Kaposi Sarcoma and HIV-associated Lymphoproliferative Disorders

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Groote Schuur Hospital
University of Cape Town
SA HIV Clinicians Society Conference 2018
24-27 October
Kaposi Sarcoma
Trends in AIDS and in Cancers among Persons with AIDS.

Stats SA Midyear population estimates 2017

- SA population 56.52 million
- HIV prevalence 12.6%
- 7.06 million HIV positive
- SA has largest no of PLWA and largest ART program worldwide
- Sept 2016: universal ART eligibility

Stats SA midyear statistical release P0302 accessed online 9 August 2018; Cornell et al JIAS 2017
Incidence of Kaposi Sarcoma in South Africa

South African National Cancer Registry 2014

- Pathology-based registry
- Within top 10 cancers for males and females
- 3rd commonest cancer in Black men
- 5th commonest cancer in Black women

Comparison of KS risk in HIV+ve adults across 5 continents: A Multiregional Multicohort Study

- KS incidence rates per 100000 person-years in adults who started ART after 1995
  - South Africa 280 (95% CI 238-328)
  - Latin America 244 (203-295)
  - North America 237 (207-271)
  - Europe 180 (172-190)
  - Asia-Pacific 52 (19-137)

- Risk 6X more in MSM
- Risk 5X higher in SA women than European women

From CANSA factsheets accessed online

AIDS-defining Cancer Project Working Group for IeDEA and COHERE in Eurocord, Clin Infec Diseases 2017
Risk Factors for KS

21 European Cohort studies
- Incidence highest 6 months after starting ART
- Low CD4 counts
- Elevated viral load is a later risk factor

6 Southern African Cohorts IeDEA-SA database
- Risk increased with age
- Low CD4 counts
- Adults, Male sex
- Starting ART at WHO stage IV

Wyss et al COHERE in Eurocord, Clin Infec Dis 2016; Rohner et al, J Aquir Immune Defic Syndr 2014

Comparison of KS risk in HIV+ve adults across 5 continents: A Multiregional Multicohort Study

From: AIDS-defining Cancer Project Working Group for IeDEA and COHERE in Eurocord, Clin Infec Dis 2017
Declining incidence of Kaposi Sarcoma at GSH Oncology

New Kaposi Sarcoma referrals

Chart showing the number of Kaposi Sarcoma referrals from 2007 to 2017, with a decline in referrals over the years.
From Sengayi et al: Survival changes over time in AIDS-KS patients treated at SBAH

Presenting Symptoms

- Cutaneous lesions: patch, plaque, nodule, fungating, ulcerated
- Mucosal lesions: oral, eye, nasal
- Lymphoedema: legs, genitalia, face, arms
- Lymphadenopathy
  - Kaposi Sarcoma
  - TB or other infections
  - Lymphoma
  - Multicentric Castleman Disease
- Visceral involvement
  - Pulmonary
  - Gastrointestinal
  - Other organs: liver, spleen, etc

KS IRIS

Within 3 months of initiating ART:
- Unexpected progression of pre-existing KS lesions
- New KS lesions
- Involvement of new sites
- Atypical clinical, histologic or radiologic findings
- Rapid onset

With suppressed viral load

Incidence 2.5 times higher in African vs European cohorts

Letang et al, AIDS 2013
Kaposi Sarcoma

- Angiogenic, inflammatory tumor of endothelial cells
- Caused by KSHV/HHV8
  - Gamma-2-herpesvirus closely related to EBV
  - 6 subtypes and 13 variants
  - Also causes Castleman’s and Primary Effusion Lymphoma
- Seroprevalence of KSHV parallels KS incidence
  - US and Europe <10%
  - Sub Sahara Africa ~50%
  - South African studies: 35-49%

Thomas F Schulz and Ethel Cesarian

“Kaposi sarcoma is an unusual tumour. Several of its features suggest that unlike other cancers, it may not result from a transformation event that results in autonomously growing tumour cells, but represents the combined effects of a virus with angiogenic properties and local or systemic inflammation”


KSHV / HHV-8

- Virus is latent in majority of infected cells
  - Viral genome maintained in extrachromosomal episome within the nucleus
  - evades immune detection
- Spontaneously enters lytic cycle
  - Expression of viral replicative and structural genes
  - Cell lysis and release of progeny virions capable of infecting more cells
- KSHV gene products
  - Latent genes promote cell proliferation eg LANA1 and 2
  - Lytic genes provide paracrine signals to adjacent latently-infected cells eg KSHV G-protein coupled receptor
- HIV transactivating protein upregulates HIV gene expression resulting in cytokine, growth factor and adhesion molecule production and angiogenesis

Horenstein et al, J Cut Path 2008; Wood and Fellar, Can Cell Int,2008
Kaposi Sarcoma-associated Herpesvirus: mechanisms of oncogenesis
Thomas F Schulz¹,² and Ethel Cesearman³
Levels of Kaposi’s sarcoma-associated herpesvirus (KSHV) in whole-blood and effusion fluid samples from patients with Kaposi’s sarcoma (KS), Castleman multicentric disease (MCD), and primary effusion lymphoma (PEL) at the time of KSHV-associated disease diagnosis.

- Broccolo et al (J Clin Vir 2016): plasma HHV8 viral load correlated with response to treatment
- Jary et al (J Clin Micro 2018): KSHV viral load useful for diagnosis and monitoring of KSHV-associated diseases
Is there a genetic susceptibility to develop KS?

EPHA2: Eph receptor A2 protein tyrosine Kinase receptor
- host receptor for entry of KSHV into endothelial cells
- Implicated in oncogenesis in various cancers

3 HIV+ cohorts: KS+KSHV+; KS-KSHV+ and KS-KSHV-
- Extract DNA from peripheral blood and sequence the EPHA2 coding region
  - 31.6% of KS negative cohort was KSHV positive

Variation across EPHA2 coding region associated with KS particularly in protein tyrosine kinase domain (exons 12-15)
Treatment of Kaposi Sarcoma
### AIDS Clinical Trials Group Staging

<table>
<thead>
<tr>
<th></th>
<th>Good risk (all of the following)</th>
<th>Poor risk (any of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour (T)</strong></td>
<td>T0 skin and/or lymph nodes and/or minimal oral disease</td>
<td>T1 oedema or ulceration extensive oral KS visceral KS (non-nodal)</td>
</tr>
<tr>
<td><strong>Immune system (I)</strong></td>
<td>I0 CD4 ≥ 200 (150)</td>
<td>I1 CD4 &lt; 200 (150)</td>
</tr>
<tr>
<td><strong>Systemic illness (S)</strong></td>
<td>S0 no opportunistic infections or thrush no B-symptoms KPS ≥ 70</td>
<td>S1 opportunistic infections, B-symptoms or other HIV-related illnesses KPS &lt; 70</td>
</tr>
</tbody>
</table>
Basic Treatment Algorithm for KS

T0 KS
Not mutilating
ARVs

T1 or cosmetically unacceptable KS
ARVs
Manage life-threatening OIs

Localised disease:
Intralesional therapy or Radiotherapy
Chemotherapy

Radiotherapy to localized residual
NCCN Guidelines Version 1.2018
AIDS-Related Kaposi Sarcoma

PRINCIPLES OF THERAPY:

• Individual KS lesions may be distinct clones that arise due to the common risk factors of immunosuppression and persistent HHV-8 infection as opposed to metastases. Treatment of existing disease therefore may not prevent occurrence of future lesions.

• Reconstitution of immune function, maintenance of viral suppression, and avoidance of additional immunosuppression are critical to prevention of additional KS lesions and maintenance of response to therapy. For AIDS-related KS, it is important to work with an HIV specialist to optimize suppression of HIV and reconstitution of immune function with ART. Important examples of iatrogenic immunosuppression, which may promote KS, include not only systemic but local glucocorticoids (ie, inhaled, topical, intra-articular). Note that KS may flare in a remote location from the site of local glucocorticoids. Patients requiring rituximab for treatment of NHL with coexisting KS or multicentric Castleman's disease may develop flares of KS or incident KS. This may be mitigated by use of concurrent chemotherapy active against both KS and disease for which rituximab is prescribed (ie, doxorubicin).

• Persons with AIDS-related KS, especially those with advanced immunosuppression, are at increased risk of opportunistic infections (OIs), marrow suppression with neutropenic fever, or thrombocytopenic bleeding and should be monitored closely. It is important to collaborate with an HIV specialist to ensure adequate OI prophylaxis appropriate to CD4+ T-cell count (which may temporarily decrease with cytotoxic chemotherapy). Growth factor support may be needed to facilitate systemic therapy.

• Lymphedema and soft tissue infections: KS is often complicated by lymphedema with increased risk of cellulitis and deep tissue infections in affected limbs. Risk of severe lymphedema and delayed wound healing may be increased after radiation. Refer to a lymphedema specialist. In the setting of advanced cutaneous disease, radiation should be reserved for circumstances when systemic therapy is not feasible with the goal of palliation or short-term disease management until systemic therapy may be delivered. Note that treatment responses may be delayed in the context of significant lymphedema.

GOALS OF THERAPY:

• Patients with limited cutaneous disease that is asymptomatic and cosmetically acceptable may be observed while continuing ART with optimization of immune function and HIV viral suppression as above. Remissions or stable disease may occur with ART and optimization of immune function and HIV viral suppression alone.

• Patients with symptomatic or cosmetically unacceptable disease should use the most minimally invasive and least toxic therapy to control disease. A limited number of cycles of systemic therapy (eg, 3–6) may be sufficient for those initiating or re-initiating ART.

• Patients with advanced symptomatic cutaneous, visceral, nodal, or oral disease should be treated with systemic therapy with the goal of reducing or reversing symptoms, lymphedema, or threat to organ function. Complete remissions are rare.

• Treatment is typically continued until unacceptable toxicity or plateau in response; maintenance therapy beyond 2 cycles of systemic therapy after determination of plateau is not recommended. If response is then clinically acceptable, patients may be observed on ART alone. Otherwise, alternative therapy should be initiated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 1.2018
AIDS-Related Kaposi Sarcoma

SYSTEMIC THERAPY

- Liposomal doxorubicin\(^1,2\) (preferred)
  - 20 mg/m\(^2\) IV every 3 weeks
- Paclitaxel\(^2\)
  - 100 mg/m\(^2\) IV every 2 weeks (premedication with dexamethasone 10 mg at time of administration is acceptable for prevention of hypersensitivity reaction)

If tolerated and durable response (≥3 months) to first-line systemic therapy
- Repeat of first-line systemic therapy
- Alternate first-line systemic therapy

If no response to first-line systemic therapy
- Alternate first-line systemic therapy\(^d\)

Subsequent systemic therapy options for relapsed/refractory therapy
- Preferred regimen:
  - Pomalidomide\(^2\)
    - 5 mg/d orally for 21 days of each 28-day cycle
- Other regimens (in alphabetical order):
  - Bevacizumab\(^4\)
    - 15 mg/kg IV on days 1 and 8 and then every 3 weeks
  - Etoposide\(^5\)
    - 50 mg/d orally for 7 days of each 21-day cycle
  - Gemcitabine\(^6\)
    - 1000 mg IV every 2 weeks
  - Imatinib\(^7\)
    - 400 mg/d orally
  - Interferon alfa-2a\(^8\)
    - 1 million International Units SC daily
  - Nab-paclitaxel\(^9\)
    - 100 mg IV days 1, 8, and 15 of each 28-day cycle
  - Thalidomide\(^10\)
    - 200 mg/d orally (starting dose, titrated to effect and tolerability)
  - Vinorelbine\(^11\)
    - 30 mg/m\(^2\) every 2 weeks

\(^a\)See references for regimens on KS-D 2 of 2.
\(^b\)Due to risk of cardiotoxicity, perform echocardiogram prior to initial and repeat course of liposomal doxorubicin and limit lifetime dose to 400–450 mg/m\(^2\).
\(^d\)Consider repeating any prior systemic therapy that was tolerated and resulted in a durable response.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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### Table 4: Combination Chemotherapy for treatment of AIDS–KS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Patients (N)</th>
<th>Response rate (%)</th>
</tr>
</thead>
</table>
| Northfelt<sup>19</sup> | Doxorubicin 20 mg/m²  
Bleomycin 10 mg/m²  
Vincristine 1 mg every 2 weeks | 125          | 25                |
| Stewart<sup>53</sup> | Bleomycin 15 UI/m²  
Vincristine 2 mg every 3 weeks | 120          | 23                |
| Gill<sup>21</sup> | Doxorubicin 10 mg/m²  
Bleomycin 15 UI  
Vincristine 1 mg every 2 weeks | 111          | 28                |
| Gill<sup>70</sup> | Doxorubicin 20 mg/m²  
Bleomycin 10 mg/m²  
Vincristine 1.4 mg/m² every 2 weeks | 61           | 88                |
| Laubesten<sup>78</sup> | Doxorubicin 40 mg/m²  
Bleomycin 15 UI/m²  
Vinblastine 6 mg/m² every 28 days | 31           | 84                |

None of the studies cited above was controlled for the use of HAART in addition to chemotherapy.

* Limited number of cycles (six).

### Table 2: Liposomal anthracyclines for the treatment of AIDS–KS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Patients (N)</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martín-Carbonero&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Liposomal doxorubicin 20 mg/m² every 3 weeks</td>
<td>13</td>
<td>76</td>
</tr>
<tr>
<td>Tulpule&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Liposomal daunorubicin 60 mg/m² every 2 weeks</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>Northfelt&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Liposomal doxorubicin 20 mg/m² every 2 weeks</td>
<td>133</td>
<td>46</td>
</tr>
<tr>
<td>Stewart&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Liposomal doxorubicin 20 mg/m² every 3 weeks</td>
<td>121</td>
<td>59</td>
</tr>
<tr>
<td>Girard&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Liposomal daunorubicin 40 mg/m² every 2 weeks</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Gill&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Liposomal daunorubicin 40 mg/m² every 2 weeks</td>
<td>116</td>
<td>25</td>
</tr>
</tbody>
</table>

<sup>a</sup> Only in this study all patients had used HAART in addition to chemotherapy.

<sup>b</sup> Limited number of cycles (six).

<sup>c</sup> Complete or partial resolution of pulmonary symptom (shortness of breath) in patients with pulmonary AIDS–KS.
A Randomized Comparison of Three Chemotherapy Regimens as an Adjunct to Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

Progression-free survival by treatment group
(numbers of participants as of the time of the last DSMB review prior to arm closure)

- 20% PFS difference
  - CI for difference excludes zero difference
  - Prediction showed low chance of showing NI and current result unlikely to change
  - Ad-hoc summary showed better response with PTX as second-line therapy than BV

- 39.4% PFS difference
  - More than -25% team threshold
  - Consistent trend over time that ET worse than PTX
  - CI for difference almost excludes zero difference
  - Prediction showed low chance of showing NI

Margaret Borok and Susan Krown for AMC: abstract presented at the 22nd International AIDS Conference July 2018
Review of patients with Epidemic Kaposi Sarcoma seen over a 2-year period (2013-2014) at Groote Schuur Hospital.
Njiraini PN, Mohamed Z (MMed unpublished data)

- 166 cases identified
  - 38 excluded from analysis due to no chemo or concomitant MCD
  - 58% male
  - Median age 36.5 yrs (18-63)
  - 87.5% Black African (9.4% mixed race)
  - 10.2% not South African
  - 96.9% on ARVs
- 73% clinical diagnosis (no histology)
- Median CD4 164 (1-700)
- Concurrent TB: 31.3%
  - (20.3% history of TB)

67% Overall response to chemo (BV)
Median cycle of response = 7
SURVEILLANCE

- For patients not requiring active therapy and with no signs of progression
  - Every 3 months for year 1, then every 4-6 months for year 2, then every 6-12 months thereafter
    - History and physical exam
      - including history of additional immunosuppression such as transplant/glucocorticoids
    - CBC, differential, comprehensive metabolic panel, T-cell subsets (CD4+ T-cell count), and HIV viral load
    - Assess ART compliance

- Photography of oral, conjunctival, and cutaneous lesions (with reference unit of measure in picture) for documentation of extent of disease if change in disease is noted

- If signs and symptoms concerning for visceral involvement or prior to new therapy if progression/refractory disease
  - Stool hemoccult
  - Chest x-ray or chest CT with contrast
  - EGD/colonoscopy
  - Bronchoscopy

As KSHV is not eradicated with treatment of KS, the risk for future KS persists even after complete remission. Optimization and monitoring of HIV control and immune function is important to minimize this risk. This risk depends on immune function and generally decreases with immune reconstitution. However, KS can persist, relapse, or present even in the setting of normal values of T-cell subsets. Less frequent (every 6–12 mo) oncology monitoring may be appropriate for selected patients with undetectable HIV viral loads, normal T-cell subsets, and stable KS for 2 or more years as long as the patient has regular follow-up with an HIV provider.
Radiotherapy

- For localised disease
- Longer course fractionated RT better response and longer control than single fraction 8Gy
- 40Gy 83% CR vs 8Gy 50% CR
- But can repeat single fraction
- Side-effects: skin reaction, lymphoedema, mucositis
HIV-associated Lymphoproliferative Disorders
Multicentric Castleman’s disease

- Lymphoproliferative disorder associated with HHV8
- “Waxing and waning” acute febrile illness characterized by lymphadenopathy, splenomegaly and anaemia
- Excess IL6 production results in constitutional symptoms and biochemical and haematological abnormalities
- Hyaline vascular, plasma cell and mixed variants
- CD20+ve, HHV8
Changing trends of KS and MCD at GSH Oncology

New Kaposi Sarcoma

Multicentric Castleman Disease

GSH data
Simultaneous KS + MCD

- lymph node KS 27%
- mucocutaneous KS 18%
- L/N and MC KS 5%

HHV8 stain

Slide provided courtesy of Dr D Chetty NHLS GSH
Multicentric Castleman’s disease

- Treatment in resource-limited setting
  - ARVs
  - Supportive therapy
  - 6-8 cycles CHOP
  - Severe cytokine-induced cytopaenias: weekly Etoposide 100mg/m² until counts improve. Follow with CHOP
  - Rituximab not available for MCD in state sector

- NCCN guidelines
  - Active disease but no organ failure: Rituximab +/- liposomal doxorubicin +/- prednisone OR Zidovudine + ganciclovir/valganciclovir
  - Combination therapy +/- Rituximab (CHOP, CVAD, CVP, lipos doxo)

- Gerard et al (Blood 2012):
  - 113 patients (1996-2011), 42% had Rituximab
  - Rituximab associated with 11 fold decrease in risk of developing NHL

- Bower et al (JCO 2011):
  - 61 patients since 2000, 49 received Rituximab +/- Etoposide
  - OS 90% at 5 years vs 42% without Rituximab

- Pria et al (Blood 2017):
  - 84 patients treated with Rituximab-based therapy
  - 5 year relapse-free survival 82%
  - Median time to relapse 30 months

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Mechanism of Action</th>
<th>When to Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m² weekly ×4 wk</td>
<td>Depletes IL-6-secreting CD20⁺ B cells</td>
<td>Mild symptomatic disease</td>
</tr>
<tr>
<td>Rituximab + liposomal doxorubicin</td>
<td>Rituximab 375 mg/m² + liposomal doxorubicin 20 mg/m² every 3 wk until response plateau</td>
<td>Addition of cytotoxic chemotherapy to treat CD20⁻ MCD plasmablasts and KS spindle cells</td>
<td>Aggressive disease and/or concurrent KS</td>
</tr>
<tr>
<td>Rituximab + etoposide</td>
<td>Rituximab 375 mg/m² + etoposide 100 mg/m² IV weekly ×4 wk</td>
<td>Addition of cytotoxic chemotherapy to treat CD20⁻ MCD plasmablasts</td>
<td>Aggressive disease</td>
</tr>
<tr>
<td>AZT + valganciclovir</td>
<td>Zidovudine 600 mg PO every 6 h + valganciclovir 900 mg PO every 12 h, d 1–7 of 21-d cycle</td>
<td>Virus-activated cytotoxic therapy</td>
<td>Mild disease with concurrent KS and/or patients allergic to rituximab</td>
</tr>
</tbody>
</table>
HIV-associated lymphomas

- **AIDS-defining lymphomas** are defined as aggressive B-cell non-Hodgkin’s lymphomas arising in patients who have HIV
  - Burkitt’s
  - Diffuse Large B-cell
  - Primary CNS
  - Plasmablastic
  - Primary Effusion Lymphoma

- HIV also increases the risk of classic Hodgkin lymphoma but this is not “AIDS-defining”

- **Non EBV-related lymphoproliferative disorders**
  - KSHV-related Multicentric Castleman’s disease
  - Primary Effusion lymphoma
EBV-associated Lymphomas

- EBV-associated lymphomas are heterogeneous in terms of pathology, pathogenic pathways and cellular derivation

- Pathogenesis
  - Impaired immune surveillance, loss of EBV-specific T-cell response
  - Chronic B-cell activation
  - Viral cooperation
  - Genetic alterations

- High incidence of lymphomas in HIV persist despite immune reconstitution due to ART

Carbone et al, Curr opin Hiv AIDS 2017; Gloghini et al, Sem Cancer Biol 2013
Ann Oncol | © The Author 2015. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oup.com.

- Systematic review of 19 studies
- A significant improvement in CR rate and survival seen with more effective HIV therapy
Workup

- Excision biopsy with immunophenotyping to establish diagnosis
- B-symptoms, comorbidities, meds, ARVs
- Physical exam, PS
- FBC&diff, CUE, LDH, LFT, uric acid, CMP
- Hep B, CD4, Viral load
- PET-CT or CT neck, chest, pelvis
- BMAT
- Lumbar puncture in selected cases
- ECHO or ERNA
Diffuse Large B-cell lymphoma

- Immunohistochemistry:
  - Pan-B markers +ve (CD19, CD20, CD22, CD79a)
  - 30-60% CD10+
  - 60-90% BCL6+
  - 35-65% IRF4/MUM1+
  - Ki67>40%
  - 20-30% BCL2+
- Cell of origin (COO): germinal centre B (GCB) vs activated B-cell (ABC)

- Treatment: R-EPOCH vs R-CHOP
Treatment of HIV-related DLBCL

- Spina and Tirelli (Cancer in AIDS 2005): noted that Rituximab improved outcome in HIV-related lymphomas but should be used cautiously in patients with CD4 count <50

- Sparano et al (Blood 2010): concurrent vs sequential Rituximab plus infusional EPOCH
  - 106 patients enrolled, both arms experimental
  - 2-year PFS 66% for concurrent vs 63% for sequential Rituximab
Sparano et al (Blood 2010): concurrent Rituximab and infusional EPOCH is effective for HIV-associated lymphoma

- Patients who had not been established on ARVs deferred treatment until completion of R-EPOCH
- Rituximab given with each cycle or weeklyX6 after 6 cycles of EPOCH
- 96 hour continuous infusion of Etoposide, Doxorubicin and Vincristine and 5 days oral Prednisone plus bolus cyclophosphamide on day 5
- Filgrastim from day 6 until neutrophil recovery
- Prophylactic Bactrim, fluconazole, ciproflox
- All patients need a port
- AEs: 43% grade 3-4 neutropenia, 16% febrile neutropenia and 27% infection in concurrent arm

Joseph A. Sparano et al. Blood 2010;115:3008-3016
Kaplan-Meier plots comparing OS for HIV-positive patients with DLBCL treated with EPOCH vs CHOP and R-EPOCH vs R-CHOP.

- Barta 2013 (Blood 2013): pooled analysis of 1546 patients from 19 trials
  - Rituximab associated with higher CR rate
  - Infusional EPOCH resulted in better OS in DLBCL (HR 0.33, 95% CI 0.11-0.85, p=0.31)
  - R-EPOCH better OS than R-CHOP but borderline statistically significant
  - Concurrent ART associated with better CR rates

Kaplan-Meier plots comparing the OS for HIV-positive patients with DLBCL treated with rituximab-containing regimens vs non-rituximab-containing regimens.

Coutinho et al (AIDS 2014): Outcome with RCHOP in ART era

- 97 HIV+ compared to 208 HIV-ve patients
- HIV+ patients with DLBCL had more B-symptoms and extranodal disease than HIV-ve
- HIV+ patients had significantly longer 5yr DFS: 94% in HIV+ vs 77% in HIV-ve (p=0.03)
- Lymphoma-related factors (IPI) and complete response rate were predictive of survival

HIV status does not impair the outcome of patients diagnosed with diffuse large B-cell lymphoma treated with R-CHOP in the cART era

Coutinho, Rita; Pria, Alessia D.; Gandhi, Shreyans; Bailey, Katharine; Fields, Paul; Cwynarski, Kate; Wilson, Andrew; Papanastasopoulos, Panagiotis; Tenant-Flowers, Melinda; Webb, Andrew; Burns, Fiona; Marcus, Robert E.; Orkin, Chloe; Montoto, Silvia; Bower, Mark


doi: 10.1097/QAD.0000000000000133

Kaplan-Meyer curves for overall survival and cause-specific survival for patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP according to HIV status. (a) HIV-positive patients (grey line) with DLBCL treated with R-CHOP achieved significantly better overall survival compared with HIV-negative patients (black line;P=0.03); (b) There are no significant differences in cause-specific survival according to HIV status (P=0.09).
Baptista et al (AIDS 2015): Clinical features and outcome with RCHOP in ART era

- 81 HIV+ compared to 84 HIV-ve patients
- HIV+ patients with DLBCL had worse PS, more B-symptoms and higher stage than HIV-ve
- Prior AIDS-defining illness is the strongest negative predictive factor for OS
- CR rate and 5yr DFS similar but OS worse in HIV+ compared to HIV-ve

HIV-infection impact on clinical-biological features and outcome of diffuse large B-cell lymphoma treated with R-CHOP in the combination antiretroviral therapy era

Baptista, Maria Joao; Garcia, Olga; Morgades, Mireia; Gonzalez-Barca, Eva; Miralles, Pilar; Lopez-Guillermo, Armando; Abella, Eugenia; Moreno, Miriam; Sancho, Juan-Manuel; Feliu, Evarist; Ribera, Josep-Maria; Navarro, Jose-Tomas

doi: 10.1097/QAD.0000000000000624

Kaplan-Meier plots comparing overall survival and disease-free survival in HIV-Infected vs. HIV-uninfected patients with diffuse large B-cell lymphoma treated with R-CHOP. (a) OS of the whole series of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP. (b) DFS of the whole series of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP. (c) OS of the subgroups with high IPI scores (3-5) of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP. (d) DFS of the subgroups with high IPI scores (3-5) of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP.
CI, confidence interval; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index; OS, overall survival.
**Besson et al (AIDS 2017):**
Outcome in modern ARV era

- 52 HIV+ DLBCL had same PFS after RCHOP as HIV-ve cohort. 2yr OS and PFS 75%
- Factors associated with progression or death: poor PS, more than 1 EN site and high IPI
Prognostic factors

As summarized from the 5 studies cited above
- International Prognostic Index
- Prior AIDS-defining illness
- Complete response rate
  - Use of Rituximab
  - Concurrent ARVs

Cingolani et al (Plos 1 2017): Survival and predictors of death in people with HIV-associated lymphoma compared to those in the general population
- Older age and high IPI associated with increased risk of death
- Female sex associated with reduced risk of death
- “In NHL HIV was no longer an independent predictor of death after controlling for Rituximab use and IPI”
High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations

- Present with poor prognostic indicators eg high LDH, high IPI, BM and CNS involvement
- Inferior outcomes with standard R-CHOP
- Suggested treatment regimens:
  - DA-EPOCH-R
  - RHyperCVAD
  - R-CODOX-RM-IVAC
Plasmablastic lymphoma

- **Immunophenotype**
  - Positive: CD 138, CD 38, IRF4/MUM1, Ki 67>90%
  - Negative: CD20, CD45, PAX5

- **Allie et al (Oral Oncology 2017)**
  - Plasmablastic lymphoma is the commonest head and neck lymphoma diagnosed in HIV-positive patients at Wits
  - 1993-2012: 56% PBL, 43.9% DLBCL and 25% BL

- **GSH data presented 2013**
  - 46 HIV positive PBL seen from 2004-2012
  - Median OS St 1-2 (oral) 30 months vs 8 months for extraoral disease
Plasmablastic lymphoma treatment

  - 20 patients were HIV positive (11 HIV status unknown)
  - Patients who received CHOP had better OS than hyperCVAD (p=0.078)
  - Age, stage and EBV positivity were significant prognostic factors
- Pinnix et al (Clin Lymphoma Myeloma Leuk 2016)
  - 10 cases of stage 1 and 2 PBL, 2 HIV-positive
  - Doxorubicin-based chemo and ISRT resulted in 90% 2yr PFS and 100% 2yr OS
- Tchernonog et al (Annals of Oncology 2017): 135 patients, 56 HIV positive
  - Median OS 32 months
  - HIV positive had better OS
  - CR rate same for CHOP vs intensive chemo
  - IPI, chemotherapy and CR rate associated with survival benefit
Hodgkin Lymphoma

- 90% of cases associated with EBV
- Present with more advanced disease, extranodal involvement and bone marrow infiltration
  - L Swart et al GSH cohort 2005-2012: 61% bone marrow infiltration in HIV-positive HL; BMT provided diagnosis of HL in 17%
- Mixed cellularity and lymphocyte-depleted subtypes more common in HIV positive
- ABVD is treatment of choice
  - BEACOPP regimen not recommended due to myelotoxicity
- Adverse reactions due to drug interactions: Vinblastine and boosted PIs lopinavir/ritonavir inhibits CYP3A4
- PET-guided therapy is feasible
Role of Radiotherapy

- Follow ILROG guidelines
- Radical: Involved site radiotherapy as consolidation or for previously bulky disease
  - St 1 and 2 DLBCL treated with RCHOP
  - St 1 and 2 PBL treated with CHOP
  - 30-36Gy consolidation if CR after chemotherapy
- Palliative: relapsed or refractory disease
  - 40Gy if localized residual disease post chemo (not for HD salvage therapy)
  - Palliation: 3GyX10 or 4GyX5
Relapsed or refractory disease

- Patients compliant on ARVs with suppressed viral load, good PS, normal cardiac, pulmonary and renal function are considered for high-dose chemo and SCT

- Palliative chemotherapy

- Palliative radiotherapy

OS and PFS for HIV-infected and noninfected patients.

Antiretroviral and chemotherapy drug interactions

  - PI-based ART in patients receiving chemotherapy for lymphoma results in a lower 1 year survival when compared to NNRTI
  - Trend towards more bone marrow toxicity resulting in treatment delays and dose reductions in patients on PI-based ART
- PI’s inhibit CYP3A4 (necessary for metabolizing cytotoxics) resulting in increased drug exposure and toxicity
- PI’s include lopinavir/ritonavir (Kaletra), atazanavir etc
- NNRTI’s include efavirenze, nevirapine
- Fixed dose combination in SA: tenofovir (NtRTI), emtricitabine (NRTI) and efavirenze (NNRTI)
Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study

Foca et al HIV Medicine 2018: Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study, First published: 04 June 2018, DOI: (10.1111/hiv.12624)
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Foca et al HIV Medicine 2018: Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study, First published: 04 June 2018, DOI: (10.1111/hiv.12624)
To be or not to be HIV+, that is no longer the question

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In this issue of Blood, Noy et al report the outcomes of HIV-infected patients with Burkitt lymphoma (BL) treated with a modified cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC)-rituximab regimen that rival outcomes seen in HIV-uninfected patients.1
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And thank you to our many brave and wonderful patients

Groote Schuur Hospital