HIV-Associated Malignancies

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Objectives

1. Describe the types of malignancies commonly found in children and adolescents with human immunodeficiency virus (HIV)/AIDS.
2. Present an overview of the following HIV-associated pediatric and adolescent cancers: non-Hodgkin's lymphoma (NHL), Kaposi sarcoma (KS), leiomyosarcoma, cervical carcinoma, and anal cancer.
3. Discuss the clinical manifestations and treatment of the various HIV-associated malignancies.
4. Discuss the specific supportive-care measures necessary for children receiving chemotherapy and radiation therapy.

Key Points

1. Children with HIV infection are at increased risk of developing malignancies as a result of the dysregulated immune system and the interplay of other oncogenic viruses.
2. The most common malignancies found in children with HIV/AIDS are NHL, KS, and leiomyosarcoma.
3. Treatment for HIV-associated malignancies may be complicated by HIV-associated organ dysfunction, infectious complications, and drug interactions between chemotherapy and antiretroviral drugs as well as combined immunosuppression between HIV infection and chemotherapy.
4. Treatment of HIV infection with highly active antiretroviral therapy is critical to the treatment of HIV-related malignancies and must be instituted alongside chemotherapy.

Overview

Evidence of the relationship between human immunodeficiency virus (HIV) and cancer became evident early in the HIV/AIDS epidemic. In 1981, the U.S. Centers for Disease Control and Prevention (CDC) described a clustering of cases of Kaposi sarcoma (KS), until then a rare form of cancer, among homosexual men in New York and California. The following year, the CDC reported a clustering of cases of gay men in San Francisco with diffuse, undifferentiated non-Hodgkin's lymphoma (NHL), another rare cancer. In time, it became apparent that these unusual forms of cancer were appearing as a result of infection with HIV. However, this association would not be limited to these two forms of malignancy. Many other neoplastic disorders, most notably primary central nervous system (CNS) lymphoma, leiomyosarcoma, anal cancer, and cervical cancer, have also been linked to HIV infection.

This module will discuss the relationship between HIV and malignancy, with special attention to the tumors most commonly seen in the pediatric and adolescent populations. An overview of the epidemiology of HIV-related malignancy will be followed by discussions of the pathogenesis, clinical manifestations, and treatment of each cancer.

Epidemiology and Pathogenesis

Malignancy occurs much more commonly in HIV-infected children than in uninfected children. HIV-infected children are at about a 40 times higher risk of developing malignancy than the general population. Among HIV-infected children in the United States, the incidence of malignancy is about one case per 1,000 children per year. In contrast, the incidence of cancer among all U.S. children is about one to two cases per 10,000 per year.

Children with HIV also have a predilection for developing rare tumors. In the general U.S. pediatric population, leukemia and brain tumors make up almost all new cases of malignancy each year. However, among U.S. children infected with HIV, NHL is the most common type of cancer, followed by KS and leiomyosarcoma.

In response to these epidemiologic data, the CDC added NHL, primary CNS lymphoma (PCNSL), and KS to the list of Category C symptoms (AIDS-defining illnesses) for children and has added leiomyosarcoma to the list of Category B (symptomatic HIV-infection entities not included in Category C) symptoms. The World Health Organization lists all of these under Clinical Stage 4 and does not classify leiomyosarcoma. (See the chapter on HIV/AIDS diagnostic criteria for a discussion of the CDC and WHO clinical categories.)

Furthermore, invasive cervical cancer occurs much more commonly in female HIV-infected adolescents (and adults) than in the general population. As a result, the CDC included invasive cervical cancer as a Category C symptom for HIV-infected adolescents (and adults) and has added cervical dysplasia (moderate to severe) and noninvasive cervical carcinoma to the list of Category B symptoms for adolescents (and adults). The WHO classifies invasive cervical cancer as Clinical Stage 4 and does not classify cervical dysplasia and noninvasive cervical cancer.

Though not listed in the CDC revised classification or WHO Clinical Staging classification systems, cancers such as Hodgkin's disease, anal cancer, lung cancer, lip cancer, and testicular cancer are also more common with HIV infection.

The incidence of cancer is lower among children with HIV than among adults with HIV (0.1% per year versus 4% per year). Also, the relative incidence of specific cancers differs between children and adults. For example, in the United States, KS is the most common HIV-associated cancer in adults with HIV, whereas it is much less common in children with HIV. In contrast, leiomyosarcoma is found more commonly among children than among adults with HIV.

Regional variations in the prevalence of pediatric HIV-related malignancy exist. Although NHL is the most common pediatric HIV-related malignancy in the United States, KS remains the most common pediatric HIV-related malignancy in sub-Saharan Africa. Why these differences exist is not entirely clear. However, the prevalence of human herpesvirus 8 (HHV-8), the virus necessary for the development of KS, is much higher in central Africa than in the United States.

The pathogenesis of HIV-related malignancy is related to several factors. HIV weakens the immune system, thus diminishing the body's innate tumor surveillance ability, much in the way that immunosuppressive agents put transplant patients at risk of malignancy. Furthermore, viruses such as the Epstein-Barr virus (EBV), human papilloma virus (HPV), and HHV-8 interact with HIV to create an environment that enhances tumor growth. The relationship between HIV-related malignancy and certain viruses is well established. For example, nearly every case of KS is linked with the presence of HHV-8, and nearly every case of HIV-related PCNSL is linked with the presence of EBV infection. Also, EBV is often isolated from HIV-related leiomyosarcoma, systemic NHL, and Hodgkin's disease.

Common Cancers Diagnosed in HIV-Infected Children and Adolescents

Non-Hodgkin's Lymphoma

The spectrum of HIV lymphoid malignancies spans lymphoproliferative disease such as lymphoid interstitial pneumonitis to high-grade NHL and CNS lymphoma as well as Hodgkin's disease. NHL is the most common HIV-related malignancy (HRM) and usually presents as an extranodal high-grade B-cell lymphoma, although T-cell malignancies can be seen as well. One study from Malawi demonstrated that more than half of the cancers in children with HIV infection were lymphomas.

NHL accounts for about 7% of cancers among all U.S. children younger than 20 years. In contrast, NHL is one of the most common types of malignancy among HIV-infected children, accounting for more than 80% of HIV-related cancers. HIV-infected children most commonly develop Burkitt's (small noncleaved cell) lymphoma and immunoblastic (large cell) lymphoma.

Clinical presentation. HIV-infected children who are diagnosed with NHL often have extranodal disease (disease spread outside the lymph nodes) at the time of presentation. Indeed, the cancer will probably have already metastasized to such places as the brain, bone marrow, and gastrointestinal tract.

Symptoms of cancer, including NHL, can be indistinguishable from symptoms of chronic HIV infection. Symptoms such as fever, fatigue, weight

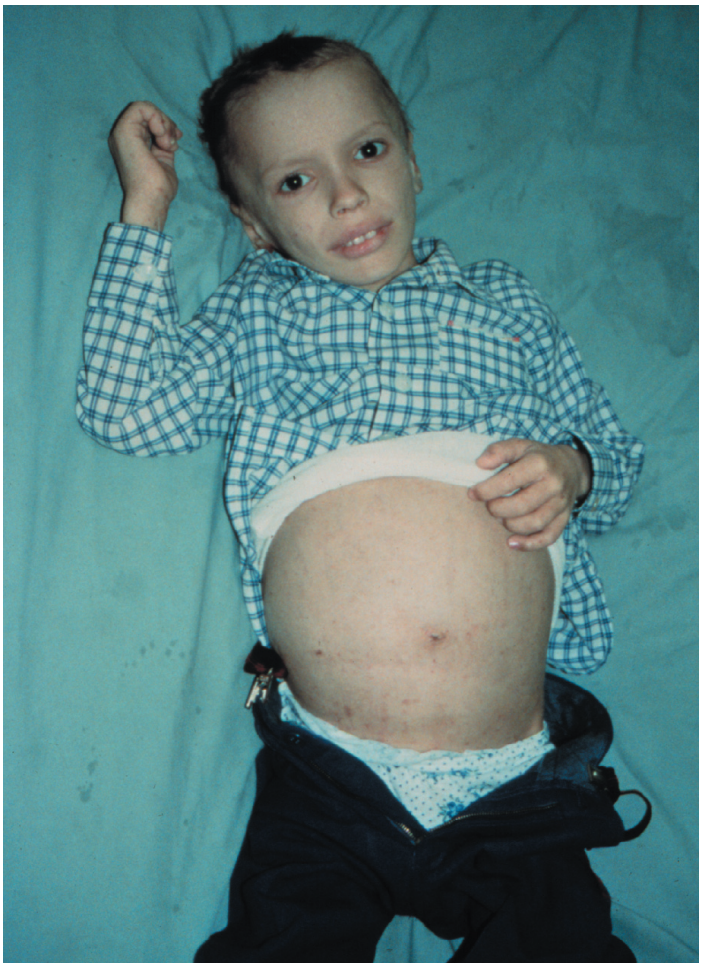

Figure 1. *Romanian child with abdominal NHL*

loss, night sweats, anorexia, hepatosplenomegaly, and lymphadenopathy may reflect underlying HIV infection, but they may also reflect the presence of lymphoma. NHL includes many organ-specific symptoms (**Table 1**).

Diagnosis and staging. Diagnosis of NHL is made through biopsy of affected tissue. Staging involves the use of computed tomography (CT) scans (particularly of the head, abdomen, and pelvis), bone marrow biopsy, and cerebrospinal fluid (CSF) analysis.

Prognosis is better in patients with $CD4^+$ counts greater than 100 per microliter, a near-normal serum lactate dehydrogenase level, no history of opportunistic infections, and a good performance status (i.e., the ability to function at a near-normal ability during daily activities).

Treatment. The therapies used in HIV NHL in children have been varied, including standard chemotherapy regimens, the current first line of which is CHOP, a regimen combining cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin), and prednisone. Other variations such as BACOD (bleomycin, Adriamycin, cyclophosphamide, Oncovin, dexamethasone) and ABVD (Adriamycin, bleomycin, vincristine, dexamethasone) or some combination of these have been attempted in small case series. The results were poor, with median survival of 6 months. The experience in adults in the pre-highly active antiretroviral therapy (HAART) era has been equally disappointing. However, meta-analysis of these various regimens revealed cyclophosphamide and methotrexate to be most active, whereas dose escalation of doxorubicin, prednisone, and vincristine was clinically and statistically insignificant. These studies have led to the use cyclophosphamide and methotrexate at high dose rates with successful treatment of children along with well-tolerated toxicity (per National Cancer Institute protocol). Because HIV NHL often spreads to the brain, treatment includes CNS prophylaxis with intrathecal (chemotherapy into the spinal fluid) methotrexate or cytarabine.

Table 1. Site-dependent symptoms of NHL

Mediastinal or pharyngeal tumor	Abdominal tumor
Cough Decreased breath sounds Nasal flaring Retractions Tachypnea	Abdominal distension Ascites Jaundice Pain Palpable mass
CNS disease	Maxillofacial tumor
Cranial nerve palsies Developmental delay Gait instability Headache Hemiparesis	Asymmetric facial expression Jaw mass Numbness of the chin (peripheral facial nerve compression)

Primary CNS Lymphoma

PCNSL is a subtype of NHL that is limited to the brain tissue. PCNSL is much more common in HIV-infected children than in uninfected children. The differential diagnosis of CNS lymphoma includes opportunistic infections such as toxoplasmosis or cryptococcosis. Unlike adults with HIV, in whom toxoplasmosis is the most common cause of a brain mass, PCNSL is the most common cause of an isolated brain mass in HIV-infected children. One should suspect PCNSL in any HIV-infected child with neurological abnormalities accompanied by mass lesions on a CT or magnetic resonance imaging scan of the brain. Although about 30%-50% of HIV-related systemic lymphomas are associated with EBV, HIV-related PCNSL appears to have a near-100% association with EBV.

Diagnosis. Diagnosis of PCNSL begins with cytological assessment of the CSF for malignant cells. These cells are present in up to 23% of patients. Analysis of CSF for the presence of EBV DNA by using polymerase chain reaction is also useful in suggesting the presence of PCNSL. Definitive diagnosis of PCNSL requires a brain biopsy. Assessment of serum for toxoplasma immunoglobulin G can help in determining the likelihood of CNS infection with toxoplasmosis. Negative titers make toxoplasmosis an unlikely diagnosis. Imaging can be helpful in distinguishing between the two diagnoses. Multiple ring-enhancing lesions on CT or magnetic resonance imaging are more suggestive of toxoplasmosis, whereas single lesions are more likely to be PCNSL.

Treatment. Treatment for PCNSL involves either the use of whole-brain radiation or high-dose intravenous (IV) methotrexate along with intrathecal therapy. Unfortunately, prognosis for this tumor remains poor. Without treatment, survival is less than 1 month; with treatment, survival is 2-4 months.

When a definitive diagnosis cannot be made and toxoplasmosis is under serious consideration as the etiology of disease, a trial of therapy for toxoplasmosis can help determine the true diagnosis. Lesions' failing to respond would be suggestive of and near diagnostic for PCNSL.

Lymphoproliferative Disorders

Children with HIV are at high risk of developing lymphoproliferative disorders. Examples include lymphoid interstitial pneumonitis, pulmonary lymphoid hyperplasia, diffuse interstitial lymphocytosis syndrome, and mucosa-associated lymphoid tumors.

Lymphoproliferative disorders respond well to HAART. If the lymphoproliferative disorder progresses to lymphoma, the treatment would then be as described earlier for HIV-related NHL.

Kaposi Sarcoma

KS was first described in 1872 by the Hungarian physician Moritz Kaposi as a disease of "multiple idiopathic pigmented hemangiosarcomas" affecting mainly men older than 40 years. In the era of HIV/AIDS, KS became the first AIDS-defining cancer, initially noted in men who have sex with men. In the United States, KS is the AIDS-defining illness in less than 1% of children younger than 13 years, increasing to 3% in the adolescent years. Where the prevalence of infection with HIV and HHV-8 is higher, these numbers are dramatically increased. In Zambia, for example, KS accounts for almost 20% of all childhood cancers.

Pathogenesis. Immunosuppression is believed to be an integral factor in the pathogenesis of KS. An increased incidence of KS is found in other immunosuppressed patients, in particular among transplant patients receiving immunosuppressive agents. Recent data have also revealed a strong link between underlying infection with HHV-8 and the development of KS. HHV-8 has also been implicated in the pathogenesis of other neoplastic conditions, such as primary effusion lymphoma (a rare form of NHL also known as body cavity lymphoma) as well as multicentric Castleman's disease (a rare disorder of the lymph nodes). Finally, the pathogenesis of KS depends strongly on angiogenesis, or the proliferation of new blood vessels, and medications are being explored to target this aspect of KS development.

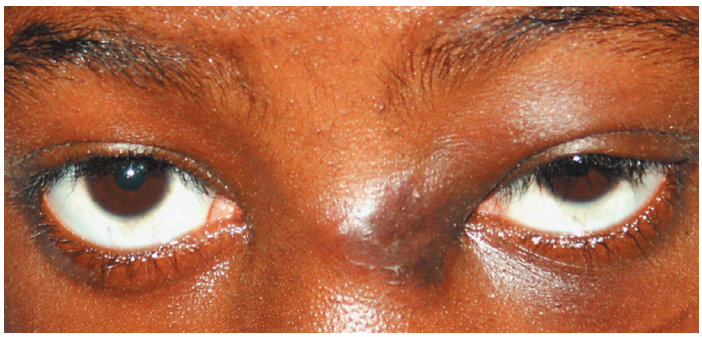

Figure 2. *Typical cutaneous Kaposi's sarcoma lesion*

Clinical presentation. KS most commonly affects the skin and oral mucosa. Its lesions are often found on the tip of the nose; on the trunk, arms, or neck; or in the mouth. On patients with dark skin, the lesions appear as dark plaques or nodules. On lighter-skinned people, the lesions are reddish-purplish or brownish. Skin lesions may first appear as erythematous macules, but over time they darken and become raised or nodular. Cutaneous lesions, specifically of the lower extremities, have been associated with peripheral edema, which can be debilitating. Nearly 30% of patients with KS also have lesions of the oral mucosa, most commonly on the hard palate. As these lesions grow, they may interfere with eating and speaking.

The differential diagnosis for cutaneous KS lesions includes hemangiomas, nevi, dermatofibromas, and bacillary angiomatosis. Distinguishing bacillary angiomatosis from KS is particularly important, because bacillary angiomatosis is caused by gram-negative bacteria (a *Bartonella* species) and thus may be readily treated with antibiotics. When necessary, performing a punch biopsy will help in making the correct diagnosis.

In addition to causing skin disease, KS may spread to the lymphatic system, the lungs, and the digestive tract. A physical exam may reveal lymphadenopathy (enlarged lymph nodes), which may be firm and nontender. Lesions in the oral mucosa often correlate with the presence of other gastrointestinal lesions. These lesions may be asymptomatic (often found at autopsy) or can lead to such problems as diarrhea and rectal bleeding. Metastases to the lungs may cause shortness of breath or hemoptysis (bloody cough). Though less common, some patients may present with pulmonary or gastrointestinal KS with no apparent skin lesions.

Treatment of localized disease. Most forms of KS will regress with the initiation of HAART, with response rates of 60%-80%. Thus, one should always incorporate treatment with antiretrovirals in the treatment of KS. Incorporating a protease inhibitor is more effective than a non-protease inhibitor regimen for KS in adults. This finding has not been clearly demonstrated in the pediatric population, and studies need to be carried out to unequivocally confirm such in this population.

For patients who do not respond adequately to antiretroviral therapy alone, other forms of treatment are effective. One can treat isolated lesions on the skin or in the mouth with alitretinoin gel, intralesional vinblastine, liquid nitrogen, laser ablation, or radiotherapy.

Subcutaneous interferon α (IFN-α) has been used in children with early disease. Though IFN-α can induce clinical responses in 32%-40% of patients, the development of flulike symptoms, such as fever, chills, headaches, and myalgias, often complicates IFN-α therapy. Nonsteroidal anti-inflammatory agents may help ameliorate some of these symptoms.

Treatment of diffuse disease. For patients with widespread cutaneous disease or organ involvement, systemic chemotherapy is often required. Currently, the treatment of choice is liposomal doxorubicin or liposomal daunorubicin, where response rates of 40%-80% have been demonstrated with liposomal doxorubicin at 20 mg/m^2 of body surface area every 2 or 3 weeks for six cycles. Recent studies have shown them to be more effective and less toxic than combination chemotherapy, which usually includes doxorubicin, vincristine, and bleomycin and which until recently was the standard of care. Side effects of liposomal doxorubicin and daunorubicin include myelosuppression and alopecia. Liposomal doxorubicin has also been associated with hand-foot syndrome (painful erythema and desquamation of the palms and soles).

One older study compared dactinomycin plus vincristine versus both plus imidazole carboxamide (DTIC) and demonstrated 94% complete remission with DTIC compared with 55% complete remission without it.

When liposomal agents fail, paclitaxel (Taxol) is often used next. Response rates of 70%-90% have been reported. Paclitaxel has been associated with myelosuppression, alopecia, peripheral neuropathy, and hypersensitivity reactions.

Though treatment of KS has evolved tremendously since the onset of the HIV epidemic, there is no effective cure for this cancer. The goal of treatment should be the palliation of symptoms. However, experimental therapy with angiogenesis inhibitors is being explored and is expected to be promising given what is known about the pathogenesis of KS.

Smooth-Muscle Tumors: Leiomyosarcoma

Leiomyosarcoma occurs rarely in children without HIV infection, and the incidence is estimated to be only two cases per 10 million children annually. However, with the onset of the AIDS epidemic, increased numbers of leiomyosarcoma have been reported in HIV-infected children. One large case series of HIV-infected children with cancer reported that 17% of their patients had leiomyosarcoma. This increased incidence in HIV-infected children led the CDC to classify leiomyosarcoma as a Category B symptom. Interestingly, there has not been a parallel rise in the incidence of leiomyosarcoma in HIV-infected adults.

The etiology of HIV-related leiomyosarcoma is unknown. However, EBV has been isolated in relatively high titers from leiomyosarcomas in pediatric patients with HIV. Also, these tumors present relatively late in the course of children with AIDS, suggesting a role of chronic immune suppression in tumor pathogenesis.

Clinical Presentation. Leiomyosarcoma most commonly presents within the gastrointestinal tract. Children with HIV, however, may present with tumors in unusual locations, such as the lungs, spleen, adrenal glands, pleural space, or intracranially. The course of the disease varies, with slow-growing tumors often not requiring intervention, whereas more aggressive, disseminated tumors require multimodal treatment with surgery and chemotherapy.

Gastrointestinal lesions may cause abdominal pain, rectal bleeding with anemia, abdominal masses, and bowel obstruction. Children with lung disease may appear cyanotic (blue around the face or lips). Respiratory insufficiency may be related to bronchial obstruction causing wheezing or secondary to persistent respiratory infections. Chest radiography often shows multiple pulmonary nodules. Children with brain lesions often show signs of increased intracranial pressure, such as nausea, vomiting, and headaches. Other neurological findings may also be present, such as visual disturbances, gait instability, and difficulty with coordination.

Treatment. Because smooth-muscle tumors are not particularly responsive to chemotherapy or radiotherapy, surgery is the treatment of choice. When surgery fails or is not an option, treatment involves the regimen VAC (vincristine, actinomycin, cyclophosphamide), often alternating with VAdriaC (Adriamycin in place of actinomycin). Ifosfamide and etoposide can be used as another alternating regimen. The course of therapy is generally 6 months to 1 year. Radiation therapy is sometimes given in addition to chemotherapy.

Cervical Cancer

Cervical cancer is the second most common cancer in women worldwide. Furthermore, HIV-infected women develop cervical cancer more often than non-HIV-infected women. For women with HIV, the risk of developing invasive cervical cancer is five to nine times as high as that for women without HIV. These findings have recently been confirmed in other parts of the world. In Nigeria, for example, one study found that high-grade lesions occurred more than three times more often in women with HIV infection than in women without infection. Because of this increased risk in HIV-infected women, the CDC added invasive cervical cancer to the list of AIDS-defining illnesses for adolescents and adults (WHO Clinical Stage 4) and has added moderate to severe cervical dysplasia and cervical carcinoma in situ to the list of Category B symptoms for these age groups.

Pathogenesis. HPV is a sexually transmitted virus that has been implicated in the development of cervical cancer. HPV is found in more than 99% of cervical cancer specimens; types 16 and 18 make up more than 60% of these oncogenic HPV subtypes.

HIV-infected women are more likely to be infected with HPV, to be infected with multiple types of HPV, and to have persistent HPV infection than are HIV-negative women. Also, HIV-positive women are more likely to develop cervical dysplasia when infected with HPV than are women who are HIV negative. Several studies comparing women with cervical dysplasia found that risk factors for dysplasia included HIV-positive status and persistent HPV infection. Interestingly, unlike other HIV-related malignancies, there has not been a consistent relation to CD4 count.

Screening and prevention. The Papanicolaou (Pap) smear is an important screening tool for early detection of cervical cancer in all sexually active women. Most preventive health guidelines recommend that all sexually active adolescents obtain yearly Pap smears. However, because of the heightened risk of cervical cancer in HIV-positive women, both the U.S. Public Health Service and

the Infectious Diseases Society of America recommend Pap smears every 6 months for all HIV-infected women during the first year after HIV diagnosis, with yearly Pap smears thereafter if the initial two smears are negative.

Conventional Pap smears are as sensitive and specific in women with HIV as in women without HIV. HPV DNA tests of cervical cell scrapings are not recommended as a screening tool, although they may assist in triaging women without HIV to colposcopy in the presence of low-grade squamous intraepithelial lesions.

Although HPV is sexually transmitted, male condoms do not decrease HPV transmission to women. Male condoms may offer a protective benefit to men, but study results have been conflicting and often confounded. Data on female condoms and spermicidals are scant. Unlike other bacterial and viral sexually transmitted infections, including HIV, HPV also infects external genital tissue, which may account for the lack of protection via barrier methods. Although barrier and microbicidal methods may theoretically decrease viral exposure, they have not been proven to have a protective effect.

The ultimate primary prevention of genital HPV may be a vaccine, one of which completed clinical trials and became available in June 2007. It covers the two most common serotypes of HPV. Please refer to the module covering immunizations for more information.

Management of abnormal Pap smear results. Pap smears that are abnormal often require further investigation with colposcopy—especially for women infected with HIV. For example, HIV-infected women are more likely (>10%) to have high-grade squamous intraepithelial lesions on workup of ASCUS (atypical squamous cells of undetermined significance) than are women who are HIV negative, and therefore even ASCUS should be colposcopically evaluated in HIV-positive women, regardless of HPV status. Colposcopy here should be used to examine the vagina and vulva in addition to the cervix, given the increased risk of other genital tract dysplasias and cancers in HIV-positive women.

Dysplasia, specifically low-grade squamous intraepithelial lesions that persist for more than 1 or 2 years and high-grade squamous intraepithelial lesions, should be treated with excision or ablation. Conical excision may be accomplished through laser, "cold knife," or loop electrosurgical excisional procedure cautery. Ablative modalities include laser and liquid nitrogen (cryotherapy). Postexcisional bleeding was substantially higher (>20%) in a small series of women with HIV.

Women with HIV are more likely to have multiple recurrences of dysplasia after therapy than women without HIV infection (62% and 18%, respectively), independent of ablational or excisional procedure type. Thus, HIV-infected women require diligent gynecologic follow-up. Women on HAART may have a more favorable natural history of dysplasia, although the data are inconclusive. Although women on HAART may have better immune control of their HPV, they may be at increased risk of infection with multiple HPV strains.

Treatment. Cervical cancer is managed through surgery with or without radiation and chemotherapy, depending on the extent of invasion. Recurrence or persistence of cervical cancer occurs in 35% of women. Patients with HIV have a higher mortality rate from cervical cancer than HIV-negative women. The data on the effect of HAART on cervical cancer progression is limited; long-term follow-up of larger groups of women is needed.

Early detection is crucial. One recent retrospective study in Nigeria demonstrated that 86% of 36 cases of confirmed cervical cancer were late stage at presentation, mitigating the ability to effectively treat these women.

Anal Cancer

Anal cancer is uncommon; however, the incidence is increasing in the population at risk, particularly those infected with HPV and HIV. The National Cancer Institute estimated 4,000 cases of anal cancer in 2004. The incidence is 35 times greater in men who are receptive for anal intercourse than in the general population in the United States. It is not limited to men, however, and women who practice anoreceptive intercourse, as a means to maintain virginity, for example, are also considered to be at high risk. About 85% of patients with anal cancer were found to have HPV infection as well. The association between AIDS and anal cancer is strong, although it is currently not categorized as an AIDS-defining illness. Individuals tend to have persistent HPV infection and high viral loads, contributing to the development of cancer.

Table 2. Supportive care for children receiving chemotherapy

Symptom	Definition	Management	Care Guidelines
Neutropenia	Absolute neutrophil count <1000/mL	• Monitor for fever, skin ulcerations, pain, respiratory symptoms, stomatitis, perirectal pain, and fissures • Obtain blood (including central line) and urine cultures and provide broad-spectrum antibiotics for fever >38.5°C or >38°C three times in 24 h • Detailed exam to identify source with further workup when necessary	Neutropenic precautions • Monitor temperature • Avoid ill contacts, fresh flowers, unpasteurized foods, and dental work • Avoid invasive procedures including rectal temperatures and exams, urinary catheterization and intramuscular injections • Antibiotics
Thrombocytopenia	Platelet count <100,000/μL	• Assess for bleeding, bruising, petechiae, purpura • Transfuse platelets 10 mL/kg to keep platelets >20,000 • Keep platelets >50,000 if active bleeding, before lumbar puncture or intramuscular injections, and other minor procedures other than bone marrow procedures	Thrombocytopenic precautions • Avoid procedures if possible • No rectal temperatures or exams • Use pressure dressing for bone marrow procedures • Transfusion therapy
Anemia	Hemoglobin <10 g/dL	• Assess for tachycardia, murmur, pallor, tachypnea, dyspnea, level of consciousness • Transfuse with leukoreduced, irradiated packed red blood cells 10-15 mL/kg when necessary when symptomatic or hemoglobin <7 g/dL	• Monitor for associated symptoms of fatigue, irritability, shortness of breath, chest pain with exertion, and headaches • Transfusion therapy
Nausea and Vomiting		• Serotonin receptor antagonists: ondansetron 4 mg p.o./IV t.i.d. (4-11 yrs old), 8 mg p.o./IV t.i.d. (>11 yrs old). Give just prior to chemotherapy for prevention of N/V • Phenothiazines (>2 yrs old): Promethazine 0.25 mg/kg of body wt p.o./IV every 6 h when necessary; max dose, 50 mg • Dexamethasone 6 mg/m2 IV as one dose with the first daily dose of ondansetron • Other antiemetics: dimenhydrinate, lorazepam, granisetron, dolasetron, prochlorperazine, chlorpromazine, meclizine, dronabinol	• Assess frequency of vomiting and level of hydration • Strict monitoring of input and output • Offer small quantities of food • IV hydration and oral rehydration solution as needed • Antiemetic therapy, use to prevent N/V
Mucositis	Breakdown of oral and/or gastrointestinal mucosa with or without secondary infection	• Rinse with a solution of 1 tablespoon of salt and baking soda in 1 L of water for several minutes 4–6 times per day • Acetaminophen 10–15 mg/kg p.o. every 4 h and/or codeine 1 mg/kg every 6 h • Severe mucositis may require morphine therapy for pain • Benadryl:Maalox:Viscous Lidocaine at 1:1:0.5 solution swish and spit every 4-6 h • Nystatin oral suspension 100,000 U/mL, 5 mL p.o. swish and swallow every 4-6 h	• Frequent oral examination for evidence of erythema and ulcers • Meticulous oral hygiene when awake • Pain medication therapy

p.o., per os; N/V, nausea and vomiting; t.i.d., three times daily.

The pathogenesis of anal cancer is felt to be equivalent to that of cervical cancer, in which HIV probably interacts and affects the oncogenicity of HPV, leading to malignant change.

The therapy of anal cancer is combined-modality treatment with chemotherapy and radiation. Most patients will have clinical regression. Peddada et al. demonstrated that all HIV-positive patients achieved complete remission with radiation along with 5-fluorouracil and mitomycin on day 1.

Postchemotherapy and Radiation Therapy Care and Considerations

Supportive care for patients receiving chemotherapy is important and should include *Pneumocystis jirovecii* prophylaxis, regardless of the $CD4^+$ count; monitoring for fevers and infections during periods of neutropenia; thrombocytopenic precautions when the patient has a decreased platelet count; and blood transfusion therapy and epoetin therapy for symptomatic anemia (**Table 2**).

General side effects of radiation therapy include radiation dermatitis (skin inflammation) and myelosuppression (suppression of the bone marrow). Site-specific side effects may also occur. Children receiving radiation therapy who experience side effects will require symptom management (**Table 3**).

Children receiving IFN-α therapy may experience flu-like symptoms (fever, chills, muscle or joint pain, headache), fatigue and malaise, anorexia (loss of appetite), diarrhea, changes in mental status (e.g., poor concentration, somnolence, depression, forgetfulness, irritability), abnormal liver function tests, neutropenia, thrombocytopenia, and bone pain.

Avoid using zidovudine along with myelosuppressive (bone marrow toxic) chemotherapy, if possible, because the combination may heighten the potential for anemia, neutropenia, and thrombocytopenia.

Childhood cancer chemotherapy and radiation may cause several acute as well as late effects (**Table 4**). Late effects in long-term survivors might include neurocognitive deficits, neuroendocrine disturbances, gonadal dysfunction, secondary tumors, and multiorgan damage. Radiation to the brain or intrathecal chemotherapy places long-term survivors of childhood cancer at risk of cognitive deficits and developmental delay. Risk factors for therapy-induced neurocognitive damage include early

Table 3. Symptom management for children receiving radiation therapy

Symptoms	Management	Care Guidelines
N/V	See Table 2	
Mucositis	See Table 2	
Skin toxicity	• Aloe vera lotion 4–6 times daily • Diphenhydramine 1 mg/kg/dose p.o. every 6 h when necessary for itching • 1% Hydrocortisone cream for itching or moderate erythema • Silvadene cream 1–2 times daily for moist desquamation	• Frequent skin exam for erythema, erosions, ulcers, blisters • Avoid excess heat and cold, sun exposure, and perfumed ointments • Use gentle soap; rinse off and pat dry • Avoid adhesive tape or perfumed lotions in the radiation field • Do not scrub skin when removing ink markings • Assess for pain and provide medications as needed
Enteritis	• Loperamide 1 mg p.o. t.i.d. (2–5 yrs old); 2 mg p.o. b.i.d. (6–8 yrs old); 2 mg p.o. t.i.d. (8-12 yrs old) • 3- to 4-day rest period from radiation therapy if dehydration occurs	• Assess frequency of diarrhea • Monitor level of hydration • Restrict roughage in diet • Restrict dietary lactose • Provide elemental diet to relieve symptoms • Strict monitoring of input and output • Daily weight assessment • IV or oral hydration as needed • Antidiarrheal medications

N/V, nausea and vomiting; p.o., per os; b.i.d.; twice daily; t.i.d., three times daily.

Table 4. Chemotherapy agents and side effect profiles

Agent	Class	Action	Side Effects
Actinomycin-D	Antitumor antibiotic	Stimulates apoptosis; inhibits topoisomerase II	N/V, alopecia, mucositis, vesicant, hepatic vaso-occlusive disease
Bleomycin	Antitumor antibiotic	Oxidative cleavage of DNA	N/V, pulmonary fibrosis, mucositis, alopecia, hypersensitivity
Cyclophosphamide	Alkylating agent	Prevents DNA synthesis through alkylation of DNA and RNA	Myelosuppression, N/V, cystitis, water retention, cardiac, second cancers
Cytarabine	Antimetabolite	Inhibits DNA polymerase, cell cycle specific for S phase	Myelosuppression, N/V, mucositis, eye irritation
Daunomycin	Anthracycline antibiotic	Stimulates apoptosis; inhibits topoisomerase II	Mucositis, N/V, myelosuppression, vesicant, cardiac (acute and long term), secondary cancer
Dexamethasone	Steroid	Induces lymphoblast apoptosis	Hypertension, polyphagia, water retention, moon facies, nightmares, immunosuppression
Doxorubicin	Anthracycline antibiotic	Stimulates apoptosis; inhibits topoisomerase II	Mucositis, N/V, alopecia, myelosuppression, vesicant, cardiac (acute and long term), secondary cancer
Etoposide	Epipodophyllotoxin	Antimitotic agent binds tubulin	Mucositis, myelosuppression, alopecia, N/V, secondary leukemia, hypersensitivity
Ifosfamide	Alkylating agent	Prevents DNA synthesis through alkylation of DNA and RNA	Myelosuppression, N/V, cystitis, water retention, cardiac, renal
Methotrexate	Antifolate antimetabolite	Inhibits thymidylate and purine synthesis	Mucositis, mild myelosuppression, neurotoxicity, hepatic toxicity, renal toxicity
Paclitaxel	Taxol	Blocks microtubule depolarization	Hypersensitivity, mucositis, alopecia, myelosuppression, cardiac, EtOH poisoning
Prednisone	Steroid	Induces lymphoblast apoptosis	Hypertension, polyphagia, water retention, moon facies, nightmares, immunosuppression
Vincristine	Vinca alkaloid	Antimitotic agent M phase specific and active in S phase	Neurotoxicity, vesicant, alopecia, syndrome of inappropriate antidiuretic hormone, fatal if given intrathecally

N/V, nausea and vomiting.

age at the time of therapy, high doses of therapy, and use of intrathecal or systemic methotrexate as part of the chemotherapy regimen.

Irradiation and some chemotherapeutics may affect hearing, vision, and dentition. Systemic effects may include hepatotoxicity, renal toxicity, cardiac toxicity (primarily by anthracyclines and thoracic radiation), vascular damage, lung fibrosis, endocrine dysfunction (particularly thyroid disturbance and growth effects), osteoporosis, and sterility. Second malignant neoplasms are 6.38 (95% confidence interval, 5.69-7.13) times as likely among childhood cancer survivors as in the general population, with breast and secondary leukemias occurring at up to 16 and 19 times the expected incidence rates, respectively. In a childhood cancer survivor study, second malignant neoplasms of any type were reported to be independently and statistically significantly associated with younger age of the child at primary cancer diagnosis, primary childhood Hodgkin's disease or soft-tissue sarcoma, female sex, and increased exposure to anthracyclines and/or epipodophyllotoxins.

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