risk category groups, in all age groups and in different countries with similar epidemiologic and clinical-pathologic features. Systemic NHL constitutes 70% of all cases and the remaining 30% are primary CNS lymphomas (PCNSL). In HAART-treated patients, the incidence of systemic NHL remains quite stable, whereas the incidence of PCNSL decreases considerably.

Pathology

AIDS-related NHL (AIDS-NHL) are characterized by a diffuse growth pattern, cellular pleomorphism, high-grade morphology, and B-cell derivation.

AIDS-NHL include systemic lymphomas, primary brain lymphomas, primary effusion lymphoma and plasmoblastic lymphoma of the oral cavity.

a) Systemic NHL

Systemic AIDS-NHL are a heterogeneous group of malignancies displaying a B-cell phenotype. The overwhelming majority of systemic AIDS-NHL fall within three working formulation histologic categories [19]: small noncleaved cell lymphoma (SNCCCL) which includes classic Burkitt's lymphoma and Burkitt-like lymphoma; large

noncleaved cell lymphoma (LNCCL) ; and large cell immunoblastic lymphoma plasmacytoid (IBL-P).

A correct differential diagnosis between these three types of NHL is clinically relevant, because of the different behavior and prognosis of these lymphomas.

b) **Primary central nervous system lymphoma**

PCNSL represent a more uniform group. Histologically, the overwhelming majority is represented by DLCL, which usually display histologic features consistent with IBL-P.

c) **Body cavity-based lymphoma/primary effusion lymphoma (BCBL/PEL)**

The broad category of lymphomas involving the serous body cavities includes all NHL associated with a malignant effusion. Cases of NHL presenting in the serous body cavities in the absence of clinically identifiable tumor masses are defined as primary lymphomatous effusions, whereas secondary lymphomatous effusions are malignant effusions complicating a clinically evident solid NHL through contiguous spread of tumor cells into the body cavities [20].

A peculiar type of primary lymphomatous effusion has been recognized as an individual entity based on its distinctive biologic features and its consistent association with HHV-8 [21]. Because of its peculiar and predominant tropism for the serous cavities of the body, this type of B-cell NHL has been designated body cavity-based lymphoma (BCBL) [20]. In the USA, BCBL has also been termed as primary effusion lymphoma (PEL) [21].

Clinically, BCBL/PEL is characterized by growth in liquid phase in the absence of detectable tumor masses. Pathologically, however, autopsy and computed tomography scan studies have consistently revealed that BCBL/PEL presents as multiple small tumor foci involving the serous membranes, which appear irregularly thickened. Thus, the basic feature of BCBL/PEL is a striking predilection for diffuse spreading along the serous membranes without infiltrative or destructive growth patterns.

Cytomorphologic features of BCBL/PEL cells bridge those of large cell immunoblastic and anaplastic large cell lymphomas. The most common appearance is of a pleomorphic mixture of immunoblast-like cells and other cell types including anaplastic, multilobated or multinucleated large cells resembling the Reed-Sternberg cells of Hodgkin's disease.

d) **Plasmablastic lymphoma of the oral cavity (PBL)**

AIDS-NHL may occur anywhere in the head and neck area. The tumor has been observed in a variety of sites including the gingiva, palate, tongue, tonsil, nasopharynx, orbit, parotid, maxillary sinus, soft tissue and hypopharynx. Most AIDS-NHL of the head and neck are morphologically similar to other lymph nodal or extranodal systemic AIDS-NHL and express B-cell markers.

A particular type of lymphoma involves the oral cavity [22]. This lymphoma has been designated as "plasmablastic lymphoma" in accordance with its plasmablastic morphology and immunohistologic features [22]. The incidence is 2%-3% and the prognosis poor. Its association with HHV-8 is debated.

Pathogenetic heterogeneity of AIDS-NHL

The pathologic heterogeneity of AIDS-related lymphomas correlates with the heterogeneity of the molecular lesions associated with these lymphomas. SNCCCL displaying features of classic Burkitt's lymphoma selectively associates with activation of C-myc, whereas rearrangements of bcl-6 are restricted to a subset of DLCL. Infection by HHV-8 clusters with BCBL/PEL ; conversely, infection by EBV occurs in different lymphoma types. However, only IBL-P express the EBV-encoded latent membrane protein-1 (LMP-1) [23].

Clinical features

AIDS-NHL is often widespread at initial presentation with a high frequency of systemic "B" symptoms. At the time of diagnosis approximately 75% of patients have advanced disease with frequent involvement of extranodal sites, the most common being the CNS, bone marrow, gastrointestinal tract and liver.

20% to 40% of patients have meningeal involvement at presentation [24], and gastrointestinal tract involvement, sometimes at multiple sites, develops in 10% to 40% of cases.

BCBL usually remains strictly localized to the body cavity of origin and only infrequently spreads to local lymph nodes or distant sites.

PCNSL is a manifestation of very advanced HIV-1 disease (usually the CD4 cell count at diagnosis is < 50/ μ L). The lymphoma develops as single or multiple lesions in the deep regions of white matter, in basal ganglia and in cerebellum. The clinical presentation of PCNSL is not specific and approximately 50% of patients present with lethargy, confusion and personality change, whereas many others lack lateralizing neurological signs.

Diagnosis

The diagnosis of NHL should be made by histologic examination of the tissue obtained by incisional or excisional biopsy, although it may be possible to make an adequate diagnosis from needle aspiration cytology, especially for patients in poor clinical conditions. Staging evaluation of patients should include bone marrow aspiration and biopsy, lumbar puncture, computed tomography scan of the chest, abdomen, pelvis and brain.

A major clinical problem with PCNSL is its correct identification. When CT scan or MRI identify an intracranial mass in an HIV-1-infected individual, the patient is usually first treated with antitoxoplasmosis therapy, and brain biopsy is considered only after treatment failure. Unfortunately, neurologic deterioration occurs in non-responders, who frequently become ineligible for brain biopsy or adequate therapy. Despite the fact that early brain biopsy should be considered for any patient with negative toxoplasmosis serology or for those who worsen within the first week of antitoxoplasmosis treatment, this approach is often impossible due to lack of

consent of the patients or family members to this risky procedure.

To avoid the need for brain biopsy, positron emission tomography (PET) and thallium single photon emission computed tomography (SPECT) might be used to distinguish tumor from CNS infection, offering the opportunity of rapid diagnosis [25]. The predictive value of PET and SPECT is further enhanced by molecular analysis of EBV DNA sequences in cerebrospinal fluid, since positive detection is considered a sensitive and specific marker of PCNSL [25-26].

Therapy

The optimal therapy for AIDS-NHL has not been entirely defined, as poor bone marrow reserve and underlying HIV-1 immunodeficiency challenge the optimal management of systemic NHL. Effective combination chemotherapy is essential, and regimens should include intrathecal chemotherapy, as either a prophylactic or therapeutic modality.

Most clinicians initially favored attenuated doses of aggressive regimens such as methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethazone (M-BACOD), without or in combination with antiretroviral therapy. Low-dose M-BACOD yielded a complete response (CR) rate of 41% with a median overall survival of six months for all patients and a disease-free survival of three months [27].

Presently used protocols take into account a stratification of patients into "low" and "high" risk categories, based on the presence or absence of prognostic factors. The intensive ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) regimen administered to patients without opportunistic infections and with a good performance status shows a median survival of 16 months for complete responders.

On the other hand, patients in "high" risk categories may be treated with cyclophosphamide-doxorubicin-vincristine and prednisone (CHOP)-like regimens, also at reduced dosage with a palliative intent. Our recommendations are to give intensive chemotherapy regimens (such as CHOP) to low risk category patients and conservative chemotherapy regimens (i.e., low-dose CHOP regimens) to "high" risk patients.

On the basis of data of published trials it seems reasonable to use HAART and chemotherapy to treat patients with newly diagnosed AIDS-related lymphoma, as this approach appears to have benefits in terms of increased tolerability of dose-intensive chemotherapy, higher rates of complete remission, and longer survival [28].

Prognosis

The prognosis for AIDS-NHL is very poor, with an overall survival of 12 months. Nevertheless, some prognostic factors for survival have been identified. The classic prognostic criteria of the general population (i.e., age, performance status, stage, extranodal involvement) have to be supplemented by host prognostic criteria in the

HIV-1 setting, namely, low CD4 cell count ($< 100/\mu\text{L}$) and a previous AIDS diagnosis. Patients with a low CD4 cell count and a previous AIDS diagnosis have a median survival of three months, whereas patients without these adverse prognostic factors have a median survival of 12 months.

HODGKIN'S DISEASE

AIDS-HD is the most common non-AIDS defining tumor and the relative risk (RR) for HD in HIV-1-infected individuals is 7.6-8.9 [31-32].

The histological diagnosis of HD is still based on the presence of classical Reed-Sternberg (RS) cells in an appropriate cellular background. HD occurring in HIV-1-infected persons exhibits pathological features which are different from those of HD in the general population, and is characterized by the predominance of unfavorable histological subtypes, mixed cellularity being the most frequently diagnosed [1]. A high frequency of EBV association has been shown in HD tissues from HIV-1-infected people.

The disease has a widespread extent at presentation and frequent systemic "B" symptoms (70%-96% of patients). Around 75% of patients had advanced disease stages (stage III-IV according to Ann Arbor staging classification) with a frequent involvement of extranodal sites, the most common being bone marrow, liver and spleen. Bone marrow involvement occurs in 40%-50% of patients, and may be the first indication of the presence of HD in 20% of cases [1]. HD tends to develop as an early manifestation of HIV-1 infection with a higher median CD4 cell count (around $300/\mu\text{L}$), than HIV-1 diffuse large cell lymphoma [1]. Staging evaluation of patients should include a bone marrow biopsy, and CT scan of the chest, abdomen and pelvis.

The optimal therapy has not been defined. Most patients are treated with combination chemotherapy regimens, but the response rate remains poorer than that of HD in the general population. The CR rate ranges from 46% to 65% with a median survival of one year and the two-year disease-free survival rate is 50%.

The use of epirubicin, bleomycin, vinblastine and prednisone (EBVP) chemotherapy in combination with antiretroviral therapy and primary use of G-CFS appears to be promising, allowing a median survival of 16 months, with a survival rate of 32% and a disease-free survival of 53% at 36 months in a single study [31].

CERVICAL CANCER

A strong epidemiological association exists between several types of HPV (subtypes 16, 18, 31, 33 and 35) and cervical carcinoma. This risk is particularly elevated in women with AIDS who have a higher incidence of coinfection by HPV and who may lack sufficient immune surveillance of HPV infection owing to HIV-1-associated T-cell immunodeficiencies.

ANAL CANCER

Cervical intraepithelial neoplasia (CIN) has been increasingly diagnosed in HIV-1-infected women [32] and invasive cervical cancer (ICC) is currently considered an AIDS-defining condition. CIN in HIV-1-infected women is usually associated with high-grade histology (CIN II-III), more extensive and/or multifocal disease, and disseminated lower genital tract human papilloma virus (HPV-related lesions). Other risk factors, such as multiple sexual partners, early parity, early coitarche, cigarette smoking, sexually transmitted disease, are often present in these women.

Squamous neoplasia of the cervix is best understood as a continuum of a single disease approach. This continuum is histologically represented as a progression of changes beginning with CIN1 (mild dysplasia), followed by CIN2 (moderate dysplasia) and CIN3 (severe dysplasia), and eventually resulting in invasive cervical cancer.

The median time of progression of CIN1 to CIN3 is approximately seven years, whereas the development of invasive carcinoma from CIN3 may require an additional five to seven years [33].

CIN is more common in patients with symptomatic HIV-1 infection and with CD4 cell count $< 200/\mu\text{L}$. Similarly, HIV-1-infected women who are symptomatic or severely CD4-depleted appear to be at highest risk for the development of ICC.

In 1993, the CDC recommended annual Papanicolaou smears for HIV-1-infected women who have had two successive adequate and normal smears more than six months apart [34]. However, many clinicians have opted to perform semiannual or more frequent pap testing with or without colposcopy. The rationale for this approach includes the fact that HIV-1-infected women are usually being seen in the health care system more often than once a year for other reasons, the high rate of inflammation that may obscure a small lesion, and the high incidence of concurrent vulvar, vaginal and anal neoplasia seen in this group. A thorough annual examination including visual inspection of the anus, vulva and vagina, as well as pap smear and screening colposcopy should be considered the minimal appropriate evaluation in HIV-infected patients with less than 200 CD4 cells/ μL .

Standard treatments for CIN have utilized excisional or ablative techniques and include cryosurgery, laser ablation, loop electrosurgical excision procedure (LEEP) excision, and cone biopsy.

Observation of early lesions for a period of three to six months may also be appropriate, because early CIN may regress spontaneously and is unlikely to progress to invasive disease.

Overall, current treatment strategies for CIN appear to be partially effective in HIV-1-infected women. Women with CD4 cell count $< 500/\mu\text{L}$ are most likely to develop recurrent disease, but even those with CD4 count $> 500/\mu\text{L}$ have higher recurrence rates than non-HIV-1-infected women.

Epidemiological studies showed an increase in the incidence of anal cancer in the AIDS era, and there is strong evidence of a relationship between HIV-1-induced immunodeficiency, HPV infection and the development of anal intraepithelial neoplasia (AIN) [35]. AIN is also more common among HIV-1-infected persons with lower CD4 cell count or more advanced clinical stage.

A screening strategy including pap smear, anoscopy and anal colposcopy is useful to detect AIN or invasive anal cancer. Patients with normal findings or mild dysplasia on initial pap smear should undergo follow-up screening every 6-12 months. Those with moderate or severe dysplasia must undergo anoscopy with biopsy similarly to those patients with abnormalities initially noted on physical examination.

A person with HIV-1 infection and anal neoplasia should receive the standard treatment for the specific stage of the disease. However, general health status and stage of HIV-1 disease must be considered when planning therapy. In particular, ablative therapy or electrocautery, cryoablation or laser ablation may be performed at the discretion of the treating physician for patients with AIN-2 or AIN-3. For invasive anal cancer the combination of surgery, radiotherapy and chemotherapy should be considered.

OTHER TUMORS

Skin cancer

HIV-1-infected patients may be at increased risk for the development of cutaneous neoplasms, and basal cell carcinoma is increasingly observed [36]. These tumors are mostly superficial, multicentric, and located on the trunk. Interestingly, there seems to be no association between the degree of immunosuppression and the number of cutaneous neoplasms or the occurrence of squamous cell carcinoma. Typically, basal carcinoma occurs on sun-exposed parts of the body; lesions are usually small, pearly bordered papules or nodules with superficial telangiectasias.

Squamous cell carcinoma of the skin has also been reported in HIV setting. These lesions tend to recur up to 20%, following curettage and electrodesiccation, unlike basal cell carcinoma, for which acceptable cure rates are obtained with this approach.

Only a few cases of melanoma in HIV-1-infected patients have been described. All patients had systemic metastasis and this suggests that malignant melanoma in HIV setting may have a tendency toward early dissemination.

Other risk factors for the development of cutaneous malignancies appear applicable to HIV-infected individuals as well and include fair skin, a positive family history and excessive exposure to sunlight. Concurrent HPV infection is also an important cofactor.

Standard treatment approaches for non-melanoma-

tous skin lesions, such as curettage and electrodesiccation, may need to be modified for HIV-1-infected individuals. Wider excisions of squamous cell carcinoma may be warranted because of the high reported recurrence rate. Perhaps most importantly, close inspection and the surveillance of the skin is warranted in these patients with prompt biopsy of any suspicious lesion.

Lung cancer

Hundreds of cases of lung cancer have been observed in HIV-1-infected patients, but epidemiological data do not definitively support the existence of an increased risk for the development of this tumor [37].

Many features of lung cancer in HIV-1-infected individuals differ from the disease in the general population. The median age at diagnosis ranges from 38 to 47 years compared with 55 to 70 years in the general population; adenocarcinoma predominates as histological subtype, ranging from 30% to 100% of cases, whereas small-cell histology is rare (10% of cases). In contrast, in the general population adenocarcinoma, squamous-cell and small-cell carcinoma each account for approximately one-third of cases.

Severe immunodeficiency may not be a significant cofactor in the pathogenesis of lung cancer in HIV-1-infected patients, because the median CD4 cell count ranged from 120 to 288/ μ L. Overall, tobacco smoking is the major carcinogen in HIV-1-infected patients, being present in more than 90% of cases as in the general population. However, it is likely that HIV-1-infected patients, especially those who are IVDUs, smoked more cigarettes per day than individuals of the general population. More than 70% of HIV-1-infected patients present with advanced (stages III-IV according to TNM classification) or inoperable disease, including 55% with metastasis at the time of diagnosis.

The typical symptoms of lung cancer (cough, chest pain, hemoptysis, dyspnea) do not distinguish HIV-1-infected from non-HIV-infected patients. However, diagnosis of lung cancer may be delayed in HIV-1-infected patients, because signs and symptoms of the disease may be similar to those of common pulmonary opportunistic infections.

Lung cancer must be considered in the differential diagnosis of an abnormal chest X-ray film, especially if one or more of the following features are present: a mass lesion in the lung, unilateral hilar adenopathy, rib destruction, Pancoast's syndrome, hard and/or fixed scalene lymphadenopathy, phrenic and/or left recurrent nerve paralysis and paraneoplastic syndromes commonly associated with lung cancer.

The outcome of patients with lung cancer and HIV-1 infection is very poor, with a median survival of around six months and with 10% of survivors at one year from diagnosis [37].

The same therapeutic strategies as in the general population can be used, if HIV-1 is under control. In contrast, lung cancer may be approached with only a palliative strategy in patients with AIDS.

Testicular germ-cell cancers

Testicular germ-cell cancers are relatively rare and among the most curable malignancies. However, they are relatively common diseases in young men between 15 and 35 years of age, in whom HIV-1 infection is not uncommon. Therefore, these malignancies should not be expected to be a rare event in young men with HIV-1 infection, and cohort data from the Pittsburgh area multicenter AIDS cohort study indicate that HIV-1-infected homosexual men have a significant increase in the incidence of testicular cancer (around four-fold) compared to that of the general population [38].

The natural history of these diseases in HIV-1 setting seems similar to that in the general population. The ratio of seminoma to non-seminoma germ-cell tumors has varied in the reported series.

The risk of testicular cancer does not appear directly related to the level of immune function. Overall, approximately 60% to 80% of patients have clinical stage I and II (i.e., disease confined to the testis and retroperitoneal lymph nodes), and only 20%-30% have clinical stage III (i.e., disseminated disease above the diaphragm or visceral disease), again a proportion similar to that observed in the general population.

In the majority of cases testicular tumors are painless, but approximately 30% of patients have moderate testicular pain, and cough (pulmonary metastasis), abdominal pain (lymph node or retroperitoneal soft tissue metastasis, hydronephrosis) or weight loss may all occur.

The diagnosis of testicular germ-cell cancer should be made by radical inguinal orchiectomy. Staging evaluation should include two more marker studies (i.e., chorionic gonadotropin, alphafetoprotein and lactic acid dehydrogenase), chest radiographs and abdominal CT scan. The presence of persistent generalized lymphadenopathy should be considered, in order not to overstage carcinoma by abdominal CT scan. In patients with normal serum markers and limited abdominal lymphadenopathy benign enlargement of lymph nodes should be suspected and careful surveillance alone may be reasonable after orchiectomy.

For early-stage seminoma, the standard treatment is radiotherapy, while for advanced disease, it is combined treatment that includes chemotherapy (cisplatin, etoposide and bleomycin or cisplatin, vinblastin and bleomycin) and radiotherapy. The majority of HIV-1-infected patients with germ-cell tumors tolerate standard therapy and obtain cure rates similar to that of HIV-uninfected patients (around 90%).

HAART AND CHEMOTHERAPY

Several questions such as feasibility, toxicity and drug-drug interactions face the oncologist using the combination of HAART and chemotherapy for the management of patients with malignancies and HIV-1 infection. Most clinicians would recommend continuation of HAART until unacceptable toxicity occurs. In our experience on

patients with systemic AIDS-NHL the concomitant use of HAART and CHOP, significantly increases the incidence of severe anemia, severe neutropenia and neurotoxicity in comparison to those patients treated with CHOP but without HAART.

As regards drug-drug interaction, both protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized by the liver via the cytochrome p450 3A family. Anthracyclines, the vinca alkaloids and etoposide are metabolized in the same way. Significant alterations in the disposition of vincristine and doxorubicin but not of prednisone or cyclophosphamide may result from the concomitant use of protease inhibitor and CHOP.

CONCLUSIONS

The prognosis of HIV-1-associated cancers has improved considerably in recent years, due to the better clinical conditions of patients (in turn due to the availability of HAART) and the more effective and better tailored chemotherapeutic regimens. Unfortunately, such improvements have been limited to rich, well-developed countries. In less developed countries, the situation is gloomy. In Africa, where B-cell non-Hodgkin's lymphomas and Kaposi's sarcomas are the predominant AIDS-associated cancers [39], treatment is not affordable by the vast majority of patients, and they simply die. Hence, we are left with the paradox of leaving untreated the very populations who should benefit most from improvement in treatments. Sadly, we are very far from finding a remedy to this unfortunate situation.

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