How to incorporate data from molecular studies (i.e. Gene expression profiling, FISH) into the front-line and second-line therapy for lymphoma patients

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Professor of Medicine  
Director of the Lymphoma Translational Research Program  
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Can an understanding of biology improve management of lymphoma?

• Lymphoma is a heterogeneous disease with significant clinical variation

• Understanding lymphomagenesis may improve management by enabling:
  – Better classification
  – Rational treatment approaches based on disease biology
Case study: initial presentation

Patient
- 60-year-old African-American male

Presenting complaints
- Enlarged submandibular mass noticed 2 weeks ago during shaving
- Fatigue
Lymphoma is a heterogeneous disease comprised of multiple subtypes

Non-Hodgkin lymphoma (NHL) (70,130)¹

Hodgkin lymphoma (HL) (9,060)¹

Non-Hodgkin lymphoma²

Hodgkin lymphoma³

T-cell lymphomas

B-cell lymphomas

Lymphocyte-predominant Hodgkin lymphoma

T-cell lymphoma⁴

B-cell lymphoma²

Lymphocyte development is a complex process that occurs in discrete steps\textsuperscript{1-3}

Despite the oncogenic dangers associated with genomic instability and mutation…

…lymphoid cells purposely alter their DNA during development to maximize the diversity and effector functions of their antigen receptors.
Stages of B-cell development are defined by surface antigen expression\textsuperscript{1-3}

Lymphoma subtypes arise from different stages of B-cell development

- Pro/pre
  - Bone marrow: B lymphoblastic leukemia/lymphoma
  - Interfollicular area: Mantle cell lymphoma

- Mature
  - Follicular area: Follicular lymphoma
  - Perifollicular area: Follicular lymphoma
  - Burkitt lymphoma
  - DLBCL (some)
  - Hodgkin lymphoma

- Plasma cell
  - Multiple myeloma
  - Plasmacytoma
  - Plasma cell leukemia

Stages of T-cell development are defined by surface antigen expression.

Prothymocyte
Cortical thymocyte
Medullary thymocyte
T cell

CD7
CD2/CD5
CD3
CD4
CD8
TDT*

*Terminal deoxynucleotidyl transferase.

Lymphoma subtypes arise from different stages of T-cell development\textsuperscript{1,2}

- **Pro/thymocyte**: Lymphoma subtypes arising from this stage include:
  - T lymphoblastic leukemia/lymphoma
  - Hepatosplenic T-cell lymphoma
  - Cutaneous γδ T-cell lymphoma
  - Adult T-cell leukemia/lymphoma, HTLV1

- **Innate immunity**: Subtypes associated with innate immunity include:
  - PTCL-NOS, ALCL, AITL, enteropathy-associated TCL
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Mycosis fungoides

- **Acquired immunity**: Lymphoma subtypes arising from this stage include:
  - Hepatosplenic TCL

\textsuperscript{1} Swerdlow SH et al, eds. \textit{WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues}. 4th ed. Lyon, France: IARC; 2008.
Understanding lymphoma classification

- Follicles made of B-cells, when malignant called B-cell follicular lymphoma.
- Dark rim of cells around follicles are mantle zones, when malignant, B-cell mantle cell lymphoma.
- Pale pink area with small cells immediately next to the mantle zone is marginal zone, when malignant marginal zone lymphoma. If this type of lymphoma is in soft tissue, extra nodal marginal zone lymphoma.
- Interfollicular areas composed of T-cells, when malignant, T-cell lymphomas.
Lymphoma diagnosis requires a multidisciplinary team approach\textsuperscript{1,2}

FC = flow cytometry; IHC = immunohistochemistry
A systematic approach to diagnosing suspected lymphoid cancers is recommended\textsuperscript{1,2}

**History and physical:** suspect lymphoid malignancy

- Laboratory tests
- Diagnostic imaging
- Lymph node biopsy

**Fresh biopsy tissue:**
- Flow cytometric immunophenotyping
- Cytogenetics/molecular genetics
- Snap-freeze for future studies

**Paraffin-embedded tissue:**
- Routine formalin fixation
- Immunohistochemistry
- FISH (whole sections or disaggregated nuclei)

Is this diagnostic algorithm consistent with what is standard practice at your medical center?

\textsuperscript{2} Wilkins BS. *J Clin Pathol.* 2011;64(6):466-476.
Are we looking at lymphoid cancer?

Excisional lymph node biopsy

Lymphoid cells

Small cells

Large cells
Case study: morphology
What is the likely diagnosis?
Immunophenotyping lymphomas involves multiple cell surface antigens\textsuperscript{1,2}

Which markers would be part of your initial analysis?

Targeting lymphoma with monoclonal antibodies: multiple receptors and antigens that can be targeted

Survival signals

NF-κB
ERK
PI3K/AKT/mTOR

Death signals

JAK/STAT
Caspase activation

Rituximab: The first targeted therapy for Non-Hodgkin’s Lymphoma

Human κ constant regions

Fab binds CD20 antigen present in B-cells

Crosslinking of the Fc portion mediates rituximab antitumor activity
Antigen Expression in B-Cell Lineage

- **Stem cell**
- **Pre-B**
- **Early B**
- **Intermediate B**
- **Mature B**
- **Plasmacytoid B**
- **Plasma**

- **ALL**
- **CLL, PLL**
- **Burkitt’s, FL, DLCL, HCL**
- **WM**
- **MM**

- ±CD5
- CD19
- CD20
- CD22
- CD52

? ?
Randomized studies evaluating rituximab-chemotherapy in diffuse large B-cell lymphoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Patient population</th>
<th>Treatment arm (Number of patients per arm)</th>
<th>Response rate (%)</th>
<th>PFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GELA (Coiffier et al, 2002)</td>
<td>III</td>
<td>Elderly patients with DLBCL (N=399)</td>
<td>R-CHOPx8 (202) vs. CHOPx8 (197)</td>
<td>83 vs. 69 (P=0.05)</td>
<td>At 5 years 57 vs. 38 (P&lt;0.001)</td>
<td>At 5 years 70 vs. 57 (P=0.007)</td>
</tr>
<tr>
<td>MInT (Pfreundschuh et al, 2006)</td>
<td>III</td>
<td>Young patients with untreated DLBCL stage I bulky or II-IV, (N=823)</td>
<td>R-CHOPx6 (413) vs. CHOPx6 (410)</td>
<td>86 vs. 68 (P&lt;0.01)</td>
<td>At 34 months 85 vs. 68 (P&lt;0.0001)</td>
<td>At 34 months 93 vs. 84 (P=0.0001)</td>
</tr>
<tr>
<td>RICOVER-60 (Pfreundschuh et al, 2008)</td>
<td>III</td>
<td>Elderly patients with untreated DLBCL (N=1222)</td>
<td>CHOPx6-14 (307) CHOPx8-14 (305) RCHOPx6-14 (306) RCHOPx8-14 (304)</td>
<td>68 vs. 72 (P=0.31) 78 (P=0.007) 76 (P=0.037)</td>
<td>At 3 years 56.9 vs. 56.9 (P=0.615) 73.4 (P&lt;0.0001) 68.8 (P&lt;0.0001)</td>
<td>At 3 years 67.7 vs. 66 (P=0.835) 78.1 (P=0.018) 72.5 (P=0.26)</td>
</tr>
<tr>
<td>ECOG 4494 (Morrison et al, 2006)</td>
<td>III</td>
<td>Elderly patients with untreated DLBCL (N=632)</td>
<td>CHOPx6 (279) R-CHOPx6 (267) Responders were then randomized to RM or observation</td>
<td>77% vs. 76% before second randomization</td>
<td>At 3 years, FFS 39 vs. 52 (P=0.03) *After excluding RM patients</td>
<td>At 3 years, 57 vs. 67 (P=0.05) *After excluding RM patients</td>
</tr>
</tbody>
</table>
Prognostic Impact of Germinal Center B-cell (GCB)/ Activated B-Cell (ABC) Classification Analysed by Immunochemistry, FISH Analysis and GEP, In R/R DLBCL: The Bio-CORAL Study

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th>%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>63%</td>
<td>-</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>38%</td>
<td>-</td>
</tr>
<tr>
<td>R-ICE</td>
<td>63.5%</td>
<td>-</td>
</tr>
<tr>
<td>R-DHAP</td>
<td>63%</td>
<td>-</td>
</tr>
<tr>
<td>No Prior Rituximab</td>
<td>83%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Prior Rituximab</td>
<td>51%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Relapsed &gt; 12 months</td>
<td>88%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Refractory &lt; 12 months</td>
<td>46%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>sIPI 0-1</td>
<td>71%</td>
<td>&lt; .0002</td>
</tr>
<tr>
<td>sIPI 2-3</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

**Strategies tested to improve the clinical outcome of DLBCL patients**

<table>
<thead>
<tr>
<th>Modality investigated</th>
<th>Improvement in response rate</th>
<th>Improvement in PFS or OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Dense</strong> R-CHOP14 vs. R-CHOP-21 LNH03-6B GELA study</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Increase number of cycles</strong> R-CHOP x 6 vs. R-CHOP x 8 (RICOVER study)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Adding chemotherapy agents</strong> R-CHOP vs. R-DA-EPOCH (Intergroup study CALGB50303/ECOG/SWOG)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>High dose chemotherapy and autologous stem cell support (HDC0ASCS)</strong> in first remission for high risk DLBCL (Stiff et al., JCO 2011, #8011)</td>
<td>No</td>
<td>Favor in PFS at 2-years (69% vs. 56%, P=0.005). Study included CHOP and R-CHOP treated patients</td>
</tr>
<tr>
<td><strong>Increasing intensity regimen</strong> without HDC-ASCT R-CHOP vs. R-Mega-CHOP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Rituximab Maintenance</strong> (ECOG 4494 and CORAL studies)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Current areas of research in aggressive B-cell lymphoma

1) Predicting patients that are less likely to respond to rituximab-CHOP in the front-line setting

2) The identification of key-regulatory pathways present in relapsed/refractory DLBCL

3) Can the targeting those pathways translate into clinical benefit?
Gene-expression profiling subdivides morphologically indistinguishable DLBCL tumors into three distinct cell-of-origin (COO) subtypes.
# PFS and overall survival for each DLBCL molecular subtype

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Regimen</th>
<th>3-year PFS rate</th>
<th>3-year overall survival rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC DLBCL</td>
<td>R-CHOP</td>
<td>40%</td>
<td>Approximately 45%</td>
<td>Lenz et al. (2008)²⁹</td>
</tr>
<tr>
<td>GCB DLBCL</td>
<td>R-CHOP</td>
<td>74%</td>
<td>Approximately 80%</td>
<td>Lenz et al. (2008)²⁹</td>
</tr>
<tr>
<td>PMBL</td>
<td>DA-EPOCH-R</td>
<td>100%*</td>
<td>97%*</td>
<td>Dunleavy et al. (2013)¹⁶</td>
</tr>
</tbody>
</table>

*At 5 years. Abbreviations: ABC, activated B-cell; DA-EPOCH-R, dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell; PFS, progression-free survival; PMBL, primary mediastinal B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Oncogenic mechanisms and potential targets in DLBCL subtypes

<table>
<thead>
<tr>
<th>DLBCL subtype</th>
<th>Cell of origin</th>
<th>Oncogenic mechanisms</th>
<th>Potential targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCB</td>
<td>Germinal centre B-cell</td>
<td><em>BCL2 translocation</em></td>
<td>BCL6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡EZH2 mutations</td>
<td>EZH2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§PTEN deletions</td>
<td>PI3K/Akt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of PTEN expression</td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>Post-germinl centre B-cell</td>
<td>†NF-κB activation</td>
<td>BCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡CARD11 mutations</td>
<td>CBM complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡MYD88 mutations</td>
<td>IRAK-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡CD79B mutations</td>
<td>JAK–STAT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A20 deletions</td>
<td></td>
</tr>
<tr>
<td>PMBL</td>
<td>Post-thymic B-cell</td>
<td>†NF-κB activation</td>
<td>JAK–STAT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡9p24 amplification</td>
<td>PD-1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡REL amplification</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡JAK2 mutations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>‡CIITA translocations</td>
<td></td>
</tr>
</tbody>
</table>
Molecular Profiling in DLBCL

Rosenwald et al., NEJM 2002
Hans et al., Blood 2004
Choi et al., Clin Cancer Res 2009
DLBCL with a non-GCB phenotype by IHC had an inferior PFS and OS following R-CHOP-21 than GCB-DLBCL.
New strategies to improve clinical outcome

Target the “bad lymphomas” ? - Should we treat based on COO or IHC results. If so with what?
Targeting the cell of origin

• Lenalidomide appears effective in relapsed DLBCL, ~30% ORR

• Non-GCB phenotype had a higher ORR as compared with GCB

• Ongoing phase II study prospectively randomizing patients based on COO
Final Results of Phase II Study of Lenalidomide Plus Rituximab-CHOP21 in Elderly Untreated DLBCL Focusing on Cell of Origin: REAL07 Trial of the Fondazione Italiana Linfomi

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>CR</th>
<th>PR</th>
<th>2-yr OS</th>
<th>2-yr PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (49)</td>
<td>92%</td>
<td>86%</td>
<td>6%</td>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>GCB (16)</td>
<td>88%</td>
<td>81%</td>
<td></td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>non-GCB (16)</td>
<td>88%</td>
<td>88%</td>
<td></td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

Chiappella A et al. ASH 2013 Abstract 850
PFS by GCB versus Non-GCB Subtype with R2CHOP versus R-CHOP

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Proportion Event-free</th>
<th>Proportion Event-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>12</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>18</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>24</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>30</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>36</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**GCB (n = 59)**

**Non-GCB (n = 28)**

**p = 0.004**

**R2CHOP**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Proportion Event-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
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<tr>
<td>24</td>
<td>0.7</td>
</tr>
<tr>
<td>30</td>
<td>0.6</td>
</tr>
<tr>
<td>36</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**GCB (n = 18)**

**Non-GCB (n = 15)**

**p = not significant**

*Nowakowski GS al. Proc ASH 2012;Abstract 689.*
c-MYC expression in DLBCL

- 9% of newly diagnosed DLBCL appear to harbor the myc translocation
- Myc+ DLBCL have an overall poor prognosis when treated with R-CHOP
- Ki-67 score cannot identify patients at high risk of harboring the MYC rearrangement
- Patients with MYC+ DLBCL should be treated with aggressive regimens or referred to a clinical trial

*Savage K et al., Blood 2009*
Impact of Induction Regimen and Stem Cell Transplantation on Outcomes in Patients with Double Hit Lymphoma: A Large Multicenter Retrospective Analysis

Figure 2. Kaplan-Meier curves comparing the long-term (A) progression-free survival (PFS) and overall survival (OS) of the entire cohort; PFS (B) and OS (C) by induction regimen; PFS (D) and OS (E) comparing R-CHOP to other intensified induction regimens (ie, DA-EPOCH, Hyper CVAD, and CODOX-M/IVAC). Abbreviations: R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-Hyper CVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with methotrexate and cytarabine; R-CODOX-M/IVAC, rituximab, cyclophosphamide, vincristine, dexamethasone, methotrexate, ifosfamide, etoposide, cytarabine.

Impact of Induction Regimen and Stem Cell Transplantation on Outcomes in Patients with Double Hit Lymphoma: A Large Multicenter Retrospective Analysis

Figure 3. Kaplan-Meier curves demonstrate overall survival (OS) by (A) use of SCT, as compared to observation, among those in first complete remission (CR); OS by (B) those who were positive for central nervous system (CNS) involvement at time of diagnosis, as compared to those who did and did not receive CNS-directed prophylaxis (PPX); and OS for (C) those with relapsed/refractory disease based on whether salvage therapy was administered.
Mantle Cell Lymphoma

- Classified as unique entity in 1992
- Mantle cell lymphoma (MCL) comprises 5–10% of all non-Hodgkin's lymphomas. Approximately 2,000 cases per year in US
- Characteristic bcl-1 translocation = t(11;14)
- Mantle cell lymphoma (MCL) has an aggressive clinical course with a median survival < 3 years and is incurable with conventional chemotherapy.
  - CHOP: 40% CR rate, Median PFS of 1-2 yrs and OS of 3 yrs.
  - HDT with auto SCT = 2-4 year DFS of 30%
  - Rituximab alone* (n=81): ORR = 37% (14% CR), Median DR = 1.2 years

<table>
<thead>
<tr>
<th>Cell cycle</th>
<th>DNA damage response</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1, G2, M</td>
<td>ATR, ATM</td>
</tr>
<tr>
<td>cdk4/cyclin D1</td>
<td>Deletion 11q22-23</td>
</tr>
<tr>
<td>RB1</td>
<td>Mutations ATM locus</td>
</tr>
<tr>
<td></td>
<td>Stabilization of p53</td>
</tr>
<tr>
<td></td>
<td>INK4/ARF</td>
</tr>
<tr>
<td></td>
<td>p16</td>
</tr>
<tr>
<td></td>
<td>p21</td>
</tr>
<tr>
<td></td>
<td>p27, p53</td>
</tr>
<tr>
<td></td>
<td>G1/S arrest</td>
</tr>
<tr>
<td></td>
<td>G1/S arrest</td>
</tr>
<tr>
<td></td>
<td>DNA repair</td>
</tr>
<tr>
<td></td>
<td>Apoptosis</td>
</tr>
</tbody>
</table>
Mantle Cell Lymphoma: Outcomes of patients treated with R-CHOP

Mantle Cell Lymphoma: R-CHOP vs R-Hyper CVAD

Vose et al, Procc Am Soc Clin Onc 2006; 7511a
Mantle Cell Lymphoma: R-CHOP vs R-Hyper CVAD

Vose et al, Procc Am Soc Clin Onc 2006; 7511a
Mantle Cell Lymphoma: a case for early transplantation

Overall survival from time of transplantation by disease status.

Progression-free survival from time of transplantation by disease status

## T-cell lymphoma

is a heterogeneous disease comprised of multiple subtypes\(^1,2\)

<table>
<thead>
<tr>
<th>Leukemic or disseminated</th>
<th>Cutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T-cell prolymphocytic leukemia</td>
<td>• Mycosis fungoides</td>
</tr>
<tr>
<td>• T-cell large granular lymphocytic leukemia</td>
<td>• Sézary syndrome</td>
</tr>
<tr>
<td>• Chronic lymphoproliferative disorders of NK cells*</td>
<td>• Primary cutaneous CD30-positive lymphoproliferative disorders</td>
</tr>
<tr>
<td>• Aggressive NK-cell leukemia</td>
<td>• Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>• Adult T-cell lymphoma/leukemia (HTLV1-positive)</td>
<td>• Lymphomatoid papulosis</td>
</tr>
<tr>
<td>• Systemic Epstein-Barr virus (EBV)–positive lymphoproliferative disorders of childhood</td>
<td></td>
</tr>
</tbody>
</table>

### Nodal

- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative*
- Peripheral T-cell lymphoma, not otherwise specified

### Extranodal

- Extracutaneous NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma

*Provisional entity.

Goal: to evaluate the role of clinical data in T-cell lymphoma diagnosis
1,314 cases were reviewed by expert hematopathologists and classified according to WHO criteria

Relative frequencies of mature T-cell lymphomas
International T-Cell Lymphoma Project: pathology findings and clinical outcomes (continued)

- Found that diagnosing distinct T-cell lymphoma subtypes can be challenging
- Subsets with specific diagnostic markers have higher rates of diagnostic accuracy (agreement with consensus diagnosis)

<table>
<thead>
<tr>
<th>Good (&gt;90% agreement)</th>
<th>Generally poor (&lt;85% agreement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL, ALK-positive: 97%</td>
<td>Primary cutaneous ALCL: 66%</td>
</tr>
<tr>
<td>ATLL: 93%</td>
<td>Hepatosplenic: 72%</td>
</tr>
<tr>
<td>NKTCL: 92%</td>
<td>ALCL, ALK-negative: 74%</td>
</tr>
<tr>
<td></td>
<td>PTCL-NOS: 75%</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous panniculitis-like: 75%</td>
</tr>
<tr>
<td></td>
<td>EATL: 79%</td>
</tr>
<tr>
<td></td>
<td>AITL: 81%</td>
</tr>
</tbody>
</table>

- The addition of clinical data can aid the diagnosis of certain lymphomas:
  - When experts were provided with HTLV-1 status, 39% of PTCL-NOS cases were changed to ATLL
- 10.4% of lymphoma cases could not be classified or were misdiagnosed

2008 World Health Organization classification of PTCL

Mature T-cell neoplasms

**Cutaneous**
- Mycosis Fungoides (MF)
- Sézary Syndrome
- Primary Cutaneous CD30+ T-Cell Disorders
- Primary Cutaneous ALCL
- Primary Cutaneous γδ TCL
- Primary Cutaneous CD8+ aggressive epidermotropic
- Primary Cutaneous CD4+ small/medium

**Extranodal**
- NK/TCL Nasal Type
- Enteropathy-Associated TCL
- Hepatosplenic TCL
- Subcutaneous Panniculitis-Like TCL
- Systemic EBV+ T-cell childhood lymphoprolif
- Hydroa Vacciniforme-like

**Nodal**
- Peripheral TCL-NOS
- Anaplastic Large Cell Lymphoma (ALK +)
- Anaplastic Large Cell Lymphoma (ALK -)
- Angioimmunoblastic TCL

**Leukemic**
- Adult T-Cell Leukemia/Lymphoma
- T-cell Prolymphocytic Leukemia
- T-Cell Large Granular Lymphocytic Leukemia

*Provisional entity.

PTCL prognosis by subtype

ALK-negative ALCL has a better prognosis than PTCL-NOS

5-year overall survival of ALK-negative ALCL and PTCL-NOS (CD30+ ≥80% of cells)
