Novel treatment strategies in peripheral T-cell lymphomas

Prof. Paolo Corradini
Dept. of Hematology and Bone Marrow Transplantation
Chair of Hematology University of Milano,
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
In a large international study, T-cell and NK-cell neoplasms accounted for only 12% of all non-Hodgkin lymphomas.

Only 20% Long-term Survivors With Anthracycline-based Therapy

## Treatment Guidelines for PTCL: Still CHOP Based

<table>
<thead>
<tr>
<th>First-line Therapy</th>
<th>Clinical trial (preferred)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALCL, ALK+ histology</td>
</tr>
<tr>
<td></td>
<td>• CHOP-21</td>
</tr>
<tr>
<td></td>
<td>• CHOEPP-21</td>
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<tr>
<td></td>
<td>Other histologies (ALCL, ALK-; PTCL-NOS; AITL; EATL), regimens that can be used include:</td>
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<tr>
<td></td>
<td>• CHOEPP</td>
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<tr>
<td></td>
<td>• CHOP-14</td>
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<td></td>
<td>• CHOP-21</td>
</tr>
<tr>
<td></td>
<td>• CHOP followed by ICE</td>
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<tr>
<td></td>
<td>• CHOP followed by IVE, alternating with intermediate-dose methotrexate (Newcastle regimen)</td>
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<tr>
<td></td>
<td>• Dose-adjusted EPOCH</td>
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<tr>
<td></td>
<td>• HyperCVAD, alternating with high-dose methotrexate and cytarabine</td>
</tr>
</tbody>
</table>

| First-line Consolidation | All patients except low risk (aaIPI) should be considered for high-dose therapy and stem cell rescue; ALCL, ALK+ is a subtype with good prognosis and does not need consolidative transplant if in remission |

German High-Grade Lymphoma Study Group: T-Cell Lymphoma Cohort Analysis

• 320 patients with mature nodal or extranodal T-cell or NK-cell lymphoma treated on 7 phase II or III studies (1993-2007)
  • ALK positive: 78 patients (24.4%)
  • ALK negative: 113 patients (35.3%)
  • Treated with CHOP ± etoposide: 100%

• Patients younger than 60 yrs of age with normal LDH
  • Addition of etoposide to CHOP improved 3-yr EFS: 75% vs 51% with CHOP alone (p = 0.003)

ALK, anaplastic large cell lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; LDH, lactate dehydrogenase

Adding Etoposide to CHOP: German High-Grade NHL Study Group Analysis

<table>
<thead>
<tr>
<th>PTCL Subtype</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL, ALK+</td>
<td>78</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>113</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>70</td>
</tr>
<tr>
<td>AITL</td>
<td>28</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>320</strong></td>
</tr>
</tbody>
</table>

EFS, aged < 60 yrs

EFS, ALCL, ALK+

EFS, other subtypes

p = 0.003

EFS, event-free survival;

CHOEP, CHOP + etoposide

### Autologous SCT in First Remission: Prospective Studies

<table>
<thead>
<tr>
<th>Study Author (Yr)</th>
<th>n</th>
<th>Regimen</th>
<th>Transplanted, %</th>
<th>Outcomes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corradini (2006)</td>
<td>62</td>
<td>Mitoxantrone/melphalan or BEAM</td>
<td>74</td>
<td>12-yr EFS: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12-yr OS: 34</td>
</tr>
<tr>
<td>Rodriguez (2007)</td>
<td>26</td>
<td>MegaCHOP ± IFE</td>
<td>73</td>
<td>3-yr PFS: 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-yr OS: 84</td>
</tr>
<tr>
<td>Mercadal (2008)</td>
<td>41</td>
<td>High-dose CHOP/ESHAP</td>
<td>41</td>
<td>4-yr PFS: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-yr OS: 39</td>
</tr>
<tr>
<td>Reimer (2009)</td>
<td>83</td>
<td>dextaBEAM or ESHAP ± TBI</td>
<td>66</td>
<td>3-yr PFS: 36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-yr OS: 48</td>
</tr>
<tr>
<td>d’ Amore (2011)</td>
<td>160</td>
<td>CHO(E)P-14 x 6 ± BEAM/BEAC</td>
<td>71</td>
<td>5-yr OS: 51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-yr PFS: 44</td>
</tr>
</tbody>
</table>

BEAC, BiCNU, etoposide, Ara-C, cyclophosphamide; BEAM, BiCNU, etoposide, ara-C, melphalan; ESHAP, etoposide, methylprednisolone, ara-C and cisplatin; IFE, ifosfamide, etoposide; TBI, total body irradiation.

**ORR pre-Tx** | 131 (82%)  
---|---  
**CR/CRu** | 82 (51%)  
**PR** | 49 (31%)  
**% Tx** | 115 (72%)  
**CR/CRu post-Tx 100d** | 90 (56%)  

6 pts inclusion criteria not fulfilled  
4 pts not evaluable response  
**Intention-to-treat population**  
25 pts primary refractory  
16 pts PD/tox/mobilisation failure/other before Tx  
25 pts PR/PD/tox  
90 pts CR/CRu 3 mo post Tx  

OS (A) and PFS (B) for the Entire NLG-T-01 Cohort and OS (C) and PFS (D) for the 4 Largest Histologic Subtypes (CHOEP-14 and Auto-sct)

The novel gold standard?

EATL, enteropathy-associated T cell lymphoma.

Intensive Chemo-immunotherapy as First-line Treatment in Adult Patients With PTCL
- GITIL and IIL national cooperative study (2006) -

AIM OF THE STUDY: A “global” approach to improve the outcome of PTCLs reducing the primary refractory and early PD patients

1. Inclusion of alemtuzumab at diagnosis
2. HD chemo before transplant with drug crossing the blood-brain barrier
3. First study with allogeneic SCT frontline
Outline of Clin A Study

- Alemtuzumab-CHOP X 2 courses → Start donor search
- 1 cycle HyperCHidam
- 2 cycle HyperCHidam
  - Genetic stratification
  - PD or SD → salvage
  - Auto-SCT
  - Allo-SCT
    - (HLA-identical sibling or one antigen mismatched unrelated donor)

HyperCHidam, Hyperfractionated cyclophosphamide with high-doses of arabinosylcytosine and methotrexate

EudraCT Number 2006-004234-33
Clin A – Survival Outcomes

- Median follow-up: 40 months
- 8 of 61 patients died for treatment-related causes with a cumulative incidence of non-relapse mortality of 13%.
New agents in the Front-Line Treatment in PTCL
Brentuximab Vedotin in the Front-Line Treatment of Patients With CD30+ Peripheral T-Cell Lymphomas: Results of a Phase I Study

- 39 treatment-naive patients with a diagnosis of CD30 + PTCL (≥ 1% CD30 expression in malignant cells)

- Two strategies for incorporating BV into treatment were examined:
  - **Sequential treatment**, in which sALCL patients received 2 cycles of 1.8 mg/kg BV followed by 6 cycles standard-dose CHOP
  - **Combination treatment**, in which patients with PTCL, including those with sALCL, received 6 cycles of BV in combination with CHP (Vincristin was omitted to eliminate the potential for additional neurotoxicity).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>sALCL ALK positive (n=6)</th>
<th>sALCL ALK negative (n=26)</th>
<th>Non-ALCL (n=7)</th>
<th>Total (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>35 (21-62)</td>
<td>60 (25-82)</td>
<td>55 (37-74)</td>
<td>57 (21-82)</td>
</tr>
<tr>
<td><strong>Disease diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLL</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ALCL</td>
<td>6</td>
<td>26</td>
<td>-</td>
<td>32</td>
</tr>
<tr>
<td>AITL</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>EATL</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PTCL NOS</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Baseline IPI score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2-3</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>4-5</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

After a median observation time of 21.4 months:

- Median PFS had not been reached
- The estimated 1-year PFS rate was 71%

Of note, no patients went on to receive consolidative ASCT or allogeneic SCT

# Ongoing phase III induction/maintenance clinical trials in treatment-naïve PTCL

<table>
<thead>
<tr>
<th>Trials</th>
<th>NCT</th>
<th>Title</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECHELON-2</td>
<td>01777152</td>
<td>A Comparison of <strong>Brentuximab Vedotin</strong> and CHP With Standard-of-care CHOP in the Treatment of Patients With CD30-positive Mature T-cell Lymphomas</td>
<td>Induction</td>
</tr>
<tr>
<td>Ro-CHOP</td>
<td>01796002</td>
<td>Phase 3 Multi-center Randomized Study to Compare Efficacy and Safety of <strong>Romidepsin</strong> CHOP (Ro-CHOP) Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma</td>
<td>Induction</td>
</tr>
<tr>
<td>A-CHOP-14</td>
<td>00725231</td>
<td>Immunotherapy in Peripheral T Cell Lymphoma - the Role of <strong>Alemtuzumab</strong> in Addition to Dose Dense CHOP</td>
<td>Induction</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>01420679</td>
<td>Study of <strong>Pralatrexate</strong> Versus Observation Following CHOP-based Chemotherapy in Previously Untreated Peripheral T-cell Lymphoma Patients</td>
<td>Maintenance</td>
</tr>
</tbody>
</table>
Protocol FIL_PTCL13

Romidepsin in combination with CHOEP as first line treatment before hematopoietic stem cell transplantation in young patients with nodal peripheral T-cell lymphomas: a phase I-II study

Principal Investigator: Prof. Paolo Corradini
Phase I/II Trial of Ro-CHOEP: Patients ≥18 yrs ≤ 65 yrs

**Phase I:** Romidepsin D1&8
- 8, 10, 12, 14 mg/m²;
- starting with 12 mg/m²

**Phase II:** Romidepsin at MTD

Ro-CHOEP21 x 3

Response Evaluation

For PR start donor search

<PR

Other treatments (investigators’ choice)

CR or PR

Ro-CHOEP21 x 3

Pre SCT Response Evaluation followed by one DHAP course and Stem Cell Harvest

PR
- Donor: yes
  - ALLO - SCT
- no
  - AUTO - SCT

CR

PD

Other treatments (investigators’ choice)

Follow-up
Conclusions

• There is a clear unmet clinical need for PTCL patients
  • Disease biology and classification have to be improved
  • Long-term survival is poor (20 -25% with anthracyclin-based treatment)
• Current treatment guidelines are still CHOP-based
• Up-front autologous transplantation has improved PFS in responding patients
• Ongoing studies investigate combinations with romidepsin and CHOP/CHOEP, or BV or Pralatrexate
New agents in relapsed/refractory PTCL

• The historical outcomes for patients with relapsed disease have been especially dismal
• In a recent retrospective study on 153 patients with relapsed or refractory PTCLs who did not undergo transplant, the reported median OS was only 5.5 months and the PFS 3.1 months (1)
• These data do not capture possible gains from novel agents, since patients included in the study had been diagnosed prior to 2010, before the approval of the new drugs.

# Studies in relapsed/refractory PTCL

<table>
<thead>
<tr>
<th>Agents</th>
<th>Patients</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>PFS (months)</th>
<th>DOR (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab</td>
<td>34</td>
<td>41%</td>
<td>24%</td>
<td>2.6</td>
<td>7.6</td>
<td>NA</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>111</td>
<td>29%</td>
<td>11%</td>
<td>3.5</td>
<td>10.1</td>
<td>14.5</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>130</td>
<td>25%</td>
<td>15%</td>
<td>4</td>
<td>17</td>
<td>11.3</td>
</tr>
<tr>
<td>Belinostat</td>
<td>129</td>
<td>26%</td>
<td>10%</td>
<td>NA</td>
<td>8.3</td>
<td>NA</td>
</tr>
</tbody>
</table>

2) Damaj et al. J Clin Oncol 31:104-110  
5) O’Connor et al, J Clin Oncol 2013; 31 (Suppl 15): 8507 ABSTRACT
The PROPEL Trial

- **111 patients** with independently confirmed R/R PTCL received **PRALATREXATE IV** at 30 mg/m²/wk for 6 weeks in 7-week cycles, until progression or unacceptable toxicity
  - ORR 29% (CR 11%)
  - Median DoR 10.1 months
  - Median PFS 3.5 months
  - Median OS 14.5 months
- Most common grade 3 to 4 adverse events: thrombocytopenia (32%), mucositis (22%), neutropenia (22%)

Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy

- 130 patients with histologically confirmed R/R PTCL received ROMIDEPSIN at 14 mg/m2 as IV infusion on days 1, 8, and 15 every 28 days, for up to 6 cycles
- ORR 25%
- CR/CRu 15%
- Median DoR 17 months
- The most common grade 3 adverse events were thrombocytopenia (24%), neutropenia (20%), and infections (all types, 19%).

The BENTLY Trial

• 60 patients with histologically confirmed peripheral T-cell lymphoma or cutaneous T-cell lymphoma, who progressed after one or more lines of prior chemotherapy, received BENDAMUSTINE at 120 mg/m2 per day on days 1 - 2 every 3 weeks for six cycles.

• In the intent-to-treat population:
  • ORR 50%
  • CR 28%
  • DoR 3.5 months
  • PFS 3.6 months; OS 6.2 months

• The most frequent grade 3 to 4 adverse events were neutropenia (30%), thrombocytopenia (24%), and infections (20%).

Damaj et al. *J Clin Oncol* 31:104-110
Objective responses in relapsed T-cell lymphomas with single-agent brentuximab

This phase 2, open-label, multicenter study was initiated to evaluate the efficacy and safety of single-agent BV in R/R T cell lymphomas

• Brentuximab vedotin 1.8 mg/kg was administered every 3 weeks until progression or unacceptable toxicity.

Inclusion criteria:

• Histologically confirmed mature T-cell lymphoma with any detectable CD30 expression per institutional laboratory using IHC

• Patients who have had at least one prior systemic therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AITL (n=13)</th>
<th>PTCL (n=22)</th>
<th>All patients (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>64 (55-79)</td>
<td>64.5 (33-83)</td>
<td>64 (33-83)</td>
</tr>
<tr>
<td><strong>CD30 expression per central laboratory, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9 (69)</td>
<td>17 (77)</td>
<td>26 (74)</td>
</tr>
<tr>
<td>Negative</td>
<td>2 (15)</td>
<td>4 (18)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Missing or NA</td>
<td>2 (15)</td>
<td>1 (5)</td>
<td>3 (9)</td>
</tr>
<tr>
<td><strong>Disease status relative to front-line therapy, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>9 (69)</td>
<td>17 (77)</td>
<td>26 (74)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>4 (31)</td>
<td>5 (23)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Median number of prior cancer-related therapy (range)</td>
<td>3 (1-4)</td>
<td>2 (1-9)</td>
<td>2 (1-9)</td>
</tr>
</tbody>
</table>

After a median follow up from first dose of 2.7 months:
• Median PFS 2.6 months

For all patients
ORR 41%
CR 24%

Median PFS for AILT: 6.7 months
Median PFS for PTCL: 1.6 months

There was no apparent correlation between response and CD30 expression:

- 64% of ORR in the 14 patients with ≤ 15% CD30 expression by central review.