Prognostic Factors for PTCL

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Distribution of 1314 Cases by Consensus Diagnosis

- Peripheral T-cell lymphoma (PTCL): 25.9%
- Lymphomatoid papulosis: 12.2%
- Angioimmunoblastic: 18.5%
- Adult T-cell leukemia/lymphoma: 9.6%
- Anaplastic large cell lymphoma (ALCL), ALK+: 6.6%
- Anaplastic large cell lymphoma (ALCL), ALK-: 5.5%
- Enteropathy-type T-cell: 1.7%
- Primary cutaneous ALCL: 1.4%
- Hepatosplenic T-cell: 0.9%
- Subcutaneous panniculitis-like: 2.5%
- Unclassified PTCL: 1.0%
- Other disorders: 0.9%
Overall Survival of PTCL

1314 cases
From 22 centers worldwide
All reviewed by a panel of experts
Treated between 1990 and 2002

International T-cell Lymphoma Project
Overall Survival AITL vs PTCL-NOS

p=0.80

5 year OS ~30%
PTCL-NOS: OS by IPI

Overall Survival Based on Prognostic Score

PTCL-U by IPI


Categories of Prognostic Factors

• Clinical Characteristics – Age, stage, ENS, PS, BM+ (IPI, PIT)
• Laboratory Tests – LDH, monocytosis, B2M
• Histology of PTCL – Subtypes of T-cell NHL
• Genomics of PTCL – new models
## Biologic Prognostic Markers in PTCL

<table>
<thead>
<tr>
<th>Prognostic Marker</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV +</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Ki-67% &gt; 80</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Cytotoxic granule expression</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>T-helper receptor profile – CCR3 or CCR5</td>
<td>Favorable</td>
</tr>
<tr>
<td>% transformed cells &gt; 70%</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Proliferative signature</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>NFkB signature</td>
<td>Favorable</td>
</tr>
</tbody>
</table>
Prognostic Indices for T-cell NHL

- International Prognostic Index (IPI)
- Prognostic Index for T-cell lymphoma (PIT) – uses BM+
- Modified PIT (mPIT) – BM+ changed to Ki-67 %
- International peripheral T-cell lymphoma Project (IPTCLP) – based on PTCL and AITL only
## Variables Used in Prognostic Indices for PTCL

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPI</th>
<th>PIT</th>
<th>IPTCLP</th>
<th>mPIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG &gt; 1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LDH &gt; N</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I/II vs. III/IV</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENS &gt; 1</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM +</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plt &lt; 150</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ki-67 &gt; 75%</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Overall survival of the patients with peripheral T-cell lymphoma (anaplastic large-cell lymphoma, ALK+ excluded) according to the different scores: (A) International Prognostic Index (IPI), \( P < 0.0001 \); (B) International peripheral T-cell lymphoma Project score (IPTCLP), \( P < 0.0001 \); (C) PIT, \( P < 0.0001 \) and (D) modified Prognostic Index for T-cell lymphoma (mPIT), \( P = 0.005 \).
Figure 1: Incidence rates by year, age-adjusted to the 2000 US population, expressed per 100,000 population (A); and proportion of PTCL cases by histologic subtype (B). PTCL, peripheral T-cell lymphoma; PTCL-NOS, PTCL not otherwise specified; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; AITL, angioimmunoblastic T-cell lymphoma; ENKTL, extranodal NK/T-cell lymphoma, nasal type. (N= 8802 in SEER 2000-2010)

Multivariate analysis of Survival

- Age > 55 years – 1 point
- African American Race – 1 point
- Histology
  - HSTL, EATL, ENKTL, T-PLL – 2 points
  - PTCL-NOS, AITL, ATLL, ALCL – 1 point
  - SCPTL, T-LGL – 0 points
- Advanced stage – 1 point

Factors predicting survival in peripheral T-cell lymphoma in the USA: a population-based analysis of 8802 patients in the modern era

Factors predicting survival in peripheral T-cell lymphoma in the USA: a population-based analysis of 8802 patients in the modern era

Factors predicting survival in peripheral T-cell lymphoma in the USA: a population-based analysis of 8802 patients in the modern era

Survival according to the new prognostic index. For NKT-cell – nasal type

1. B symptoms
2. Stage ≥ III
3. LDH > normal
4. LN N1-N3, not M1
Analysis of Angioimmunoblastic T-cell lymphoma of the IPTCLP

- 243 AITL patients, Validation GELA cohort
- Standard IPI evaluated
- Alternative Prognostic Index for AITL (PIAI)
  - Age > 60
  - PS ≥ 2
  - ENS > 1
  - B-symptoms present
  - Platelet count < 150K

Overall survival (OS) for patients with angioimmunoblastic T-cell lymphoma (AITL) using the (A) International Prognostic Index, (B) Prognostic Index for Peripheral T-Cell Lymphoma, Unspecified (PIT), and (C) Prognostic Index for AITL (PIAI); (D) OS for GELA...
Survival of Relapsing PTCL

153 Relapsed patients
89 treated with chemotherapy; no HSCT
52% PTCL NOS
Median time to PD: 6.7 months
Better outcome with good PS

NOS, not otherwise specified; PD, progressive disease; PS, performance status; PTCL, peripheral T-cell lymphoma

Table 3.

Multivariate Analysis of Prognostic Factors for Second PFS and OS After Relapse or Progression in Chemotherapy-Treated Group (n = 89)

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Second PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PS ≥ 2</td>
<td>1.66</td>
<td>1.05 to 2.63</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>.987</td>
<td>—</td>
</tr>
<tr>
<td>Type of chemotherapy</td>
<td>.638</td>
<td>—</td>
</tr>
<tr>
<td>Combination chemotherapy</td>
<td>0.63</td>
<td>0.40 to 0.99</td>
</tr>
<tr>
<td>Time to relapse, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6-12</td>
<td>0.37</td>
<td>0.21 to 0.67</td>
</tr>
<tr>
<td>12-24</td>
<td>0.42</td>
<td>0.22 to 0.81</td>
</tr>
<tr>
<td>&gt; 24</td>
<td>0.23</td>
<td>0.41 to 0.99</td>
</tr>
<tr>
<td>Response to prior therapy</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

German Prospective Trial of ASCT in First Remission

- PIT group 1: 0 risk factors
- PIT group 2: 1 risk factor
- PIT group 3: 2 risk factors
- PIT group 4: 3-4 risk factors

- N = 83 untreated patients
- CHOP x 4-6
- If ≥ PR, dexamBEAM or ESHAP
- dexamBEAM or ESHAP ± TBI, ASCT
- Median follow-up: 33 mos

Molecular Prognostic Indices

• PTCL- NOS: many different entities
• AITL – model using
  – P53 upregulation signal
  – Cytotoxic phenotype
  – Monocytic/dendritic signature
  – B-cell signature
Refinement of molecular diagnostic signatures for PTCL subgroups

Unique molecular signatures were identified for major PTCL entities


Lymphoma and Leukemia Molecular Profiling Project (LLMPP) initiative
Gene expression-based molecular predictors of the major subgroups of PTCL

- More than half of the PTCL-NOS cases were not molecularly classified

International peripheral T-cell lymphoma Project
- of 152 PTCL-NOS cases, a subset of cases were classified into
  i. AITL [14%]
  ii. ALK(-)ALCL [11%]
  iii. ATLL [03%]
  iv. γδ- PTCL [09%]

- Of 117 AITL cases 26 cases (22%) changed to PTCL-NOS.
### Survival prediction on AITL: role of tumor microenvironment

<table>
<thead>
<tr>
<th>Signature Cluster</th>
<th>Effect of high expression</th>
<th>Training p-value</th>
<th>Validation p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 upregulated signature</td>
<td>Poor prognosis</td>
<td>0.001</td>
<td>0.014</td>
</tr>
<tr>
<td>Cytotoxic signature</td>
<td>Poor prognosis</td>
<td>0.005</td>
<td>0.046</td>
</tr>
<tr>
<td>Monocytic/dendritic signature</td>
<td>Poor prognosis</td>
<td>0.011</td>
<td>0.010</td>
</tr>
<tr>
<td>B- cell signature</td>
<td>Good prognosis</td>
<td>0.002</td>
<td>0.017</td>
</tr>
</tbody>
</table>

- Tumor microenvironment significantly influences the prognosis in AITL
- Role of macrophages (M1) vs (M2) and dendritic cells are being investigated
Identification of cytotoxic (αβ) PTCL group from PTCL-NOS

(A) Hierarchical clustering

Dendrogram for clustering PTCL-NOS cases using centered correlation and complete linkage

(B) Expression of the CT-PTCL signature in normal CD8+ T-cells stimulated with anti-CD3, anti-CD28 and IL12 for various time intervals (hours)

(C) GSEA analysis

IFNγ-responsive genes and CD8+ T-cell gene signature

(D) Survival of the CT-PTCL group

OS and EFS survival curves for CT-PTCL and PTCL-NOS

(E) Granzyme B expression by immunohistochemistry in CT-PTCL

Blood 2010;115:1026-1036
Prognostic gene signatures in AITL

Long term survivors with AILT do occur – further study needed to identify these patients - ?alternate therapy
Prognostic Factors for PTCL

• Clinical factors – still important. IPI, PIT, individual histologic models work for low risk groups best

• Biologic factors – pathways, molecular profiling may be more helpful in the future for treatment choices