Management of Peripheral T-Cell Lymphoma

Doug Stewart, MD
Tom Baker Cancer Centre
University of Calgary
<table>
<thead>
<tr>
<th>Conflict of Interest</th>
<th>Disclosures</th>
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<tr>
<td>Research Support-IRR</td>
<td>Roche, Sanolfi</td>
</tr>
<tr>
<td>Employee</td>
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<td>N/A</td>
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<td>Major Stockholder</td>
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<td>Honoraria</td>
<td>Roche, Lundbeck, Novartis, Celgene, Amgen, Gilead, Adienne</td>
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T-Cell Lymphomas

Objectives

● General Overview
  – Sorting through the confusion
● Anecdotal Learning Cases
  – Might help… possibly
● Take home messages
  – A few things
● Future research
  – Lots to do
Classification of T-cell Lymphomas

- Leukemic or disseminated
  - Adult T-cell Lymphoma/Leukemia (HTLV1+)
  - Prolymphocytic, LGL, NK-cell Leukemias

- Extranodal Cutaneous
  - Mycosis fungoides, Sezary syndrome
  - Cutaneous CD30+ Lymphomas (ALCL, LP)

- Extranodal-Other
  - NK/T-cell lymphoma, nasal type
  - Enteropathy associated
  - Hepatosplenic T-cell lymphoma
  - SC panniculitis-like

- Nodal
  - Peripheral T-cell NOS
  - Angioimmunoblastic
  - Anaplastic Large Cell (ALK+ or ALK-)
<table>
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<tr>
<th>Diagnosis</th>
<th>N America</th>
<th>Europe</th>
<th>Asia</th>
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<td>PTCL-NOS</td>
<td>34.4%</td>
<td>34.3%</td>
<td>22.4%</td>
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<tr>
<td>Angioimmunoblastic</td>
<td>16.0%</td>
<td>28.7%</td>
<td>17.9%</td>
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<tr>
<td>ALCL, ALK+</td>
<td>16.0%</td>
<td>6.4%</td>
<td>3.2%</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>7.8%</td>
<td>9.4%</td>
<td>2.6%</td>
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<tr>
<td>NKTCL</td>
<td>5.1%</td>
<td>4.3%</td>
<td>22.4%</td>
</tr>
<tr>
<td>ATLL</td>
<td>2.0%</td>
<td>1.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Enteropathy-type</td>
<td>5.8%</td>
<td>9.1%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Hepatosplenic</td>
<td>3.0%</td>
<td>2.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1° Cutaneous ALCL</td>
<td>5.4%</td>
<td>0.8%</td>
<td>0.7%</td>
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<td>Subcu Panniculitis</td>
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<td>0.5%</td>
<td>1.3%</td>
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<td>Unclassifiable</td>
<td>2.3%</td>
<td>3.3%</td>
<td>2.4%</td>
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Expert Agreement: Consensus Diagnosis

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<th>Diagnosis</th>
<th>Agreement</th>
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<tr>
<td>ALCL, ALK+</td>
<td>91%</td>
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<tr>
<td>ATLL</td>
<td>93%</td>
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<tr>
<td>Nasal NKTCL</td>
<td>84%</td>
</tr>
<tr>
<td>AITL</td>
<td>81%</td>
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<td>Enteropathy-type</td>
<td>79%</td>
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<tr>
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<td>74%</td>
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<tr>
<td>Panniculitis-like</td>
<td>75%</td>
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<tr>
<td>ALCL, ALK-</td>
<td>74%</td>
</tr>
<tr>
<td>Hepatosplenic</td>
<td>72%</td>
</tr>
<tr>
<td>Cutaneous ALCL</td>
<td>66%</td>
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- Consecutive series 1990-2002, non-MF, All reviewed at 5 sites

<table>
<thead>
<tr>
<th>Sites</th>
<th># Sites</th>
<th>Cases</th>
<th>%</th>
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<tr>
<td>N Am</td>
<td>6</td>
<td>333</td>
<td>25.2</td>
</tr>
<tr>
<td>Europe</td>
<td>7</td>
<td>452</td>
<td>34.2</td>
</tr>
<tr>
<td>Far East</td>
<td>8</td>
<td>535</td>
<td>40.6</td>
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Comparison of referring and final pathology for patients with T-cell lymphoma in the National Comprehensive Cancer Network.

- 131 eligible pts
- 89 with final and 42 with provisional diagnosis
- 57 (44%) had concordant results
  - 64% of those referred with a final diagnosis
- 32 pts (24%) had discordant results
  - 36% of those referred with a final diagnosis
- Rates of discordance: PTCL-NOS=19%, AITL=33%, ALK-negative ALCL=34%, ALK-positive ALCL=6%
- 14 pts, reclassification could have altered treatment
5y OS:
- ALK+ ALCL 70%
- ALK- ALCL 50%
- PTCL-NOS, AITL
- NK/T Cell 35%
- ATLL 15%
Prognosis - IPI

DLBCL

PTCL-NOS

Vose et al (ITCP). JCO. 2008
Ziepert et al. JCO. 2010
Prognosis - PIT

- Prognostic Index for PTCL-U (PIT) score
  - retrospective review of 385 cases of PTCL-U identified 4 adverse prognostic factors:
    - Age, PS, LDH, BM involvement

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<th>Group</th>
<th># adverse risk factors</th>
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<tr>
<td>1</td>
<td>0</td>
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<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>3-4</td>
</tr>
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</table>

Gallamini et al. Blood. 2004
Prognosis - PIT

5y OS:
Group 1 – 62%
Group 2 – 53%
Group 3 – 33%
Group 4 – 18%

Gallamini et al. Blood. 2004
Prognosis: the modified PIT (mPIT)

- **Univariate analysis**
  - $\text{Ki-67} \geq 80\%$, EBER, CD15, CD57

- **Multivariate analysis**
  - $\text{Ki-67} \geq 80\%$

- **Clinico-pathologic prognostic index**
  - $\text{Ki-67}$, PS, LDH, Age
  - Group 1: 0-1 factors
  - Group 2: 2 factors
  - Group 3: 3-4 factors

Went et al. JCO. 2006
PTCL Treatment Red Flags

• Treatments are based on retrospective reviews and phase II prospective data – not RCTs
• Treated similarly despite disease heterogeneity
• Treatments result in poor outcomes

CONCLUSION: We do NOT know how best to treat these diseases!
Lymphoma Treatment Advances that Improved Rates of Survival

Ortho/Megavoltage Radiotherapy for Limited Stage Lymphoma

Combination Adriamycin-based ChemoRx for Aggressive Lymphoma (CHOP, ABVD)

High Dose Therapy & Autologous SCT for Relapsed Lymphoma

Rituximab plus Chemotherapy For B-cell NHL (R-CHOP)

Dates of Pivotal Publications Resulting in Widespread Rx Implementation
SIE-SIES-GITMO guidelines for the management of adult peripheral T and NK cell lymphomas. P. Corradini, Ann Oncol epub Apr 2014

- **Nodal, intestinal, hepatosplenic TCL (not ALK+ALCL)**
  - Age $\leq 65$y: CHOP or CHOEP x6 then ASCT.
  - Age $> 65$y, CHOP or CHOPlike x6.
    - if fit, HDCT/ASCT can be considered.

- **ALK+ ALCL with IPI<3, CHOP or CHOEP x6 (no ASCT)**

- **NK/TCL nasal type:**
  - localized: IFRT 50 Gy to tumor and adjacent structures
  - systemic: L-asparaginase-based regimens (eg. SMILE).
    - ASCT should be considered during CR1.
    - IFRT to bulk or residual disease.
EMSO guidelines for the management of adult peripheral T and NK cell lymphomas.

- **Nodal TCL**
  - CHOP/CHOEP then if poor-risk TCL (IPI or PIT ≥2) ASCT in PR/CR1

- **Enteropathy-associated T-cell lymphoma (EATL)**
  - Scottish Lymphoma Group regimen
    - Ifos/Epi/Etop then ASCT

- **NK/TCL nasal type**
  - L-asparaginase and local radiotherapy
A Few Calgary Cases...
ALCL ALK+ Case

Aug 1999:
- 61yo man
- SOB, fevers, night sweats, 20lb wt loss
- large mediastinal mass: thoracotomy ALCL ALK+
- ECOG = 2
- BMBx +ve, LDH 1354
- PE Sept 1999: coumadin, then IVC filter
- PMHx: DM, hypothyroidism, HTN, OA

- 61yo man, Stage IVB, IPI=4
- What treatment would you recommend?
ALCL Case

- 61yo man, Stage IVB ALCL, IPI=4
- Treated with CHOP x 6 ending Dec 1999
- Last FU Mar 2009 (never relapsed)
  - Now on dialysis for diabetic nephropathy
ALCL ALK+

- Presentation:
  - Most common age < 40yo, (vs 40-65 ALK-) M:F 1.5:1
  - 70% Stage 3-4 (peripheral/abdo LN, marrow, END)
  - 75% B sx (esp fever)

- Morphology:
  - Large cells, abundant cytoplasm, kidney/horseshoe nuclei
  - Patterns: Common (large) 60%, Lymphohistiocytic (10%), Small cell (5-10%), Hodgkin-like (3%), Composite (15%)
  - CD2+, CD3-, CD4+, CD5+, CD8+, CD30+, ALK+, EMA+
  - 84% t(2;5)(p23;q35) ALK/NPM, 13% t(1;2)(q25;p23) TPM3

- 5yr OS 70% ALK+ vs 35% ALK- ALCL vs 20% PTCL
>50% Anaplastic Large Cell Lymphomas (ALCL) express ALK – t(2;5)(p23;q35) ALK gene chr 2 fuses with NPM on chr 5

ALK-positive LBCL: t(2;17)(p23;q23) Clathrin-ALK fusion

Crizotinib oral inhibitor of ALK and MET tyrosine kinases

Crizotinib 250 mg BID to 11 ALK+ lymphoma patients – 9 ALCL, 2 LBCL rel/refr at least 1 prior chemotherapy

ORR 10/11 (91%), CR 9/11 (82%) – ALK+ LBCL: 2/2 died within 3 months – ALCL: CR 9/9

3 yr PFS 62%, OS 73%

PTCL NOS case

- Oct 1999: 55yo woman, Hx MGUS x 10yrs
  - 2cm skin lesion on Rt breast: Bx PTCL NOS
  - Path review: CD30-, not panniculitis-like TCL
- P/E, CT CAP, BMBx all normal (resected Stage IAE)
- CHOP x3 then IFRT to breast & Ax/SC LN 35Gy/20
- Treatment completed Mar 2000.

- July 2000: skin lesions below Lt clavicle, mid-back, rt forearm. Bx; PTCL-NOS
- CT: numerous SC lesions in chest wall, abdomen and buttock. LN and spleen normal. Small pleural effusion.
- What treatment would you recommend?
PTCL NOS case

- Aug 2000: Dose intensive CEP salvage chemo - PR
- Sept 2000: BEAM/ASCT - CR
- Sept 2009: no evidence relapse
  - Still Mpr 6.3g/L IgG on SPEP
PTCL-NOS: Clinical Presentation

- Majority present with advanced disease
  - 69% stage III/IV disease
  - 21% bone marrow involvement
- B symptoms (35%)
- Nodal + extranodal involvement – 49%
  - Nodal alone – 38%
  - Extranodal alone – 13%
- Extranodal sites
  - BM (21%), liver (17%), spleen (24%)
  - Skin (16%), subcutaneous tissue (6%), lung (8%)
  - CNS less common
- It is important to rule out other entities, especially with skin involvement!

Weisenburger et al. Blood. 2011
WHO. 2008
CHOP for T-cell lymphomas
Some Generalizations (Exaggerations)

• Always Use
  – ALCL, ALK+

• Sometimes works
  – ALCL ALK-, PTCL-NOS, AITL, Enteropathy-type, Subcutaneous panniculitis-like T-cell

• Never works
  – MF, SS, T-cell large granular lymphocytic, ATLL, extranodal NKTCL, hepatosplenic TCL, T-cell prolymphocytic leukemia.

• Never Needed
  – primary cutaneous CD30+ ALCL/LP.
Patients with PTCL enrolled on prospective trials of the German High-Grade NHL study group treated with either CHOP or CHOEP

- **Age $\leq 60y$ & normal LDH, etoposide ↑ 3-yr EFS 75.4% vs. 51.0%**

Schmitz Blood 2010 116:3418-3425
HOVON prospective phase II trial
Alemtuzumab (anti-CD52) plus CHOP

- 20 pts (10 PTCL-NOS), CHOP14 x8,
  - Alemtuzumab 30 mg days 1, 5, 10 with G-CSF
  - CMV weekly monitoring
  - Acyclovir, Septra and fluconazole prophylaxis
- ORR 85%, mFFS 20mo, mOS 23mo
- CMV reactivation 35%, Hospitalizations 40%, EBV+ LPD 15%

Other studies similar: high toxicity and uncertain benefit
Kim: Cancer Chemother Pharmacol. 2007
Binder : Ann Hematol. 2013

Kluin-Nelemans et al. (HOVON) Ann Oncol. 2011
Bortezomib + CHOP for PTCL

- 46 pts
- CHOP21 x6 with Bortezomib d1,8
- ORR 76% (only 30% in NK/T cell)
- Toxicity acceptable:
  - Neutropenia most common gr 3-4 toxicity
  - Neuropathy mostly gr 1-2

Kim: ASH 2010, abstr 1791
Novel Regimens for PTCL

- **GlfOx** (Gemcitabine, Ifosfamide, Oxaliplatin)
  - 21 pts, CR 67%
  - 5yr EFS 49%
  - mOS 30.5mo
    - Corazzelli, ASH 2010, abstr 2829

- **CycloBEAP** (CHOP-like plus Bleo and Etoposide)
  - 84 pts, CR 92%
  - 5yr PFS 61%
  - 5yr OS 72%
    - Nitsu, Br J Hem 2011;153: 582-8
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<th>NCT #</th>
<th>Title</th>
<th>Setting</th>
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<td>ECHELON-2 <strong>Randomized</strong></td>
<td>01777152</td>
<td>A Comparison of Brentuximab Vedotin and CHP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas</td>
<td>Induction *Upfront consolidation with ASCT is allowed</td>
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<tr>
<td>Ro-CHOP <strong>Randomized</strong></td>
<td>01796002</td>
<td>Phase 3 Multi-center Randomized Study to Compare Efficacy and Safety of Romidepsin CHOP (Ro-CHOP) Versus CHOP in Patients WithPreviously Untreated Peripheral T-Cell Lymphoma</td>
<td>Induction</td>
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<td>A-CHOP-14</td>
<td>00725231</td>
<td>Immunotherapy in Peripheral T Cell Lymphoma - the Role of Alemtuzumab in Addition to Dose Dense CHOP</td>
<td>Maintenance</td>
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<td>Pralatrexate <strong>Randomized</strong></td>
<td>01420679</td>
<td>Study of Pralatrexate Versus Observation Following CHOP-based Chemotherapy in Previously Undiagnosed Peripheral T-cell Lymphoma Patients</td>
<td>Maintenance</td>
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Abbreviations: PTCL: peripheral T-cell lymphoma; NCT: national clinical trial;
PTCL patients transplanted in first CR do better

<table>
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<tr>
<th>Study</th>
<th>N</th>
<th>PTCL-NOS</th>
<th>SCT</th>
<th>mAge</th>
<th>EFS/PFS</th>
<th>OS</th>
<th>TRM</th>
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<tr>
<td>D’Amore. 2012.</td>
<td>160</td>
<td>62</td>
<td>115 (72%)</td>
<td>57</td>
<td>5y 44%</td>
<td>5y 51%</td>
<td>4%</td>
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<tr>
<td>Reimer. 2008.</td>
<td>83</td>
<td>32</td>
<td>55 (66%)</td>
<td>46.5</td>
<td>3y 36%</td>
<td>3y 48%</td>
<td>3.6%</td>
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<tr>
<td>Rodriguez 2007.</td>
<td>26</td>
<td>11</td>
<td>19 (73%)</td>
<td>44</td>
<td>3y 53%</td>
<td>3y 73%</td>
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<tr>
<td>Corradini. 2006.</td>
<td>62</td>
<td>28</td>
<td>46 (74%)</td>
<td>43</td>
<td>12y 30%</td>
<td>12y 34%</td>
<td>4.8%</td>
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<tr>
<td>Mercadal. 2008.</td>
<td>41</td>
<td>20</td>
<td>17 (41%)</td>
<td>47</td>
<td>4y 30%</td>
<td>4y 39%</td>
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^ ALK+ ALCL included
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<tr>
<th>(Single) Agent</th>
<th>Pts</th>
<th>ORR</th>
<th>CR</th>
<th>PFS (mos)</th>
<th>DoR (mos)</th>
<th>OS (mos)</th>
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</thead>
<tbody>
<tr>
<td>Romidepsin (JCO 2012)</td>
<td>130</td>
<td>25%</td>
<td>15%</td>
<td>4</td>
<td>17</td>
<td>11.3</td>
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<tr>
<td>Belinostat (BELIEF–ASCO a2013)</td>
<td>129</td>
<td>26%</td>
<td>10%</td>
<td>-</td>
<td>8.3</td>
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<td>Pralatrexate (PROPEL – JCO 2011)</td>
<td>111</td>
<td>29%</td>
<td>13%</td>
<td>3.5</td>
<td>10.5</td>
<td>14.5</td>
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<tr>
<td>Bendamustine (BENTLY – JCO 2013)</td>
<td>60</td>
<td>50%</td>
<td>28%</td>
<td>3.6</td>
<td>3.5</td>
<td>6.2</td>
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<tr>
<td>Brentuximab (Blood 2014)</td>
<td>35</td>
<td>41%</td>
<td>22%</td>
<td>6.7</td>
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<td>Gemcitabine (Ann Oncol 2012)</td>
<td>20</td>
<td>55%</td>
<td>30%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Alemtuzumab (Blood 2004)</td>
<td>14</td>
<td>36%</td>
<td>14%</td>
<td>-</td>
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<tr>
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<th>Pralatrexate ORR</th>
<th>Pralatrexate CR</th>
<th>Romidepsin ORR</th>
<th>Romidepsin CR</th>
<th>Belinostat ORR</th>
<th>Belinostat CR</th>
<th>Brentuximab ORR</th>
<th>Brentuximab CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL-NOS</td>
<td>31%</td>
<td>29%</td>
<td>23%</td>
<td>33%</td>
<td>8%</td>
<td>54%</td>
<td>86%</td>
<td></td>
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<tr>
<td>AITL</td>
<td>8%</td>
<td>30%</td>
<td>46%</td>
<td></td>
<td>54%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ALCL</td>
<td>29%</td>
<td>24%</td>
<td>15%</td>
<td></td>
<td></td>
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# Role of Auto/Allo SCT in R/R Disease?

<table>
<thead>
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<th>Study</th>
<th>Design</th>
<th>N</th>
<th>PTCL NOS/U</th>
<th>Auto SCT</th>
<th>Allo SCT</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>Rodriguez. JCO 2001</td>
<td>Retro</td>
<td>36</td>
<td>-</td>
<td>29</td>
<td></td>
<td>3y 28%</td>
<td>3y 36%</td>
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<tr>
<td>Rodriguez. Ann Oncol 2003</td>
<td>Pro</td>
<td>115</td>
<td>72</td>
<td>37 – CR1 78 – CR2</td>
<td>-</td>
<td>5y 49% (DFS)</td>
<td>5y 45%</td>
</tr>
<tr>
<td>Smith. BMT 2007</td>
<td>Retro</td>
<td>32</td>
<td>11</td>
<td>6 – CR1 25 – CR2</td>
<td>17 - RIC</td>
<td>5y 18% (RFS)</td>
<td>5y 34%</td>
</tr>
<tr>
<td>Corradini. JCO 2004</td>
<td>Pro</td>
<td>17</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le Gouill. JCO 2008</td>
<td>Retro</td>
<td>77</td>
<td>27</td>
<td></td>
<td></td>
<td>5y 53% (EFS)</td>
<td>5y 57%</td>
</tr>
<tr>
<td>Jacobsen. Ann Oncol 2011</td>
<td>Retro</td>
<td>52</td>
<td>20</td>
<td></td>
<td>31 – MA 21 – RIC</td>
<td>3y 30% (41% nodal)</td>
<td>3y 41%</td>
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<tr>
<td>Goldberg. Leuk Lymph 2012</td>
<td>Retro</td>
<td>34</td>
<td>7</td>
<td></td>
<td></td>
<td>2y 50%</td>
<td>2y 61%</td>
</tr>
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</table>
Angioimmunoblastic T-cell Lymphoma

AITL Case

- 1994:
  - 33yo man Dx with Stage IIIB T-cell “immunoblastic lymphoma” involving generalized nodes and spleen. CR after CHOP x6.
  - CHOP was complicated by PCP.

- 1996-1999:
  - Waxing and waning nodes, two biopsies non-diagnostic.

- 1998:
  - treated with IVIG and steroids for ITP.

- April 2000:
  - progressive inguinal adenopathy, generalized pruritis, B sx, fatigue resulting in inability to work (ECOG=2).
  - IgG=22 (6.8-18), IgA=6.6 (0.6-4.2), IgM 4.2 (0.5-3)
  - Node Bx: T-cell angioimmunoblastic lymphoma, (AILD-type).
    - T-cell receptor gene rearrangements detected.
Aug 11, 2000:
- High dose Busulfan/Fludara-ASCT
- Fully engrafted and all nodes resolved.

Sept 25, 2000:
- Fever, arthralgias, headache, malaise, fatigue, nausea.
- P/E: generalized adenopathy, massive splenomegaly.
- CBC: Hb 83, WBC 0.6, ANC 0.2, plt 27
- B12/folate normal.
- CMV Antigen negative. Parvovirus serology normal.
- CT CAP: generalized nodes, +++ splenomegaly.
- Marrow BX: no lymphoma, all cell lines present.
- Treated for ITP with steroids + IVIG: no response
Sept 30, 2000 Cervical LN BX:
- B-cell post-transplant lymphoproliferative disorder,
- IgH gene rearrangement
- High levels of EBV DNA
- PR to IVIG, ganciclovir, steroids, interferon.
- CR to Rituxan x 8 wks.
- CBC slowly improved.
• Dec 2000:
  – **PCP** (non-compliant with prophylaxis).

• March 22, 2001:
  – Rapidly progressive 13 x 9cm left neck mass and impending airway obstruction. Afebrile.
  – **CBC:** Hb 100, plt 126, WBC 3.1, ANC 2.5.

• March 2001:
  – Taken to OR.
  – *S aureus* neck abscess
  – Treated with I&D, prolonged antibiotics.
Nov 2001:
- recurrent multiple small (0.5-2cm) general adenopathy
- LN Bx: **AILD-type T-cell lymphoma**. No treatment given
- Nodes waxed and waned since the fall 2001.
- July 2002 CBC: Hb 146, WBC 4.0, plt 159, LDH 141.

Oct 2002:
- Fever, malaise, ↑ 3-4cm nodes neck, axillae and groin,
- Splenomegaly 2cm BCM.
- Hb 124, WBC 3.0, plt 96, LDH 543.

What to do?? (declined MUD alloSCT)
Oct 2002: weekly MTX chemotherapy
Feb 2003: Interferon – did not tolerate
Mar 2003: Fludarabine Mitoxantrone (intolerant to Dex)
May 2003: left inguinal RT 20Gy/5
Jun 2003: low dose CVP x8 (plt 43): PR, plts inc to 100
Dec 2003: dose reduced GDPx6: PR
July 2004: ECOG=3, B sx: Prednisone 50mg q2d: PR
Dec 2004: died
Angioimmunoblastic T-Cell Lymphoma

- Clinical:
  - Usually >55yo (but wide range)
  - Generalized lymphadenopathy (90%)
  - Fever, sweats wt loss (80%)
  - Skin rash, pruritus, effusions
  - Hepatosplenomegaly (65%)
  - Immunosuppression: CMV, PCP, TB, others
  - High risk infections with treatment
  - Secondary EBV+ and EBV- B-cell LPDs reported

- Lab
  - Anemia (75%)
  - Hemolytic anemia, cold agglutinins, ITP, RF+
  - Elevated LDH (85%)
  - Polyclonal hypergammaglobulinemia (65%)
Extranodal NK/T-cell lymphoma, nasal type, EBV+, Stage IIB, 66yo

- Oct 2010 66yo man originally from Haiti
  - recurrent sinus infections since October 10, 2009.
  - lost 30 pounds in the last two years unintentionally.
  - Multiple ENT drainage of sinuses and antibiotics
- ENT biopsy
  - polypectomy, right maxillary antrostomy, right ethmoidectomy, right frontal sinusotomy
  - Pathology reviewed by NIH.
- Dx: extranodal NK/T-cell lymphoma, nasal type, EBV positivity.
Extranodal NK/T-cell lymphoma, nasal type, EBV+, Stage IIB, 66yo

- Nov 2010: Radiotherapy 3000 cGy in 10 fractions
- Nov 2010-Apr 2011: CHOP x5 cycles
- June 2011: Relapsed in bone (tibias and femurs)
- Aug-Oct 2011- SMILE x3: clinical response but PD by MRI
- Dec 28, 2011: BEAM / ASCT
- Feb 21, 2012: PET/CT: Metabolic complete response.
- July 2014: Continued remission
Extranodal NK/T cell Lymphoma, Nasal Type

- Asia, Native American pop (Mexico, Central & S. Am)
- Strong assoc with EBV, subtype A with type II latency
  - EBNA1+, EBNA2-, LMP+ (plasma EBV QPCR useful)
- Presentation:
  - Nasal obstruction, epistaxis, mid-facial destruction
  - May disseminate to skin, GIT, neck LN. HPS possible.
- Pathology:
  - Ulceration, necrosis, angiodestructive infiltrate
  - Cell size: medium or mixed
  - CD2+ CD56+ (surface CD3-, but cytoplasmic CD3c+)
  - CD4- CD8- CD16- CD57- CD43- CD25- CD45RO-
- Survival only for localized disease treated with IFRT
Different clinical forms of NK/T-cell lymphomas.

Tse E, and Kwong Y
Blood 2013;121:4997-5005
### Chemotherapy Regimens for NK/T Cell Lymphoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Protocol</th>
</tr>
</thead>
</table>
| AspaMetDex | *Escherichia coli* L-asparaginase: 6000 U/m² IM, days 2, 4, 6, and 8  
Methotrexate: 3000 mg/m² IV, day 1  
Dexamethasone: 40 mg orally, days 1-4 |
| 2/3DeVIC | Dexamethasone: 40 mg IV, days 1-3  
Etoposide: 67 mg/m² IV, days 1-3  
Ifosfamide: 1000 mg/m² IV, days 1-3  
Carboplatin: 200 mg/m² IV, day 1 |
| VIPD | Etoposide: 100 mg/m² IV, days 1-3  
Ifosfamide: 1200 mg/m² IV, days 1-3  
Cisplatin: 33 mg/m² IV, days 1-3  
Dexamethasone: 40 mg IV or orally, days 1-4 |
| LVP | *L-asparaginase*: 6000 IU/m² IV, days 1-5  
Vincristine: 1.4/m² IV, day 1  
Prednisolone: 100 mg orally, days 1-5 |
| GELOX | Gemcitabine: 1000 mg/m² IV, days 1 and 8  
*E. coli* L-asparaginase: 6000 units/m² IM, days 1-7  
Oxaliplatin: 130 mg/m² IV, day 1 |
| SMILE | Dexamethasone: 40 mg IV or orally, days 2-4  
Methotrexate: 2000 mg/m² IV, day 1  
Ifosfamide: 1500 mg/m² IV, days 2-4  
*E. coli* L-asparaginase: 6000 U/m² IV, days 8, 10, 12, 14, 16, 18, and 20  
Etoposide: 100 mg/m² IV, days 2-4 |
<table>
<thead>
<tr>
<th>Disease</th>
<th>No.</th>
<th>Treatment</th>
<th>ORR</th>
<th>CR</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed/refractory</td>
<td>19</td>
<td>AspaMetDex</td>
<td>78%</td>
<td>61%</td>
<td>2 y: 40%</td>
<td>2 y: 40%</td>
</tr>
<tr>
<td>Newly diagnosed, relapsed/refractory, any stage</td>
<td>87</td>
<td>SMILE ± sandwiched RT (50 Gy)</td>
<td>81%</td>
<td>66%</td>
<td>5 y 50%</td>
<td>4 y DFS: 64%</td>
</tr>
<tr>
<td>Newly diagnosed, stage I/II nasal</td>
<td>18</td>
<td>RT (median 50 Gy)</td>
<td>78%</td>
<td>78%</td>
<td>5 y: 30%</td>
<td>5 y: 30.5%</td>
</tr>
<tr>
<td>Newly diagnosed, stage I/II nasal</td>
<td>31</td>
<td>RT (median 50 Gy)</td>
<td>100%</td>
<td>97%</td>
<td>5 y: 66%</td>
<td>5 y: 61%</td>
</tr>
<tr>
<td>Newly diagnosed, stage I/II nasal</td>
<td>17</td>
<td>CHOP + RT (45 Gy)</td>
<td>58%</td>
<td>58%</td>
<td>3 y: 59%</td>
<td>NR</td>
</tr>
<tr>
<td>Newly diagnosed, stage I/II nasal</td>
<td>27</td>
<td>Concurrent RT (50 Gy) + 2/3DeVIC</td>
<td>81%</td>
<td>77%</td>
<td>2 y: 78%</td>
<td>2 y: 67%</td>
</tr>
<tr>
<td>Newly diagnosed, stage I/II nasal</td>
<td>30</td>
<td>Concurrent RT (40 Gy) + cisplatin + VIPD</td>
<td>83%</td>
<td>80%</td>
<td>3 y: 86%</td>
<td>3 y: 85%</td>
</tr>
<tr>
<td>Newly diagnosed, stage I/II nasal</td>
<td>26</td>
<td>LVP + sandwiched RT (56 Gy)</td>
<td>89%</td>
<td>81%</td>
<td>2 y: 89%</td>
<td>2 y: 81%</td>
</tr>
<tr>
<td>Newly diagnosed, stage I/II nasal</td>
<td>27</td>
<td>GELOX + sandwiched RT (56 Gy)</td>
<td>96%</td>
<td>74%</td>
<td>2 y: 86%</td>
<td>2 y: 86%</td>
</tr>
<tr>
<td>Newly diagnosed, stage IV, or relapsed/refractory</td>
<td>38</td>
<td>SMILE</td>
<td>79%</td>
<td>45%</td>
<td>1 y: 55%</td>
<td>1 y: 53%</td>
</tr>
</tbody>
</table>
SMILE (Steroids, MTX, Ifos, L-Asp, Etop) for NK/T-cell Lymphoma

- 38pts with Stage IV disease
- SMILE regimen:
  - Decadron 40mg IV/po d2-4
  - MTX 2000mg/m2 IV d1
  - Ifosfamide 1500mg/m2 IV d2-4
  - L-Asparaginase 6000u/m2 IV d8,10,12,14,16,18,20
  - Etoposide 100mg/m2 IV d2-4
- ORR after 2 cycles (then RT): 79% CR 45%
- 19 then underwent ASCT
- 1yr OS 55%
- 61% serious infections, 2pts TRM
  - Yamaguchi JCO 2011 29: 4430-6
Treatment algorithm of NK/T-cell lymphoma.

Newly diagnosed NK/T-cell lymphoma

- Localized nasal
  - Chemotherapy fit
    - Sequential chemotherapy and Radiotherapy
      - SMILE with sandwiched RT
      - LVP with sandwiched RT
    - Concurrent chemotherapy and Radiotherapy
      - 2/3 deVIC + concurrent RT
      - RT + cisplatin followed by VIPD
  - Chemotherapy unfit
    - RT

- Localized non-nasal
  - Systemic chemotherapy +/- RT
  - May consider HSCT if CR

- Disseminated
  - Relapsed / refractory disease
    - Systemic chemotherapy
      - SMILE +/- RT
      - Regimens with L-asparaginase + non-MDR dependent drugs
    - Consider HSCT if CR

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Take Home Messages

• PTCL should be diagnosed by expert hematopathologists
• Prognosis is poor
  – scoring systems can separate bad from worse
• Standard therapy is not well defined
  • No randomized trials due to low incidence
  • CHOP based chemotherapy may provide an initial response but few patients achieve a durable CR
• CHOEP improves PFS in young
• ASCT in PR/CR1 may ↑PFS
# Managing T-cell Lymphomas

- **Hematopathology Review Critically Important**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL NOS</td>
<td>CHO(E)Px4-6, HDCT/ASCT PR1 or PR2</td>
</tr>
<tr>
<td>AITL</td>
<td>ABx prophylaxis, CHOP-HDCT/ASCT re-Bx if relapse</td>
</tr>
<tr>
<td>EATL</td>
<td>Resection, CHO(E)P then HDCT/ASCT</td>
</tr>
<tr>
<td>ALCL ALK+</td>
<td>CHOP (ASCT only if relapse)</td>
</tr>
<tr>
<td>ALCL skin ALK1-</td>
<td>Conservative Rx: obs, IFRT, MTX</td>
</tr>
<tr>
<td>Nasal NKTCL</td>
<td>IFRT. Consider SMILE chemo</td>
</tr>
<tr>
<td>Others</td>
<td>Novel approaches needed</td>
</tr>
<tr>
<td></td>
<td>IFRT if limited stage</td>
</tr>
<tr>
<td></td>
<td>?clinical trial, AlloSCT</td>
</tr>
</tbody>
</table>