

20. HIV-RELATED MALIGNANCIES

20.1 Kaposi's sarcoma

Kaposi's sarcoma is the most common tumour that occurs in HIV positive patients. Four clinical variants are described:

- Classical/Sporadic/Mediterranean
- Endemic African
- Organ transplant associated immunosuppression
- Epidemic (AIDS-related)

All varieties are associated with infection with Kaposi's sarcoma-related herpes virus (KSHV) or human herpes virus type 8 (HHV-8)

20.1.1 Diagnosis

Diagnosis is clinical with recognition of typical mucocutaneous lesions. A biopsy is necessary to confirm the presence of disease histologically. Lesions occur on the limbs (lower more often than upper), face (often on the nose), trunk and genitalia. Lymph nodes may be enlarged. The palate and oropharyngeal mucosa are often affected. Lesions are not usually painful or itchy. They range from hyperpigmented (reddish purple) macules to papules (several millimeters to several centimeters diameter) and may be plaque like or nodular/exophytic. Lymphoedema occurs as a result of lymphatic obstruction.

20.1.2 Staging

It is useful to stage patients. Most patients in Zimbabwe present with advanced (Clinical stage 3 or 4) disease. Kaposi's sarcoma is classified clinically as follows:

- Stage 1 - localized indolent cutaneous lesion
- Stage 2 - localized aggressive cutaneous lesion with regional lymph nodes

- Stage 3 - multiple generalised cutaneous lesions or generalized lymph node involvement
- Stage 4 - palatal or visceral disease

A = without systemic symptoms

B = with systemic symptoms of weight loss > 10% body mass, drenching night sweats, intermittent fevers

20.1.3 Investigations

Prior to commencing treatment for Kaposi's sarcoma the diagnosis should be established by histological examination of tissue biopsies. In addition it is necessary to perform a chest x-ray and to determine the HIV status of the patient. A full blood count, blood urea and electrolyte levels and liver function tests should be measured. If possible the peripheral blood CD4+ lymphocyte counts and the HIV plasma viral load should also be measured. Depending on the extent of disease and symptoms a bronchoscopy or endoscopy may be indicated.

20.1.4 Treatment

There is no known cure for KS. The goals of treatment are to:

- Alleviate symptoms
- Reduce the tumour mass
- Reduce oedema
- Prevent disease progression

Non-drug related treatment

The following may be useful for lymphoedema:

- Elevation of the limb
- Multilayer bandaging
- Compression stockings
- Manual lymphatic drainage (massage)

- **Exercise**

Radiation therapy

Radiotherapy is used to palliate for pain, fungating disease and for cosmesis. KS lesions are very radiosensitive and 90% or more of the lesions will respond to treatment.

Most of the lesions are superficial hence superficial X-rays and electron beams are suitable for these lesions. Where there is severe oedema or visceral disease mega voltage treatment is used with parallel opposing portal employed.

Most lesions will respond to 800cGy as a single fraction. Lesions on more sensitive areas eg. the mouth will require more protracted fractionation regimes to minimize side effects. Total doses of 20 Gy in 10 fractions are employed to areas such as hands, genitalia and the conjunctiva. Alternative dose schedules are 14 Gy in 4 fractions on alternate days and 30 Gy in 10 fractions in 2 weeks.

There is a dose-response relationship for these tumours with better control if higher doses are used. The choice of dose will depend on the length of survival expected.

In extensive disease lower hemi-body RT (800 cGy single fraction) and/or upper hemi-body RT (600 cGy single fraction) can be used.

Other field arrangements are determined by the extent of the disease.

Drug related treatment

Antiretroviral therapy

Highly active antiretroviral therapy should also be used to treat patients with KS.

Chemotherapy

The tumour usually responds to cytotoxic chemotherapy. However this form of treatment further suppresses the immunity in persons with AIDS. It is important to individualise treatment in each case and monitor treatment benefits and side effects. The following cytotoxic agents have been used with beneficial effects in persons with Kaposi's sarcoma:

- Combination of bleomycin and vincristine: Bleomycin 15mg/m² and vincristine 1.4mg/m² (maximum of 2mg) given every 4 weeks as an IV pulse for 4 to 6 months
- Actinomycin D is sometimes added to the above regime or used alone in children 15µgm/kg IV given daily for 5 days (maximum 500µgm per day) given for 5 days each month for 4 to 6 months
- Etoposide 150 to 200mg orally daily for five days, given as monthly 5-day pulses for 4 to 6 months
- Liposomal daunorubicin is first line chemotherapy where it is affordable; paclitaxel is used as second line chemotherapy.

Topical (intralesional) chemotherapy

Topical treatment with intralesional vinblastine or 9 cis-retinoic acid is used for scanty lesions. Dose of vinblastine is 0.2 to 0.3mg/ml solution, use 0.1ml per 0.5cm² of lesion.

Topical cryotherapy and laser therapy

Ablation of localized lesions by cryotherapy and laser therapy has been successful in endemic disease and depending on the extent of the disease may be useful in persons with epidemic disease as well.

NOTE: most patients present with multifocal lesions and a large tumour burden, thus local therapy of individual lesions is impractical except in extremely rare situations

Other modalities of treatment

- Angiotensin inhibitors e.g. thalidomide have been used. There is little evidence to support their routine use.
- Biological response modifiers e.g. interferon-α may be used
- HCG and Vitamin D have been used but the evidence for their efficacy is poor
- Future routes - targeted treatment of the KSHV (HHV8) infection

20.1.5 Symptom control / nursing care

Symptoms of pain, cough and dyspnoea are frequent and require treatment. Fungating lesions may require additional nursing and antibiotic usage. Opportunistic infections must be treated.

20.1.6 Counseling

Counseling is required with regard to the HIV infection as well as the cancer. Palliative care should begin with diagnosis and issues relating to the end of life should be discussed with the patient and his/her family before the patient is terminally ill.

20.1.7 Social services support

The vast majority of patients with KS present with advanced disease and are no longer able to work. It should be policy that all patients with AIDS-KS receive support from the AIDS levy as well as free treatment.

20.2 Cervical cancer

Cervical cancer may be the first indication of HIV infection. Pre-malignant lesions also known as squamous intraepithelial lesions (SILs) are frequently found in association with HIV infection. They may also be associated with a higher incidence of invasive lesions. Both pre-malignant and invasive lesions are associated with the human papilloma virus (HPV) of subtypes such as 16, 18, 31, 33 and 35.

20.2.1 Screening and diagnosis

Due to the asymptomatic nature of the early pre-invasive and early invasive lesions, screening of women at risk for HIV infection must be undertaken. HIV-positive women must have pelvic examination and cytological screening every six months. Those women found to have SIL will need close monitoring through repeat colposcopy.

The diagnosis of pre-invasive lesions is made from cervical cytology. Invasive lesions are usually symptomatic and clinically palpable on digital

vaginal examination. Examination under anesthesia, biopsy and histological confirmation is necessary wherever possible.

20.2.2 Staging

A number of staging systems exist, including the FIGO and the TNM systems.

20.2.3 Investigations

Women with invasive cervical cancer need complete staging and the following should be done:

- Pelvic examination
- Full blood count
- Urea and electrolytes
- Liver function tests
- CD4 lymphocyte count and viral load
- Chest X-ray
- IVU
- Lymphangiography may be useful to outline nodal disease
- CT abdomen and pelvis

20.2.4 Treatment

Non-drug related

In pre-invasive disease the following can be used:

- Cryotherapy
- Laser therapy
- Cone biopsy
- Loop electrosurgical excision procedure (LEEP)

Recurrence rates of 40-60% have been seen.

For invasive disease surgery can be performed for the same indications as in the HIV-negative individual as follows:

- Stage 1A1 - Simple hysterectomy, cone biopsy
- Stage 1A2, 1B1 and non-bulky 11A - Radical hysterectomy
- Stage 1B2 and bulky 11A -may consider adjuvant extrafascial hysterectomy where available following chemo radiation.

Radiation therapy

Most patients with invasive disease will need radiotherapy as treatment due to the advanced nature of the lesions.

This treatment is now mostly given concurrently with cisplatin-based chemotherapy (chemo radiation) and response rates are similar to the non-HIV infected.

Intracavitary brachytherapy treatment and external beam radiotherapy are both used except in the very ill patient or very advanced disease (stage 1V) when only external beam treatment is used.

Radical doses for external beam therapy are typically 40 - 50 Gy in 20 -25 fractions in 4 to 5 weeks. Intracavitary therapy is also given and doses of 21 – 25 Gy to point A in 3 –5 fractions of high dose rate brachytherapy are employed.

Palliative RT can be given to pelvic disease, bone and soft-tissue metastases, para-aortic and other nodal metastases. Typical doses would be 30 Gy in 10 fractions in 2 weeks or 45 Gy in 25 fractions in 5 weeks in the case of para-aortic lymph node RT.

20.2.5 Drug related treatment

Antiretroviral therapy

Antiretroviral drugs should be used as well as any other drugs needed to treat other co-existing HIV related illnesses.

Chemotherapy

Cisplatin has been used with varying degrees of success in persons with invasive cancer of the cervix. This is usually given together with radiotherapy

(chemo-radiation). Response rates to chemo-radiation are similar in HIV-infected and in non-HIV-infected persons.

Chemotherapy is used as part of chemo-radiation or on its own for palliation of symptoms in recurrent or metastatic disease. Cisplatin is the drug of choice and can be used as a single agent or in combination with other drugs such as bleomycin, 5-fluorouracil and vincristine. The usual dose of cisplatin is 50 mg/m². Where renal impairment is present, carboplatin can be used instead.

20.2.6 Nursing care

Meticulous management of the side effects of these treatments should be carried out. Symptomatic management of pain, nausea, diarrhoea and vomiting should be given. Special nursing care may be needed for the patient with incontinence from fistulae.

20.2.7 Counseling

- Pre and post-test counseling for HIV testing is necessary.
- Death and dying issues must be discussed at family level.
- Preparation for events such as loss of hair during treatment should be made. The possibility of sexual dysfunction and reproductive failure following treatment must be explained.
- Counseling is required with regard to the HIV infection as well as the cancer. Palliative care should begin with diagnosis and issues relating to the end of life should be discussed with the patient and his/her family before the patient is terminally ill.

20.2.8 Post Admission care

Care for the skin following protracted radiotherapy should be well explained to avoid moist desquamation.

20.2.9 Social Services Support

Most of the patients with cervical cancer have young families whom they support whilst the husbands work in town. Provision for family support during the time that they are attending treatment and in the event of disability and bereavement should be given.

20.3 Non-Hodgkins lymphoma (NHL)

The incidence of NHL is 60 times higher in individuals with HIV infection than in the general population. HIV related NHL is a result of continuous stimulation of B-cell proliferation by HIV, Epstein-Barr virus (EBV) and other infections. Over 95% of HIV related NHL tumours are of B-cell origin. They are usually of the high-grade type. NHL occurs in 10 to 15% of HIV infected patients. NHL is a more aggressive and a more malignant tumour in HIV-infected persons. The nodal form is mainly found in the neck region. Extranodal sites include the oral cavity, the sinonasal regions and the pharynx and larynx.

Clinically, presentation is usually with a nodal mass or masses. Extra-nodal presentation is also common and symptoms will vary according to the site of disease.

B symptoms (fever, weight loss, night sweats) are also common but other opportunistic infections must be excluded before labeling these as such.

The Ann Arbor classification system of staging is used.

20.3.1 Diagnosis

The diagnosis is made by histological examination of biopsied tissue and fine needle aspiration. CT scan and MRI scans of other regions like the brain, head, neck, mediastinum or abdomen because need to be performed

in order to assess the extent of the tumour as management and prognosis depend on the extent of the disease. Bone scan and bone marrow biopsy are useful for staging purposes. An examination of the cerebrospinal fluid is necessary to exclude asymptomatic leptomeningeal lymphoma, which occurs in as many as 60% of cases.

20.3.2 Investigations

- Full blood count
- Urea and electrolytes
- Liver function tests/LDH
- CD4 lymphocyte count and viral load.
- CT neck/chest/abdomen/pelvis. Other sites e.g. brain if indicated
- Bone marrow aspiration and trephine
- Spinal fluid analysis

20.3.3 Management

Non-drug related treatment

Counseling and education is important

There is no specific role of surgery in the treatment of NHL other than biopsy for confirmation of the diagnosis.

Radiation therapy

In systemic lymphoma radiotherapy is limited to the consolidation of the effects of chemotherapy.

The principles remain similar to those used for the non-HIV infected patient and involved fields or extended fields are used as appropriate.

Radiotherapy is the main treatment for primary CNS lymphomas.

Fractionated doses of 40 to 45 Gy in 20-25 fractions in 4-5 weeks are commonly used to control deposits at various sites. An additional boost to residual disease of 5-10 Gy in 3-5 fractions may be given to patients with a high performance status.

If the prognosis is poor e.g. in lymphomatous meningitis, 30 Gy in 10 fractions in 2 weeks would be best to shorten the treatments whilst giving sufficient palliation.

Radiotherapy can be used as CNS prophylaxis in cases with marrow involvement and 24Gy is given in 12 fractions in two and a half weeks. If there is known CNS involvement then a minimum of 40Gy is given at conventional fractionation.

Drug related treatment

Antiretroviral therapy

Antiretroviral drugs should be used as well as any other drugs needed to treat other co-existing HIV related illnesses.

Chemotherapy

Chemotherapy is the mainstay of treatment since dissemination of disease in the NHL patient with HIV infection is more likely and should be assumed.

It is best to use low dose or standard dose regimens in these patients.

Performance status and a CD4 count cut-off point of 100 cells /mm³ should be a guideline on whether low or standard doses should be used. In the absence of B symptoms standard doses are indicated if the CD4 count is above 100/mm³ and the disease stage is I or II.

The total number of cycles given is usually determined by the side effect profile in these patients.

The CHOP regime is commonly used at standard or reduced dosage and 4-6 cycles can be given. The standard dose regime is as follows:

Cyclophosphamide 750mg/m² IV day 1, doxorubicin 50mg/m² IV day 1, Vincristine 1.4mg/m² (max. 2mg) IV day 1 and prednisolone 60mg orally day 1-5 in divided doses.

The m-BACOD regime has also been shown to be effective in these patients and the low dose regimen is as follows:

Bleomycin 4mg/m² IV day 1, doxorubicin 25mg/m² IV day 1, cyclophosphamide 300mg/m² IV day 1, vincristine 1.4mg/m² (max. 2mg) IV day 1, dexamethasone 3mg/m² orally days 1-5, methotrexate 200mg/m² IV day 15 with folinic acid rescue of 25mg every 6hours for 4days orally, beginning 6hours after completion of methotrexate.

The CEOP regimen is a modification of CHOP where doxorubicin is replaced with epirubicin whilst achieving the same results.

CDE is also nearly as effective as the above regimens and is given as follows:

Cyclophosphamide 800mg/m² IV/96 hrs, doxorubicin 50mg/m² IV/96 hrs and etoposide 240mg/m² IV/96 hrs.

Growth factor support to reduce the myelosuppression that inevitably results is essential. Patient tolerance is greatly enhanced with the use of a myeloid hematopoietic growth factor. Salvage chemotherapy usually has no usefulness. For intracranial lymphoma, cranial radiation together with cytotoxic chemotherapy and steroids are advised.

Nursing care requirements

Vigorous management of nausea and vomiting is necessary to avoid nutritional deterioration.

Moist desquamation is more likely to occur as a side effect of radiotherapy in these patients. Clear instructions on skin care are to be given.

Other opportunistic infections must be appropriately treated.

Counseling

Pre and post-test counseling for HIV testing is necessary. Death and dying issues must be discussed at family level.

Preparation for events such as loss of hair during treatment should be made.

Social services support

With the high cost of chemotherapy drugs, financial support from organizations such as the National AIDS Council is recommended.

20.4 Ocular Surface Squamous Neoplasias

SEE CHAPTER ON OCULAR MANIFESTATIONS

A strong association has been noted between HIV infection and ocular surface squamous neoplasia. There has been a marked increase in the incidence of this cancer over the last 10 years in Zimbabwe. The exact aetiology is not known but it has been suggested that the cancer may be associated with human papilloma virus infection.

20.4.1 Diagnosis

Ocular surface squamous neoplasia appear as persistent, progressively enlarging tumours on the conjunctiva that lead to the eventual erosion of the cornea. Lesions are highly vascular, painful and irritating. The diagnosis should be confirmed by histologic examination of tumour tissue. Conjunctival cytology may be useful in identifying malignant cells.

20.4.2 Management

Counseling

All patients undergoing HIV testing should receive pre- and post-test counseling.

Non-drug related treatment

All patients need supportive therapy including advice on good nutrition and preventing transmission of infection to household contacts.

Visually impaired persons may require additional support and care.

Localised lesions may be surgically excised or removed by cryotherapy

The tumour responds to radiotherapy

Drug related treatment

Neodexone / sofradex eye drops/ ointment should be used initially to treat inflammatory lesions like phlyctenulosis

Systemic cytotoxic chemotherapy is usually necessary once the diagnosis has been confirmed or in the presence of metastasis.

Analgesics should be given for pain and discomfort.

Nursing Care Requirements

Supportive role and ensuring treatment compliance and regular follow up attendance. General nursing care and support for patient with cancer.

Post Admission Care and Discharge Plan

Long term follow-up by ophthalmologist / oncologist to monitor progress.

Early detection and treatment of other opportunistic infections. Patient should be commenced on long-term prophylactic treatment with cotrimoxazole.

Social Services Support

Patients should be encouraged to join AIDS support organisations as they may require long-term social, educational and financial assistance.