HIV Associated Lymphoma: Update 2017

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Las Vegas, NV
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Disclosure

I have nothing to disclose.
Infectious organisms can cause cancer
# 14th Report on Carcinogens

**Department of Health & Human Services, USA**

Released November 3, 2016

<table>
<thead>
<tr>
<th>Substance</th>
<th>Listing Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus type 1 (HIV-1)</td>
<td>Known to be a human carcinogen</td>
<td>Virus</td>
</tr>
<tr>
<td>Human T-cell lymphotropic virus type (HTLV-1)</td>
<td>Known to be a human carcinogen</td>
<td>Virus</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Known to be a human carcinogen</td>
<td>Virus</td>
</tr>
<tr>
<td>Kaposi sarcoma-associated herpes virus / HHV8</td>
<td>Known to be a human carcinogen</td>
<td>Virus</td>
</tr>
<tr>
<td>Merkel cell polyomavirus (MCV)</td>
<td>Known to be a human carcinogen</td>
<td>Virus</td>
</tr>
<tr>
<td>Trichloroethylene (TCE)</td>
<td>Known to be a human carcinogen</td>
<td>Industrial solvent</td>
</tr>
<tr>
<td>Cobalt and cobalt compounds that release cobalt ions in vivo</td>
<td>Reasonably anticipated to be a human carcinogen</td>
<td>A metal and its compounds</td>
</tr>
</tbody>
</table>
### International Agency for Research in Cancer (IARC)

Defines 10 organisms as well established carcinogenic agents in humans, and one (HIV-1) as a co-factor

<table>
<thead>
<tr>
<th>Organism</th>
<th>Attributable cancer(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opisthorchis and Clonorchis</td>
<td>Bile duct cancer</td>
</tr>
<tr>
<td>Schistosoma haematobium</td>
<td>Bladder cancer</td>
</tr>
<tr>
<td>H. Pylori</td>
<td>Non-cardia gastric cancer</td>
</tr>
<tr>
<td></td>
<td>Gastric cardia cancer</td>
</tr>
<tr>
<td></td>
<td>Gastric lymphoma</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Adult T cell leukemia / lymphoma</td>
</tr>
<tr>
<td>* HBV</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>* HCV</td>
<td>Liver cancer, lymphoma</td>
</tr>
<tr>
<td>* HPV</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td></td>
<td>Penile cancer</td>
</tr>
<tr>
<td></td>
<td>Vulvar cancer</td>
</tr>
<tr>
<td>* EBV</td>
<td>Hodgkins</td>
</tr>
<tr>
<td></td>
<td>NHL, Burkitt</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngeal cancer</td>
</tr>
<tr>
<td>* HHV8</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>Castleman’s related lymphoma</td>
</tr>
<tr>
<td></td>
<td>* HIV-I is a co-factor to ↑ risk.</td>
</tr>
</tbody>
</table>

* HIV-I is a co-factor to ↑ risk.
Epidemiology: Infection-Attributable Cancers

• In 2012, 14 million new cancer cases, globally
  – 15.4% attributable to organisms
    • < 5% in USA, Canada, Australia, New Zealand, some western & northern European countries
    • Overall, 25% of cancers in resource poor regions
    • Over 50% in sub-Saharan Malawai and Mozambique
• 92% of these cancers due to H. pylori, HPV, HBV, HCV
• These figures likely under-represent true incidence
• Must concentrate on prevention:
  – Vaccines (HPV, HBV)
  – Screen and treat strategies (HPV)
  – Anti-infectives (H. pylori, HCV, HIV)
Use of multiple (> 2) classes of agents to treat HIV/AIDS
GUIDELINES: DHHS

WHEN TO START ART

Recommended for **ALL** HIV-infected patients

- To prevent disease progression
- To prevent HIV transmission
  - Peri-natal (RCT)
  - Heterosexual (RCT)
  - All other risk groups (AIII)
“BIG PICTURE” STATE OF HIV / AIDS EPIDEMIC
March, 2017

• Continued effectiveness of combination anti-retrovirals
  – 25 agents now available
  – 14 combination pills with up to 4 drugs, taken once/day.
    Ex: Genvoya = Elvitravir, cobicistat, emtricitabine, tenofavir, alafenalate

• Over-all survival now approaches that of uninfected general population

• Concept of “cure” under study
  – Very early Rx of infected infants
  – SCT with insertion of HIV resistant genes
  – “Shock and kill” strategy re: latent HIV
  – MOAB against α 4β7 receptor on CD4’s

• No vaccine yet; re-testing of canary pox with HIV genes, followed by boost against gp120 – 31% efficacy in 16,000 Thai patients – now ongoing in South Africa (N = 5,400)

• Interest in vaccine to generate broadly neutralizing antibodies – slow progress

• Epidemic continues to ravage Africa
EPIDEMIOLOGY

MALIGNANCIES INCREASED AMONG HIV-INFECTED PERSONS

AIDS-Defining
- Kaposi’s Sarcoma
- High Grade B Cell Lymphoma
- Cervical Cancer

Non- AIDS Defining
- HPV-Related
  - Anal cancer
  - Oropharyngeal cancer
- HHV-8 Related
  - Castleman’s
- EBV-Related
  - Hodgkin’s lymphoma
- HCV / HBV Related
  - Liver cancer
- Lung Cancer
Relative Risk of AIDS Defining Cancers (ADC’s) in Era of HAART
Common causes of death in HIV-infected persons

(N = 3909)

AIDS deaths: ↓ 34-22%
Non AIDS cancers: ↑ 9-23%

Incidences and survival rates of AIDS lymphoma in USA (Seer Data) based on lymphoma type: 1990 - 2012

Ref: Howlander N, et al. CA EPI Biomarkers & Prev 2016; July 14; doi.10.1158/1055-9965.EPI-16-0273.
Changes in clinical context of KS and NHL among HIV infected patients in the USA

- KS or NHL diagnosed from 1996 – 2011
- Derived from 8 clinical cohorts

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>NHL</th>
<th>KS</th>
</tr>
</thead>
<tbody>
<tr>
<td>On ART &gt; 6 mos</td>
<td>3.4 fold ↑</td>
<td>710 fold ↑</td>
</tr>
<tr>
<td>CD4 &gt; 500</td>
<td>3.1 fold ↑</td>
<td>430 fold ↑</td>
</tr>
<tr>
<td>HIV RNA &lt; 500 copies/ml</td>
<td>2.9 fold ↑</td>
<td>430 fold ↑</td>
</tr>
</tbody>
</table>

↓ Risk of ADC’s continues

Infection-related vs. infection-unrelated cancers among HIV-infected persons
Effect of aging over time

* Incidence of both infection-related AND unrelated cancers increased with age.

<table>
<thead>
<tr>
<th>Factors associated with infection related cancers</th>
<th>Factors associated with non-infection associated cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts &lt; 50 Low CD4’s</td>
<td>Low CD4’s</td>
</tr>
<tr>
<td>Pts &gt; 50 Low CD4’s</td>
<td>Smoking</td>
</tr>
</tbody>
</table>

Forecast crude incidence rates of infection-related and infection-unrelated cancers (per 1000 PY’s) in 15,648 patients recruited before 2001 (EuroSIDA).

Cumulative incidence of AIDS-lymphoma among cART-naive (F/U = 13 mos) vs. cART-treated patients (F/U = 50 mos)

HBV + = 1,339 pts
HCV + = 7,507 pts

## Types of AIDS-Related Lymphomas with main viral and molecular factors associated with lymphoma genesis

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>Main Drivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell (DLBCL)</td>
<td>BCL-6, EBV / LMP-1</td>
</tr>
<tr>
<td>Burkitt Lymphoma</td>
<td>MYC, P53</td>
</tr>
<tr>
<td>Intermediate BL / DLBCL</td>
<td>MYC, BCL-2, (BLC-6)</td>
</tr>
<tr>
<td>Classical Hodgkins Lymphoma (cHL)</td>
<td>EBV / LMP1</td>
</tr>
<tr>
<td>Primary Effusion Lymphoma</td>
<td>HHV 8, EBV</td>
</tr>
<tr>
<td>Plasmablastic Lymphoma (PBL)</td>
<td>EBV, (MYC)</td>
</tr>
<tr>
<td>Primary CNS Lymphoma</td>
<td>EBV</td>
</tr>
<tr>
<td>Polymorphic B Cell Lymphoma (PTLD like)</td>
<td>EBV, LMP 1</td>
</tr>
</tbody>
</table>
Cell of Origin (COO) and Prognosis in 56 pts with HIV-DLBCL

Cell of Origin (COO) and Prognosis in HIV-DLBCL

Number 56 / 81

Treatment
AMC 010: CHOP vs R-CHOP
AMC034: R EPOCH vs EPOCH → R

Statistical differences in outcome in each of these studies

Method COO
Hans algorithm

GCB _________ 59%
Non-GCB ______ 41%

Factors associated with prognosis

Better survival
↑ K1-67

No Effect for
COO
EBV
Fox P1
Blimp 1
BCL-2

Cell of Origin (COO) and Prognosis

AIDS-DLBCL

Number of pts 29 / 33
Treatment Short Course (SC) EPOCH-RR
Method COO Hans algorithm

\[ \downarrow \]

GCB 72%
NON GCB 28%

Multi-Variate Analysis

Progression-Free Survival (↓)
COO – Non GCB

Over-all Survival (↓)
COO – Non GCB CD4 < 200

<table>
<thead>
<tr>
<th>Tumor Marker</th>
<th>HIV infected</th>
<th>HIV negative</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>80</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Advanced stage</td>
<td>48%</td>
<td>29%</td>
<td>0.01</td>
</tr>
<tr>
<td>Extranodal NHL</td>
<td>41%</td>
<td>11%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CT +/- XRT</td>
<td>88%</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>2 yr mortality</td>
<td>46%</td>
<td>16%</td>
<td>0.01</td>
</tr>
<tr>
<td>COO : GC type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>: Non-GC</td>
<td>51%</td>
<td>73%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>c-MYC</td>
<td>64%</td>
<td>32%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>BCL-6</td>
<td>45%</td>
<td>10%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CD30</td>
<td>24%</td>
<td>8%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>c-MYC + BCL2</td>
<td>25%</td>
<td>14%</td>
<td>0.07</td>
</tr>
<tr>
<td>c-MYC + BCL2 + BCL-6</td>
<td>8%</td>
<td>1%</td>
<td>0.05</td>
</tr>
<tr>
<td>Predictor: death at 2 yrs</td>
<td>c-MYC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Role of HIV-1, per se, in etiology of AIDS-related lymphoma

Main Drivers: Immunodeficiency related factors
- Oncogenic viruses
- Chronic antigenic stimulation
- Inflammatory cytokines

Potential Direct Effect of HIV-1: P17 (matrix protein of HIV-1) variants
- Insertions in C-terminal region induce structural destabilization of protein, acquiring new biologic properties conducive to lymphomagenesis
- Variants seen in ARL patients vs HIV without ARL
- Variant p17 activates PI3K/Akt pathways with proliferation and clonogenecity of B cells, mediated thru CXCR2, cellular receptor for p17

Tat protein
- 30% transgenic mice with Tat get NHL
- Tat’s IL6 and IL10
- Tat may interact with B cells in lymph tissue, leading to dysregulation of pRB/p130 oncosuppressor protein

CD40 Ligand: Co-stimulating molecule on activated T cells can be inserted at surface of HIV-1 when budding from activated CD4 cells
- Strongly activate B cells, which express Activation-Induced-Cytidine deaminase (AID) enzyme, which mediates Ig class switch and somatic hypermutation – AID induces
  - Point mutations in Ig and non-Ig genes (ex BCL-6)
  - Chromosome translocations

Role of microRNA’s in Pathogenesis of AIDS-lymphoma

Micro RNA = Short (18-25) nucleotides), non-coding double stranded RNA’s, which regulate post translational gene expression by
- inhibiting translation or
- promoting degradation of mRNA complementary sequences

Over-expression of miR 17-92 = common in all AIDS-lymphomas

Causes inhibition of p21 (a CKI, functions as regulator of cell cycle progression, at G1 & S

miR21 = most commonly over-expressed miRNA in cancer

Over-expressed in activated B cells induced by IL-4 alone or with co-stimulation induced by LPS

May help maintain B cell hyperactivation

Predictors of AIDS-Lymphoma

Low CD4 cells (< 200)

Uncontrolled HIV replication

↑ Serum free Ig light chains

↑ Serum cytokines / chemokines
  sCD27  sCD23  CXCL13  IL-6

↑ miR 21 in PB B cells (vs HIV⁺ controls or HIV⁻ NHL)
AIDS-Related Lymphoma

Treatment
## Treatment factors affecting outcomes in AIDS-related lymphoma

Pooled data from 1,546 patients from 19 prospective clinical trials

Statistically significant results

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PFS</th>
<th>Over-all survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant cART</td>
<td>↑</td>
<td></td>
<td>Trend ↑</td>
</tr>
<tr>
<td>Rituximab use</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Infusional EPOCH</td>
<td></td>
<td></td>
<td>↑ in DLBCL</td>
</tr>
<tr>
<td>Dose intensive vs CHOP Rx</td>
<td>↑</td>
<td></td>
<td>↑</td>
</tr>
</tbody>
</table>

Dose Adjusted EPOCH in AIDS-Lymphoma
Continuous Infusion over 96 Hours
NO ANTI-HIV Rx Until End of 6th Cycle of Chemo

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide</td>
<td>50 mg/m²/d</td>
<td>1-4</td>
</tr>
<tr>
<td>Oncovin</td>
<td>0.4 mg/m²/d</td>
<td>1-4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>10 mg/m²/d</td>
<td>1-4</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m²/d po</td>
<td>1-5</td>
</tr>
<tr>
<td>Cytoxan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 CD4</td>
<td>187 mg/m²</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 100 CD4</td>
<td>375 mg/m²</td>
<td>6</td>
</tr>
<tr>
<td>G-CSF</td>
<td></td>
<td>6 to ANC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5000</td>
</tr>
</tbody>
</table>

# Dose-Adjusted EPOCH in AIDS-NHL RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>CD4 &lt; 100</th>
<th>CD4 &gt; 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>39</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Median Age</td>
<td>40 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>67%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPI – 2/3 (age adjusted)</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Remission</td>
<td>74%</td>
<td>56%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Disease-Free Survival at 53 Months in 29 Patients in CR after da-EPOCH

Ref: Little RF, Pittaluga S, Grant N: Blood 2003; 101:4653.
Overall Survival on da-EPOCH, without ART
(N = 39; Median F/U = 53 months)

Ref: Little RF, Pittaluga S, Grant N: Blood 2003; 101:4653.
SHORT COURSE (SC) EPOCH-RR in AIDS-DLBCL

Results: Short course R-EPOCH-R in AIDS – DLBCL
Median F/U = 5 years

PATIENTS
N = 33; median age = 42; 76% = High-Int or Hi IPI

TREATMENT
Rituximab 375/n² day 1 and 5
IT MTX, 12 mgm/day: Days 1 and 5 of cycles 3-5 (6 total doses)
PJP and MAC prophylaxis

OUTCOME
79% needed only 3 cycles
PFS = 84%
OS = 68%

Only predictor of outcome = GC vs non GC

Outcome – AIDS DLBCL s/p SC EPOCH-RR
(N = 33; Median F/U = 5 yrs)

HIV Parameters: SC EPOCH-RR in HIV-DLBCL

Burkitt Lymphoma
Treatment Strategies

- Multiple agents, high doses, in alternating cycles
- Ex: CODOX-M; CODOX-M IVAC
- Good efficacy but high toxicity
NCI 9177 - Eligibility

- Untreated Patients
- Age ≥ 18 years
- Histologically confirmed Burkitt Lymphoma
- HIV negative and positive
- Low-risk and high-risk groups

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
Risk-Adapted DA-EPOCH-R in BL

Low-Risk

High-Risk

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
Risk-Adapted DA-EPOCH-R in BL

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
<table>
<thead>
<tr>
<th>Characteristics*</th>
<th>All</th>
<th>LR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>88</td>
<td>11</td>
<td>77</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>46y (18-78)</td>
<td>38y (19-62)</td>
<td>47y (18-78)</td>
</tr>
<tr>
<td>≥ 40 Y</td>
<td>57%</td>
<td>45%</td>
<td>58%</td>
</tr>
<tr>
<td>≥ 60 Y</td>
<td>25%</td>
<td>9%</td>
<td>27%</td>
</tr>
<tr>
<td>Male Sex</td>
<td>82%</td>
<td>64%</td>
<td>84%</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>64%</td>
<td>0</td>
<td>73%</td>
</tr>
<tr>
<td>High LDH</td>
<td>56%</td>
<td>0</td>
<td>64%</td>
</tr>
<tr>
<td>ECOG ≥ 2</td>
<td>18%</td>
<td>0</td>
<td>21%</td>
</tr>
<tr>
<td>Extra-nodal disease</td>
<td>50%</td>
<td>23%</td>
<td>58%</td>
</tr>
<tr>
<td>CNS disease</td>
<td>13%</td>
<td>0</td>
<td>15%</td>
</tr>
<tr>
<td>HIV Positive</td>
<td>24%</td>
<td>0</td>
<td>27%</td>
</tr>
</tbody>
</table>

*From 24 sites

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
Progression-Free Survival

Median follow-up 25 months

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
Overall Survival

86%

Median follow-up 25 months

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
Outcome by Risk Group - Low versus High

**DFS OVERALL SURVIVAL**

- Low-Risk: 81%
- High-Risk: 100%

P = 0.16

Median follow-up 25 months

**Ref:** Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
Outcome by HIV Status

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
Toxicity

- 3 on-treatment infectious deaths in HR arm
  - 72 y male: cycle 1
  - 59 y male: cycle 1
  - 52 y female: cycle 4

- Administered as out-patient where feasible

Ref: Dunleavy K, et al. (AMC-086 & CTSU #9177) ASH, 12/2015.
AIDS-Related NHL
Options at Relapse
Autologous hematopoietic cell transplant (SCT) in patients with relapsed or persistent AIDS-lymphoma. Prospective study of BMT-Clinical Trials Network (BMT-CTN) and AIDS Malignancy Consortium (AMC)

ISSUES ADDRESSED

Salvage chemo followed by SCT results in long term disease-free survival (or “cure”) in approximately 60 - 70% of HIV UNinfected patients

WHAT IS OUTCOME IN HIV-INFECTED?
- Survival
- Time to progression
- Progression-free survival
- Mortality from SCT
- Time to heme recovery

SPECIAL CONSIDERATIONS
- Conditioning regimen (BEAM)
- How to choose cART
- When to stop/start cART
- Are CD34 cells normally mobilized
- Immunologic recovery
- HIV virologic changes
- Unique toxicities or adverse events

Autologous progenitor cell transplant in 40 HIV-infected patients
BMT-CTN 0803 +AMC 071 Prospective Study

**Entry Criteria**

HIV infected
Over 15 yrs old
KPS > 70%

Relapsed or persistent disease:
- Diffuse large B cell
- Plasmablastic
- Burkitt or Burkitt-like
- Hodgkin’s

BM involvement < 10% after most recent salvage

Less than 4 prior therapies; ≤ 2 prior salvage regimens

MOAB or XRT “counted” as regimens

Chemo sensitive – some response to last regimen

Adequate mobilization of progenitor cells (> 1.5 x 10^6 CD34^+ / kg)

Autologous stem cell transplant in 40 HIV-infected patients
BMT-CTN 0803 + AMC 071 Trial

Method of cART use during transplant

• Review cART regimen before treatment for possible interactions
  – Ritonavir boosted PI’s: Problematic as strong CYP 3A4 inducers. Stop prior to conditioning regimen.
  – Do not use AZT: myelosuppressive
  – Stop efavirenz > 2 weeks from treatment: Long T-1/2 - washout
  – Integrase inhibitors effective, better tolerated than PI’s or non-NUC RTI’s (Torres HA, et al. Clin Microb Infect 2014; 20:672-79)
• cART uniformly stopped at start of conditioning and resumed ≥ 7 days post BEAM, or after recovery from Rx related GI toxicity
  – Median duration cART interruption = 15.5 days (11 – 40)

Autologous progenitor cell transplant in 40 HIV-infected patients with relapsed / persistent AIDS-lymphoma
BMT-CTN 0803 +AMC 071 Trial

**Hematopoietic Function**

<table>
<thead>
<tr>
<th>Mobilization of Progenitors</th>
<th>Adequate in 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEAM Conditioning Regimen</td>
<td>Days -6 to -1</td>
</tr>
<tr>
<td>Transplant</td>
<td>Day 0</td>
</tr>
<tr>
<td>- Median HPC dose received</td>
<td>3.9 x 10^6 CD34</td>
</tr>
<tr>
<td></td>
<td>(1.6 – 11 / kgm)</td>
</tr>
<tr>
<td>Median Neutrophil recovery</td>
<td>11 days</td>
</tr>
<tr>
<td>Median Platelet recovery</td>
<td>18 days</td>
</tr>
<tr>
<td>Recovery of Hematopoietic Function</td>
<td>Day + 100 = 29%</td>
</tr>
<tr>
<td></td>
<td>Day + 365 = 74%</td>
</tr>
</tbody>
</table>

Over-all and progression free survival in 40 patients s/p AuSCT for ARL or HIV- Hodgkins (BMT / CTN 083 + AMC 071 Trial)

SURVIVAL

Month 12 = 87.3%
Month 24 = 82%

PFS & TTP

Month 12 = 82.4%
Month 24 = 76.8%

Survival and progression-free survival in 40 HIV-infected patients on BMT / CTN 0803 + AMC 071 vs. 151 matched HIV-negative controls from CIBMTR Registry

Autologous progenitor cell transplant in 40 HIV-infected patients with relapsed or persistent lymphoma
BMT-CTN 0803 +AMC 071 Trial

Toxicities and Mortality

Infections → • 22 pts (55%) had 57 infections in yr post-Tx
• 11 pts (27%) had severe infections
• One death due to infection (fungal)
• No case of pneumocystis jiroveci

Organ Toxicities → • Cardiac arrest in one (death)
• Grade 4 events in 3 pts; Grade 3 in 10

Mortality → 5.2% TRM at one year
• Cardiac arrest in one
• Fungal infection in one

→ 3 deaths secondary to NHL (yr 1); one in year 2

CD4 cell reconstitution after AuSCT
BMT-CTN 0803 + AMC 071 Trial

HIV viral load over time, s/p AuSCT in BMT-CTN 0803 + AMC 071 Trial

<table>
<thead>
<tr>
<th>Time</th>
<th>Non-detectable (%)</th>
<th>Detectable</th>
<th>Median VL in Detectables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>32 (80%)</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Day 100</td>
<td>19 (70%)</td>
<td>8</td>
<td>298</td>
</tr>
<tr>
<td>Day 180</td>
<td>20 (69%)</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>Day 365</td>
<td>19 (83%)</td>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>Day 730</td>
<td>21 (80%)</td>
<td>5</td>
<td>130</td>
</tr>
</tbody>
</table>

Hodgkin’s Lymphoma
Associated with HIV
Hodgkin’s Disease in HIV Infected Patients

- **Statistically increased in HIV**
  - Further increase in era of HAART

- **Pathology**
  - Mixed cellularity most common
  - Associated with EBV in RS cells

- **Clinical**
  - Present with systemic “B” symptoms +/- pancytopenia
  - Marrow involvement in 50-60%
  - Median survival about 1.5 years after CT, prior to HAART
  - Median survival substantially higher with HAART and CT
  - Death often due to infection

Over-all Survival in 45 Patients with HIV-Related Hodgkin’s Disease, as a Function of HAART Use

83% at 4 yrs with HAART

13% at 4 yrs without HAART

OPTIMAL THERAPY FOR HIV-RELATED HODGKIN’S

ABVD with HAART
(Doxorubicin, Bleomycin, Vinblastine, DTIC)

<table>
<thead>
<tr>
<th></th>
<th>HIV positive</th>
<th>HIV negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>74%</td>
<td>79%</td>
</tr>
<tr>
<td>5 yr EFS</td>
<td>60%</td>
<td>66%</td>
</tr>
<tr>
<td>5 yr survival</td>
<td>80%</td>
<td>88%</td>
</tr>
</tbody>
</table>