

# BHIVA Guidelines for HIV-associated malignancies 2014

# Scope and purpose

- Provide guidance on best clinical practice
- Treatment and management of adults with HIV infection and malignancy
- Do not address screening for malignancy in this population

# Methodology

- Modified GRADE system for review of evidence (Appendix 1)
- Multispecialty, multidisciplinary team – Oncology, Haematology, HIV, CNS, Pharmacy
- Patient involvement
- Two patient representatives involved in all aspects of guideline development
- Additional two meetings with patients and community representatives before writing group consensus meeting and as part of public consultation process

# Summary

## HIV-associated Malignancies

- Increased risk of:
  - AIDS-defining malignancies
  - Kaposi sarcoma
  - High grade B cell non-Hodgkin lymphoma
  - Invasive cervical cancer
- Other malignancies
  - Anal cancer
  - Hodgkin lymphoma
  - Multicentric Castleman's disease
  - Testicular germ cell cancer
  - Non-small cell lung cancer
  - Hepatocellular cancer
  - Other cancers

# Summary

- For optimal care, need shared expertise and collaboration between
  - Oncology, Haematology, HIV, Palliative Care physicians
  - Clinical Nurse Specialists
  - Pharmacists
  - (see BHIVA Standards of Care for People Living with HIV 2013)
- Large centres of care with expertise and >5000 PLHIV
- Urgent referral of patients with suspected cancer, all to be seen within 2 weeks in specialist unit
- Test all for HIV
- Start cART for all patients diagnosed with cancer
- All require opportunistic infection (OI) prophylaxis

# 3. Kaposi sarcoma (KS)

- Epidemiology
  - KS is caused by KSHV/HHV-8 virus.
  - Post-cART incidence of KS has decreased (0.3 vs 1.9/1000 person years, hazard ratio 7), survival has increased
- Management
  - Always confirm histologically (**1C**)
  - Test for HIV
  - CT, bronchoscopy, endoscopy only required if symptomatic (**2D**)
  - Start cART for all patients with KS (**1B**)

## 3. Kaposi sarcoma (KS)

- Treatment
  - To (early stage KS): cART  $\pm$  local radiotherapy (RT) or intralesional vinblastine for cosmesis (**2C**)
  - T<sub>1</sub> (advanced stage KS): cART and chemotherapy (**1B**)
  - First line: liposomal anthracyclines
    - Either liposomal daunorubicin (DaunoXome™) 40 mg/m<sup>2</sup> q14d or liposomal doxorubicin (Caelyx™) 20 mg/m<sup>2</sup> q21d (**1A**)
  - Second line: if refractory to anthracycline
    - Paclitaxel (Taxol™) 100mg/m<sup>2</sup> q14d (**1C**)
- Consider clinical trial

## 4. Systemic AIDS-related non-Hodgkin lymphoma (NHL)

- Epidemiology
  - HIV increases risk of NHL
  - Second commonest tumour in PLWH
  - High-grade B cell NHL is an AIDS-defining illness
  - Presentation: advanced stage, B symptoms, extranodal disease including bone marrow is common
  - cART reduces the risk of NHL
  - Survival of NHL in PLWH is now the same as that seen in HIV-negative people
  - Prognosis depends on histological subtype and stage



## 4. Systemic AIDS-related non-Hodgkin lymphoma (NHL)

- Management
  - Confirm histologically, requires expert review
  - HIV test
  - Clinical evaluation, bloods (Table 4.1), CT, bone marrow aspirate and trephine, FDG-PET at diagnosis improves staging accuracy, CSF if CNS symptoms or involvement of paranasal sinuses, breast, paraspinal disease, testes, renal, epidural space, bone

# 4. NHL: systemic AIDS-related diffuse large B-cell lymphoma (DLBL)

- Treatment

- Start cART, opportunistic infection prophylaxis and chemotherapy (**1B**)
- First-line chemotherapy as for HIV-negative patients
  - CHOP or EPOCH
- Add rituximab (**1B**) for CD20+ NHL
  - If CD4 <50 cells/ml, close monitoring advised, OI prophylaxis, G-CSF and prompt OI treatment
- If high risk of CNS relapse (high LDH, extranodal disease and high-risk sites involved)
  - CNS prophylaxis (intrathecal (IT) and/or IV methotrexate) as for HIV-negative patients (**1C**)

## 4. NHL: Burkitt lymphoma (BL)

- High risk of CNS disease
- Treatment
  - Start cART, opportunistic infection prophylaxis and chemotherapy (**1B**)
  - First-line chemotherapy
    - CODOX-M/IVAC or DA-EPOCH (**1B**)
  - Add rituximab (**1C**)
  - Offer all BL patients prophylactic IT chemotherapy (**1B**)

# 4. NHL: relapsed/recurrent systemic NHL

- Relapsed/aggressive NHL
  - Second-line chemotherapy (**1C**) may contain platinum (**2C**)
  - If response (CR or PR), consider high-dose therapy (HDT) with autologous stem cell transplantation (ASCT)

# 5. NHL: primary CNS lymphoma (PCNSL)

- Epidemiology

- Poor prognosis
- cART reduces risk

- Diagnosis

- Presentation may be subacute/neuropsychiatric
- Craniospinal involvement only, no systemic involvement
- HIV test
- Clinical assessment, bloods including LDH, CT/MRI brain, CSF (if safe) include EBV PCR on CSF, CT CAP, USS testes
- Confirm histologically: brain biopsy is the only confirmatory test

- Treatment

- Start cART (**1C**)
- All patients with adequate performance status: consider treatment with regimen containing high-dose methotrexate (**1D**)
- Use whole-brain radiotherapy (RT) for palliation for symptom control or, as alternative to first-line treatment if risk of toxicity from high-dose IV agents unacceptable (**1C**)

# 6. NHL: primary effusion lymphoma (PEL)

- Epidemiology
  - 3% of HIV-associated NHL
  - Poor prognosis
  - Lymphomas immunostain for HHV8 (+/-EBV)
- Diagnosis
  - Requires expert histopathology review
  - Usually causes pleural or pericardial effusion or ascites without masses
  - Rare extracavity PEL presents with solid masses rather than effusions
  - Diagnosis from effusion: cellular morphology, immune phenotype, virology
  - HIV test
- Treatment
  - Chemotherapy plus cART and opportunistic infection prophylaxis (1C)
  - CHOP-like regimens (2C)
  - Consider clinical trial

# 7. NHL: plasmablastic lymphoma

- Epidemiology
  - 2.6% of HIV-associated lymphomas
  - Three types: oral mucosal (EBV+ve); extra-oral (GIT, skin, nodal, splenic) (EBV+ve); associated with multicentric Castleman's disease (HHV8+ve)
  - Requires expert histopathology review
  - HIV test
- Treatment
  - Chemotherapy plus cART and opportunistic infection prophylaxis (1C)
  - Chemotherapy: anthracycline-containing regimen (1C)

# 8. Cervical intraepithelial neoplasia (CIN) and cervical cancer

- Epidemiology
  - Related to high-risk HPV (mostly 16 and 18)
  - Cervical cancer preceded by CIN
  - 75% cases cervical cancer preventable by screening
  - Smoking increases risk
  - No change in risk of cervical cancer post cART
    - Driven by HPV
    - Increased risk of cervical cancer due to HIV much smaller than increase in HIV-related KS/NHL
    - Survival bias masks effect as PLWH population lives longer
  - Modest decreased incidence of CIN post cART
  - Increased incidence of CIN with low CD4 cell counts
- Screening
  - All HIV-infected women have annual cytology (and initial colposcopy if resources permit) (2C)
  - Same age range as for HIV-negative women (1B)



# 8. Cervical intraepithelial neoplasia (CIN) and cervical cancer

- Management
  - HIV test
- CIN 1
  - Less severe grades than CIN2: no treatment as it represents persistent HPV infection not pre-malignancy (**2B**)
- CIN 2/3
  - Manage as per UK guidelines
  - Excision: higher failure rate than in HIV-negative patients as high frequency of compromised margins on excisional specimens; higher rates of treatment failure
  - Start cART: relapse less frequent with CD4 count >200cells/ml and undetectable HIV viral load
- Invasive cervical cancer
  - Manage as per UK guidelines for HIV-negative women within MDT framework (**1B**)

# 9. Anal cancer

- Epidemiology
  - Relative risk 40–50 in HIV-positive MSM
  - Occurs at younger age in PLWH
  - Associated with high-risk HPV (mostly 16 and 18)
  - Incidence rising in post-cART era
  - May be due to longer survival with HIV allowing time for progression from HPV to AIN to invasive anal cancer
- Diagnosis
  - Role of annual cytology and anoscopy not proven: patients encouraged to check and report lumps in anal canal (BHIVA BASHH FFPRHC 2008 guidelines on anal cancer in HIV)
  - Patients may present with rectal bleeding, anal pain, incontinence, but may be asymptomatic
  - EUA anal canal and rectum, and biopsy all suspected cases (**1D**)
  - Further staging CT CAP, MRI pelvis (**1B**)

# 9. Anal cancer

- Management
  - HIV test
  - Manage in specialist centres with experience (1C)
  - Centres managing anal cancer should be able to provide high resolution anoscopy (HRA) (2D)
- Treatment
  - Start cART (1C)
  - Start OI prophylaxis (1D)
  - Chemoradiotherapy (CRT) with 5-flourouracil and mitomycin C (1A)
  - Salvage surgery may be appropriate if loco-regional disease resistance or relapse following CRT (2D)
  - Best supportive care may be more appropriate if metastatic disease or local relapse following salvage surgery (2D)
  - Advocate surveillance for AIN by HRA (2D)

# 10. Hodgkin lymphoma

- Epidemiology

- Commoner in PLWH x10–20
- Post-cART rates for CR/overall survival/disease-free survival same as for HIV-negative patients
- Increased incidence with CD4 <200 cells/ml, and CD4 count may fall 1 year pre-HL diagnosis
- EBV-driven

- Diagnosis

- Presentation in HIV infection: advanced stage, more symptoms, extranodal disease, poor performance status
- Histology EBV+ and mostly mixed cellularity (MC) or lymphocyte-depleted (LD), rather than nodular sclerosis

- Management

- HIV test
- Start cART and opportunistic infection prophylaxis (1A)
- Avoid ritonavir: risk of vinblastine-mediated neuropathy and neutropenia (1D)

# 10. Hodgkin lymphoma

- Management

- First-line ABVD-based regimens
  - Early favourable: ABVD x2-4 + IFRT 20-30Gy (**1B**)
  - Early unfavourable: ABVD x4 + IFRT 30Gy (**1B**)
  - Advanced ABVD: x6-8 +/- RT (**1B**)
- Relapse/refractory HL
  - Salvage chemotherapy
  - If chemosensitive, consolidate with HDT/ASCR (**1B**)
- Assess response to treatment: FDG-PET scan and bone marrow biopsy (**1D**)
- Assess during FU 2-4 monthly for 2 years then 3-6 monthly for a further 3 years (**1B**)
- If blood products required: give irradiated blood products

# 11. Multicentric Castleman's disease (MCD)

- Epidemiology
  - HHV8-driven: present in all instances; rise in plasma HHV8 at relapse
  - cART does not prevent MCD: can present CD4 >200 cells/ml
  - Risk of NHL x15 higher than in PLWH without MCD
- Diagnosis
  - Relapsing and remitting course
  - Biopsy lymph node histology: confirmatory stain for HHV8 and IgM lambda (**2B**)
  - Requires expert histopathology review
  - High HHV-8 blood level supports diagnosis (**2C**)
  - HIV test
- Treatment
  - First line: rituximab (**1B**)
  - Start cART and opportunistic infection prophylaxis
  - Aggressive disease add chemotherapy (**1C**)
  - Relapse: re-treat with rituximab (**1C**)
- Monitor
  - Measure HHV-8 level in blood (**1C**)
  - Rise can predict relapse (**2D**)

# 12. Testicular germ cell cancer

- Epidemiology
  - Seminoma more frequent in HIV infection 3.7% RR
  - Younger age
  - Risk of over-staging due to HIV-associated lymphadenopathy
- Management
  - HIV test
  - Chemotherapy plus cART and opportunistic infection prophylaxis (2C)
  - Treatment the same as for HIV-negative population (2C)
  - Surveillance is safe for stage I disease (2C)
  - Bleomycin can be avoided in stage I disease as low-risk (2D)

# 12. Non-small cell lung cancer

- Epidemiology
  - Increased risk in PLWH
  - Smoking, younger
- Management
  - Biopsy, CT CAP including adrenals, bone scan, (interpret FDG-PET with caution – low specificity), cranial imaging if symptoms
  - HIV test
  - Stop smoking (**1B**)
  - Offer potentially curative surgery when appropriate (**2C**)
  - Screen for activating endothelial growth factor (EGFR) mutations. If present treat with tyrosine kinase inhibitors (TKIs) (**2D**)
  - No role for screening for lung cancer in PLWH



# 12. Hepatocellular carcinoma (HCC)

- Epidemiology

- Western world: 30% PLWH co-infected with hepatitis C (HCV) (75% IVDU)
- High hepatitis B (HBV) viral load: increased risk HCC
- Low CD4 cell count: increased risk hepatitis B-associated HCC

- Management

- HIV test
- CT CAP to exclude metastases, liver USS, AFP, assess cirrhosis (fibroscan, liver biopsy)
- Treat HCC same as in HIV-negative people (2C)
- Consider liver transplantation as appropriate as for HIV-negative people (2D)
- Sorafenib is an option for advanced, inoperable HCC (2D)
- Screen cirrhotic HBV and HCV co-infected patients with liver USS (1A) and 6 monthly AFP (2C)
- Consider screening non-cirrhotic HBV co-infected patients for HCC

## 12. Other cancers

- Colorectal cancer
  - Increased risk of adenoma and adenocarcinoma in PLWH
  - Younger, more advanced disease, right-sided cancers
  - Chemotherapy and cART and opportunistic infection prophylaxis
- Skin cancer
  - Increased risk x5 SCC, BCC and x2-3 melanoma
  - Atypical presentation
  - HPV-driven cancers
  - cART and opportunistic infection prophylaxis and treatment
- Merkel cell carcinoma (MCC)

# 12. Other cancers

- Cutaneous lymphoma
  - Mycosis fungoides, Sézary syndrome
- Penis precancer (PIN) and cancer
  - PIN: increased risk in uncircumcised men
  - Penile cancer x5–6 increased risk
- Other cancers
  - AML more aggressive, increased deaths OIs
  - Head, neck and breast cancer – more aggressive
  - Prostate cancer
- Management
  - HIV test, cART and opportunistic infection prophylaxis
  - Standard care, large centre with MDT expertise

# 13. Opportunistic infection (OI) prophylaxis

- All PLWH requiring cancer treatment should be on cART (**1B**)
- *Pneumocystis jirovecii* pneumonia (PCP)
  - CD4 <200 cells/ml (**1A**), consider at higher levels when giving chemo/RT (also protects against cerebral *Toxoplasma gondii*).  
Co-trimoxazole
- Mycobacterium avium complex (MAC)
  - CD4 <50 cells/ml (**1B**) or if risk of CD4 falling below this level. Azithromycin
- Fungal infections
  - Systemic azole for all chemo/RT (**1D**)
- Bacterial infections
  - Co-trimoxazole for PCP prophylaxis may provide some protection against bacterial infections (**1C**)
  - Routine fluoroquinolone prophylaxis not recommended in low-risk patients

# 13. Opportunistic infection (OI) prophylaxis

- Herpes simplex virus (HSV)
  - Prophylaxis (aciclovir) recommended during chemotherapy (**1D**)
- Influenza virus
  - Annual vaccination (**1B**)
- Pneumococcus
  - Vaccination (**1D**)
- Hepatitis B virus (HBV)
  - Vaccination (**1D**)
- Hepatitis B virus core antibody positive
  - Treat with prophylactic antivirals in line with BHIVA hepatitis guidelines (**1B**). (If on cART, Truvada-containing regimen will provide this)