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**
  - **T0** (early stage KS): cART ± local radiotherapy (RT) or intralesional vinblastine for cosmesis *(2C)*
  - **T1** (advanced stage KS): cART and chemotherapy *(1B)*
  - **First line:** liposomal anthracyclines
    - Either liposomal daunorubicin *(DaunoXome™)* 40 mg/m² q14d or liposomal doxorubicin *(Caelyx™)* 20 mg/m² q21d *(1A)*
  - **Second line:** if refractory to anthracycline
    - Paclitaxel *(Taxol™)* 100mg/m² 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 the 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 >200 cells/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)