TLALELETSO

BOTSWANA-UPENN PARTNERSHIP

HIV UPDATE:
CANCER & HIV

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UPDATES IN HIV:

CANCER & HIV

*This month's Taleletso provides an introduction to the topic of **HIV and Cancer**.*

*This month we would also like to raise your awareness of a global cancer initiative, **MOVEMBER,** which is committed to raise money to diagnose and treat cancers in men. As part of the initiative, men all of Botswana are being encouraged to grow moustaches!*

Raised funds will fund survivorship initiatives that provide information and support for men and their families affected by prostate and testicular cancer that helps them make informed decisions and improves their quality of life.

Respectfully, Mike Reid

Malignancies were one of the earliest recognized manifestations that lead to the eventual description of the acquired immune deficiency syndrome (AIDS). Now, the World Health Organization predicts that there will be 16 million new cancer cases per year in 2020, and 70% of these will be in the developing world. The majority of malignancies in Botswana arise in HIV-infected patients receiving ART.

The concurrent management of cancer and HIV treatment can be complex, with important drug-drug interactions and overlapping toxicity. In this edition of Tlaleletso we review the common cancers seen in people living with HIV, their diagnosis and management.

KAPOSI'S SARCOMA

AIDS associated Kaposi's Sarcoma was first described in the early 1980s in the United States. It is the most common cancer affecting the HIV-infected population in Botswana. According to the National Cancer Registry, from 1998-2008, KS cases represented 21.7% of all malignancies. Of these cases, 92.1% were recorded to be HIV positive. In Zimbabwe KS is reported to represent 40% of all cancers in men[1].

Pathogenesis

KS is a spindle-cell tumor thought to derive from endothelial cell lineage. This condition carries a variable clinical course ranging from minimal mucocutaneous disease to extensive organ involvement. Human herpesvirus 8 (HHV-8) genomic sequences have been identified by polymerase chain reaction in more than 90% of all types of KS lesions suggesting a causative role.

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Kaposi's Sarcoma
Clinical Presentation:

The disease can occur in patients with a wide range of CD4 cell counts but becomes increasingly more common as immune function declines. The progression may be slow or fast.

Cutaneous lesions – Skin is the most common site of first presentation. Lesions can occur anywhere; common sites include the face (particularly the peri-orobital area and tip of the nose), external ear, on the torso and lower extremities.

Multiple skin lesions – These are most often papular (less commonly plaque-like) with associated colors ranging from hues of pink, red, purple and brown. Lesions are non-blanching, non-pruritic and painless.

Tumor-associated lymphedema - typically manifested by lower extremity or facial involvement and thought to occur secondary to obstruction of lymphatic channels. It usually appears in patients with visible cutaneous lesions and oedema may be out of proportion to the extent of visible lesions

Systemic involvement is found in less than 10% of cases and usually indicates a more advanced HIV/AIDS disease presentation. Gastrointestinal lesions can occur anywhere within the gastrointestinal tract. Lesions are often asymptomatic and clinically indolent.

However, gastrointestinal symptoms include:

- Odynophagia, dysphagia
- Nausea, vomiting, abdominal pain
- Hematemesis, hematochezia, melena
- Rare cases of bowel obstruction, perforation and protein losing enteropathy have also been reported.

Pulmonary involvement is difficult to distinguish from opportunistic infections and may be an asymptomatic radiographic finding. In a patient with KS lesions in the mouth pulmonary KS should be considered. Pulmonary KS without any lesions on the skin or in the mouth is very uncommon. Pulmonary KS is a medical emergency and these patients need to be referred to oncology immediately for initiation of systemic chemotherapy. Pleural effusions, which are often exudative and bloody, may occur. Additional symptoms include:

- Cough
- Dyspnea
- Hemoptysis
- Chest pain

Diagnosis:

Diagnosis is ideally based upon histology. However, in patients with a high clinical likelihood or those with systemic disease, chemotherapy should not be delayed while awaiting biopsy results. Imaging is not necessarily warranted and should instead be made on a case-by-case basis. Referral for biopsy for histologic confirmation of KS will depend upon facility resources. However, experienced medical officers can complete FNA and biopsy, if needed. Even if ART is chosen as the first treatment it is advisable to get a biopsy so if the ART fails one can refer to oncology when needed.

UPCOMING LECTURES

December

Holiday Quiz 2012!

January

Complicated cases: ECGs made easy

February

HIV update: new drugs

March

Complicated cases: Diabetes

April

HIV update: PMTCT

Kaposi's Sarcoma
Treatment:

No current therapy completely cures all Kaposi's Sarcoma tumors. Accordingly treatment to date has been primarily palliative. Treatment goals in KS include symptom palliation, prevention of KS progression, improvement of cosmesis and abatement of associated oedema and organ compromise.

ART: ART is a key component of the treatment of KS and should be initiated or optimized to achieve complete HIV RNA suppression in all patients with AIDS-associated KS. In those patients with KS that are failing first line therapy, urgent review by an HIV specialist is essential.

The inhibition of HIV replication and restored immunity to HHV-8 have been suggested as some of the benefits of ART. For these reasons, clinicians are recommended to start ART immediately in all adult patients diagnosed with KS once baseline laboratories have been completed. Often this may be the only treatment required. Effective antiretroviral therapy is associated with a reduction in the incidence of KS and a regression in the size and number of existing lesions. HAART also prolongs the time to treatment failure and survival time in KS.[2]

PRINCIPLES OF CANCER CARE - BOTSWANA HIV GUIDELINES 2012

Coordination of care: HIV clinicians and oncologists should work in synergy. Advise patients to share their HIV medical records with oncologists and their oncology records (i.e., chemotherapy, radiation, etc.) with HIV clinicians.

Timing of ART in Adults: Immediately Start ART once cancer is diagnosed in an HIV positive patient. In rare cases in which concurrent chemotherapy and ART cannot be given safely, ART may need to be deferred or interrupted.

Timing of ART in Children: Discuss timing of ART initiation and chemotherapy in patients with a pediatric oncologist.

Avoid AZT or CBV: Nearly all chemotherapy leads to lymphopenia and anemia, and co-administration of chemotherapy with AZT or CBV increases hematologic toxicity. Switch patients receiving AZT or CBV to ABC or TDF depending on renal function, planned chemotherapy and presence of adverse drug effects.

Exercise caution with PIs: Toxicity from chemotherapy may be increased considerably due to inhibition of hepatic metabolism. Chemotherapy doses may need to be reduced, this should be avoided if possible to ensure optimal response, or patients may need to be switched to alternative regimens during cancer treatment.

Exercise caution with TDF: In addition to direct renal toxicity from several chemotherapy agents, the dehydration that frequently accompanies cancer therapy due to diarrhea, mucositis, or nausea can quickly lead to tenofovir-related renal failure. Monitor creatinine clearance carefully.

Kaposi's Sarcoma Treatment (cont.d):

Local therapy: For some patients with painful isolated lesions whose poor clinical state precludes systemic chemotherapy, local therapy may be a viable option. Intralesional chemotherapy is very effective for cosmetic control of skin lesions and palliation of painful lesions on the soles of the feet, genitalia, oral cavity and conjunctiva. In the US, vinblastine, administered intra-lesionally, is the most used chemotherapy and yields a response rate of 70%. Side effects of intralesional chemotherapy include pain and hyperpigmentation.

Cytotoxic chemotherapy: This is reserved for patients with more advanced and or rapidly progressive disease. Chemotherapeutic options in Botswana include doxuribicin, ABV (Adriamycin, bleomycin and vincristine) and BV (bleomycin and vincristine). These should be prescribed by an oncologist.

The discovery that HHV-8 plays a role in the pathogenesis of KS, has raised the possibility of using antiviral agents that target this virus. Unfortunately, pilot data evaluating whether cidofovir to treat KS in HIV infected patients, demonstrated no evidence of effect on KS disease progression or HHV-8 viral load levels [4].

Radiotherapy: Radiotherapy is best suited for patients with single or a few locally symptomatic areas or for symptomatic disease that requires rapid tumor reduction. Complications include radiotherapy fibrosis, loss of skin compliance and chronic lymphedema.

Monitoring patients: It is important to monitor KS patients closely to determine disease progression and response to treatment. Special attention should be paid to the development of anemia, neutropenia and renal insufficiency. It should be noted that although systemic disease is usually asymptomatic, KS can also present at an advanced stage.

Pediatric Kaposi's Sarcoma: Clinical presentation and outcomes of KS in children may be quite different from what is seen in adults. All cases should be reviewed by a pediatric oncologist.

CERVICAL CANCER

Cervical cancer is the leading cause of cancer among all women in Botswana, accounting for 24% of female malignancies. Worldwide, cervical cancer is the second most common malignancy in women after breast cancer and remains the leading cause of cancer related death in developing countries.

HIV is a major risk factor for developing cervical cancer and precancerous cervical abnormalities. Although incidence and mortality of cervical cancer have fallen significantly in developed countries, 83% of all new cases that occur annually and 85% of all deaths from the disease occur in developing countries[5]. This is partly due to the high HIV prevalence and limited access to gyne-oncology care.

Cancer of the cervix starts in the cells of the cervix and is linked to the genital infection with human papilloma virus (HPV) which is the most common sexually transmitted virus. Although most cases of HPV infection clear spontaneously some may persist thorough precancerous stages into invasive disease.

Cervical cancer is the leading cause of cancer-related death among women in the developing world. Indeed, cervical cancer poses a serious threat to the long-term wellbeing of HIV positive women, who are commonly diagnosed 10 years earlier than the general population. Reasons for this include:

- Higher prevalence of persistent HPV infection.
- High prevalence of multiple high-risk HPV types.
- Higher risk of pre-cancerous lesions resulting from a higher degree of immunosupression.
- More frequent presentation of advance disease with poor prognosis.

Cervical Cancer Screening

The majority of deaths due to cervical cancer are preventable by cervical screening. Therefore all newly diagnosed HIV-infected women should undergo regular screening. In line with the National HIV/AIDS guidelines, and the new national cervical cancer prevention strategy, we recommend the following:

- All HIV-infected women (25yrs and above) should complete a screening baseline Pap smear.
- If the baseline is normal, then follow up screening should take place every 3-5 years
- If the baseline Pap smear is abnormal, the women should be referred to gynecology or colposcopy clinic for further management as follows:
  - All patients with High Grade Squamous Intraepithelial Lesions (HSIL) should be referred for colposcopy
  - All patients with persistent Low Grade Squamous Intraepithelial Lesions (LSIL) should be referred for colposcopy
  - Only patients with Atypical Squamous Cells of Uncertain Significance (ASCUS) favouring HSIL (SAC-H) should be referred for colposcopy
  - Patients with ASCUS favouring inflammation (ASC-I) may require treatment for STIs.
  - If the doctor or nurse is not sure they should contact the Women's Health Clinic at PMH IDCC ext 1630/4 or 395 1284
  - All patients with signs or symptoms which are suspicious for cervical cancer should have a speculum examination with a directed biopsy, and be tested for HIV with CD4 count. Urgent referral to gynecology for staging is mandated.

Women with a recorded abnormal Pap smears should be monitored closely and tracked in order to ensure that adequate follow up occurs.

See and Treat

Visual inspection with acetic acid (VIA) has recently emerged as an inexpensive practical alternative Pap testing. Application of 4% or 5% acetic acid to the cervix results in pre-cancerous epithelium transiently appearing white, with normal cervical squamous epithelium assuming a pink color. VIA is more sensitive but less specific than the Pap smear. VIA can also be performed by midwives, nurses and other health care workers rather than physicians. Patients identified as having evidence of pre-cancer on VIA, can then be treated with cryotherapy at the initial visit, or referred for colposcopy/loop electrosurgical excision procedure clinics, if not eligible for cryotherapy. Patient with suspected cancer should be referred to Gynecology urgently.

Community based studies have demonstrated that this 'see and treatment' approach using VIA can be a valuable addition to screening programs for cervical cancer prevention in HIV infected women. For this reason it is being adopted at several IDCC/Women's health clinics across Botswana as part of the MOH's new national cervical cancer prevention strategy.[6] The MOH will soon release a working document with screening ages/frequencies recommendations and management algorithms.

Treatment

The gold standard treatment for cervical cancer remains surgery and/or radiotherapy. Chemotherapy with radiotherapy is the standard of care for locally advanced cervical cancer. Relapse patients may receive chemotherapy only.

Curative surgery in cervical cancer aims to remove the primary tumor with all extensions in one single operation. The choice of operation procedure is determined by the disease stage.

SIGNS AND SYMPTOMS OF CERVICAL CANCER

Early	Late	Very Late
Irregular bleeding	Urinary frequency	Severe back pain
Post coital bleeding	Backache	Weight loss
Post menopausal bleeding Persistent vaginal discharge not responsive to standard STI syndromic management	Lower abdominal pains	Decreased urine output Leakage of urine or faeces through the vagina Swelling of lower limbs Breathlessness

LYMPHOMA

Cancer involving the lymph nodes is the 3rd most common cancer affecting HIV positive patients in Botswana. The etiology is largely unknown. However, several factors play an important role in development of the disease. These include infections with viruses (notably, Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8)) continuous B-cell stimulation, and immunodeficiency.

Almost all AIDS-related lymphomas are of B-cell origin and comprise a heterogeneous group of lymphomas. Different clinicopathologic categories of AIDS-related lymphomas arise from distinct B-cell subtypes and multiple factors as above interact in varying proportions to give rise to different varieties. They can be divided into 3 types on the basis of areas of involvement:

- Systemic NHL
- Primary central nervous system lymphoma (PCNSL)
- Primary effusion lymphomas ("body cavity lymphoma")

The risk for developing AIDS-related lymphoma is highest among those with advanced HIV disease. However, it can occur at any CD4 count.

Clinical Presentation

While the overall incidence of lymphomas has diminished with provision of HAART, the presenting symptoms do not appear to be appreciably affected by HAART. The presenting symptoms and signs of AIDS-related lymphomas depend on the site of involvement and the stage of the disease. Frequently, symptoms of lymphoma are initially mistaken for tuberculosis.

Prognostic Features

Poor prognostic factors for patients with AIDS Related Lymphoma include age >35 years, CD4 cell counts <100, history of other AIDS defining illness, poor performance status, elevated LDH levels, tumor bulk and/or stage of disease.

Systemic NHL

Peripheral adenopathy is the common presenting symptom. Other symptoms may be organ specific or nonspecific. Lymphoma may involve the lungs, bone marrow, gastrointestinal tract and liver.

Non-specific symptoms include: bloating, early satiety, or abdominal pain/fullness due to enlargement of the spleen. The majority of patients have constitutional ("B") symptoms at the time of presentation.

B symptoms include**:**

- Unexplained fever (>38 degrees Celsius)
- Night sweats
- 10% involuntary weight loss

Primary Central Nervous System Lymphoma

Primary presentation of CNS lymphoma is similar irrespective of HIV status. Symptoms include blurred vision, muscular weakness, sensory deficits, personality changes, depression, apathy, confusion, memory impairment, and cranial neuropathies. Lesions are most common in the cerebrum, basal ganglia and brainstem. These lesions are contrast enhancing on CT and MRI.

Diagnosis

The diagnosis of AIDS Related Lymphoma should be based on a tissue sample rather than a cytologic sample. However if no tissue sample is possible then a cytologic sample is adequate.

Laboratory: FBC, urea, uric acid, electrolytes, creatinine, and LFTs. LDH is not a diagnostic criterion, but useful for disease burden and prognosis

Imaging: CXR, abdominal CT scan for staging. (If CT is not available use ultrasound at the sites of adenopathy).

Lymphoma Treatment

ART: Concurrent chemotherapy plus ART is generally safe. All patients with HIV should commence ART before commencing chemotherapy.

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

Before initiating chemotherapy discuss drug selection with a highly qualified physician or oncologist. Chemotherapy agents including cyclophosphamide, steroids, vincristine, methotrexate, and daunorubicin are commonly available although coordination and delivery of multi-agent systemic chemotherapy and management of ensuing complications outside of Princess Marina may be challenging.

Radiotherapy: The role of radiotherapy in systemic lymphoma is limited to consolidation of the effects of chemotherapy. Treatment principles are similar to those used for treating aggressive NHL in non-HIV infected patients, and are not covered here.

NON–AIDS-DEFINING MALIGNANCIES

The term "non–AIDS-defining cancers" (NADCs) refers to neoplasms other than AIDS-defining malignancies (ie, Kaposi's sarcoma, intermediate- and high-grade B-cell non-Hodgkin's lymphoma including primary central nervous system non-Hodgkin's lymphoma, and cancer of the cervix) that occur more commonly in individuals with HIV infection.

Recently, both the spectrum and incidence of various neoplasms being reported among persons infected with HIV have increased. This emerging and crucial problem has contributed to the mortality of HIV-positive persons in the HAART era

Even in resource-poor settings, , where the availability of antiretroviral therapy is limited, NADCs have increased along with AIDS-defining cancers in the growing HIV-infected population. A recent study that compared NADC incidence rates in HIV-infected persons in Botswana and in the United States found substantially higher rates among the Botswana cohort (8.0 vs 0.5 per 1000 person-years [PY], respectively, after standardization based on the age and sex distribution of the US cohort.

Specific NADCs that appear to be increased in patients with HIV infection include anal cancer, liver cancer, Hodgkin's lymphoma, and carcinomas of the skin, including penile and vulvar/vaginal cancer.

While treatments for specific malignancies will depend upon the cancer, ART is recommended for all HIV-infected patients who are diagnosed with any cancer. Furthermore, ART should be initiated as soon as possible in such patients, regardless of CD4 count and before initiation of any chemotherapy.

SUMMARY

AIDS defining cancers remain the most common malignancies in people living with HIV

Kaposi's Sarcoma is the most common tumor associated with HIV and the key treatment is antiretroviral therapy.

Active screening of all HIV-infected women with regular Pap smear is vital to ensure that cervical cancer is detected early and treated appropriately

The use of ART in patients with malignancies is associated with improved clinical responses to chemotherapy and longer survival.

Got a clinical question about a complicated medical patient Or a patient with HIV?

Mike Reid
267 724 78 777
OR
Miriam Haverkamp
267 76516520

Want to read more? Check out the references below: