Peripheral T-cell Lymphomas
Clinical Presentation and New Drugs

Barbara Pro, MD

6th International Workshop on PET in Lymphoma  Menton,  September 20-21, 2016
T-Cell Lymphomas...Few Facts

- Accounts for ~10%-15% of all NHL
- Increasing number of subtypes
- Classification relies on
  - Morphology
  - Immunophenotype
  - Clinical/anatomical presentation
- Few recurrent genetic or molecular lesions
- Expert hematopathology review essential
- Outcomes are often poor
WHO 2008 Classification of PTCLs

Adapted from Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.

6th International Workshop on PET in Lymphoma  Menton- September 20-21, 2016
International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes

56% NODAL SUBTYPES

Table 1. Major Lymphoma Subtypes by Geographic Region

<table>
<thead>
<tr>
<th>Subtype</th>
<th>North America</th>
<th>Europe</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL-NOS</td>
<td>34.4</td>
<td>34.3</td>
<td>22.4</td>
</tr>
<tr>
<td>Angioimmunoblastic</td>
<td>16.0</td>
<td>28.7</td>
<td>17.9</td>
</tr>
<tr>
<td>ALCL, ALK positive</td>
<td>16.0</td>
<td>6.4</td>
<td>3.2</td>
</tr>
<tr>
<td>ALCL, ALK negative</td>
<td>7.8</td>
<td>9.4</td>
<td>2.6</td>
</tr>
<tr>
<td>NKTL</td>
<td>5.1</td>
<td>4.3</td>
<td>22.4</td>
</tr>
<tr>
<td>AITL</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>Primary cutaneous ALCL</td>
<td>5.4</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like</td>
<td>1.3</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Unclassifiable T-cell</td>
<td>2.3</td>
<td>3.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTL, natural killer/T-cell lymphoma.

Vose J, et al. 2008;26:4124-4130
PTCL

Multiple diseases

- AITL
- PTCL-U

**T-cell lymphomas**

- ALCL
- NK-T
- PTCL-U

**Systemic**

- Alk positive: good prognosis
- Alk negative: as bad as PTCL but...

**Cutaneous**

- Alk Spont regression in up to 25%!

**Syndrome more than disease**

- Autoimmune phenomena
- Not rare > 20% cases
- Some patients indolent course

**Response to steroids alone**

- EBV role? Rituxan?
- Role of microenvironment/angiogenesis

**EBV associated**

- Midline destructive lesions
- XRT more effective than CHT
- Fatal when disseminated

**HSL**

- Young patients
- Homing: Spleen BM
- Pancytopenia
- Median survival < 1 year

**Transplant**

**Asparaginase**

**PTCL**

- Multiple diseases
- Alk positive: good prognosis
- Alk negative: as bad as PTCL but...

**“Wastebasket”**

- Nodal disease is common
- Low-bulk
- More advanced stage

**EBV role? Rituxan? Role of microenvironment/angiogenesis**
Peripheral T-cell Lymphoma-NOS
OS and FFS

Most failures in the first 2 years
No plateau
Less than 20% are “cured”

PTCLs: Guidelines for Initial treatment

Suggested regimens:

- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- HyperCVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone) alternating with methotrexate and cytarabine
- CHOP followed by ICE (ifosfamide, carboplatin, etoposide) or
- IVE (ifosfamide, etoposide, and epirubicin) alternating with intermediate dose methotrexate (New Castle Regimen)
- Dose adjusted EPOCH

NCCN guidelines:
Clinical trials preferred with the exception of ALK + ALCL
Selected Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Histology</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>PFS / EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage KJ, et al.</td>
<td>Almost all received CHOP, retrospective PTCL-US</td>
<td>75</td>
<td>11</td>
<td>84%</td>
<td>64%</td>
<td>29% (5 yr)</td>
</tr>
<tr>
<td></td>
<td><strong>ORR 60-80%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>CR 39-60%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Lack of durable remissions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimer P, et al.</td>
<td>CHOP → ASCT, Prospective PTCL (32) / AITL / ALCL</td>
<td>83</td>
<td>65</td>
<td></td>
<td>39%</td>
<td>ASCT</td>
</tr>
<tr>
<td>Simon KJ, et al.</td>
<td>CHOP vs VIP-rABVD, Prospective PTCL (30) / AITL / ALCL</td>
<td>43</td>
<td>43</td>
<td>62%</td>
<td>39%</td>
<td>41% (2 yr)</td>
</tr>
<tr>
<td></td>
<td><strong>ORR 60-80%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>CR 39-60%</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td><strong>Lack of durable remissions</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

VIP-rABVD, etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine (VIP-reinforced-ABVD).
Novel Approaches
Adding to CHOP......
ABMT for Consolidation
Adding Etoposide to CHOP: German Prospective High-Grade NHL Studies

<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>320</td>
</tr>
</tbody>
</table>


EFS, aged < 60 yrs

PTCL Subtype n

EFS, ALCL, ALK+

Non-etoposide (n = 12)

EFS, other subtypes

EFS, aged < 60 yrs

Etoposide (n = 34)

Non-etoposide (n = 29)

Other subtypes

P = 0.003

P = 0.012

P = 0.057
Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01

90 pts (78%) in CR/CRu at 1st assessment after SCT

166 pts
CHOEP-14

115 (72%) pts
ASCT

25 (16%) pts
primary refract
4 pts
NE
16 off protocol

2 pts
TRD

28 pts
PD
Clinical case

64 y/o male
Stage IIIA T cell lymphoma
Favor “PTCL-NOS”
CHOEP X 3 cycles
PET/CT : CR
2 additional cycles of CHOEP
PFS and OS after 1\textsuperscript{st} relapse in PTCL


Median, 3.7 months

Median, 6.5 months
Targeting Peripheral T-Cell Lymphoma

**Targeting the Cancer Cell**

**Surface Antigens/Receptors**
- CD2
- CD4
- CD25
- CD30
- Chemokine receptors...

**Proteasome inhibition**
**HDAC inhibition**
**Death receptors and ligands**
**Cell-cycle arrest**
**Signal transduction inhibition**

**Targeting the Microenvironment**

**Angiogenesis**
**Immunomodulation**
**Viral pathogens**

**Genetic alterations**
- Recurrent (and maybe targetable) mutations
  - Rhoa, TET2, IDH2, DNMT3A, DUSP2
- Some subtypes have stronger epigenetic signatures

**AITL:** RHOA, TET2, IDH2, DNMT3A, CD28
Targeting Peripheral T-Cell Lymphoma

Targeting the Cancer Cell

- Surface Antigens/Receptors
  - CD2
  - CD4
  - CD25
  - CD30
  - CCR4

- Cellular Survival Mechanisms
  - Proteasome inhibition
  - HDAC inhibition
  - Death receptors and ligands
  - Cell-cycle arrest
  - Signal transduction inhibition

Targeting the Microenvironment

- Angiogenesis
- Immunomodulation
- Viral pathogens

Genetic alterations

- Recurrent (and maybe targetable) mutations
- Rhoa, TET2, IDH2, DNMT3A, DUSP2
- ALK
- Some subtypes have stronger epigenetic signatures

AIrT: RHOA, TET2, IDH2, DNMT3A, CD28
## Summary of Selected Novel agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Phase</th>
<th>Patients (n)</th>
<th>Toxicity (grade 3 or&gt;)</th>
<th>ORR</th>
<th>CRR</th>
<th>DOR (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>Folate antagonist</td>
<td>II</td>
<td>111</td>
<td>Mucositis</td>
<td>29%</td>
<td>11%</td>
<td>10.3</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>HDACi</td>
<td>II</td>
<td>130</td>
<td>Thrombocytopenia, Neutropenia, Infections</td>
<td>25%</td>
<td>14%</td>
<td>17</td>
</tr>
<tr>
<td>Belinostat</td>
<td>HDACi</td>
<td>II</td>
<td>129</td>
<td>Hematologic</td>
<td>26%</td>
<td>11%</td>
<td>8</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>ADC</td>
<td>II</td>
<td>58</td>
<td>Neuropathy</td>
<td>86%</td>
<td>57%</td>
<td>12.6</td>
</tr>
<tr>
<td><strong>Agents Under Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mogamulizumab</td>
<td>Anti-CCR4 mAb</td>
<td>II</td>
<td>37</td>
<td>Neutropenia, rash</td>
<td>34%</td>
<td>17%</td>
<td>8.2</td>
</tr>
<tr>
<td>Alisertib</td>
<td>Aurora A Ki</td>
<td>II</td>
<td>37</td>
<td>Hematologic, FN</td>
<td>24%</td>
<td>5%</td>
<td>NR</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>PI3Ki</td>
<td>I</td>
<td>33</td>
<td>Transaminitis, rash, Neutropenia</td>
<td>47%</td>
<td>12%</td>
<td>NR</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALKi</td>
<td>II</td>
<td>9</td>
<td></td>
<td>100%</td>
<td>100%</td>
<td>2-yr PFS 64%</td>
</tr>
</tbody>
</table>
Classes of HDACi are based on chemical structure

- Not all HDACi have the same specificity or affinity for the 11 different target HDACs

Impact on multiple tumor pathways by targeting both histone and non-histone substrates

Bolden et al., Nat Rev Drug Discovery. 2006; 5, 769.
Romidepsin-Pivotal Study-Design

- Phase 2, open-label, single-arm, international study
- N = 131 patients enrolled; 130 with histopathologically confirmed PTCL
- Dosing: romidepsin 14 mg/m² (4-hour intravenous infusion) on days 1, 8, and 15 of a 28-day cycle × 6 cycles
  - Patients with SD or response could continue to receive treatment beyond 6 cycles at discretion of patient and investigator

<table>
<thead>
<tr>
<th>Best response</th>
<th>PTCL-NOS (n=69)</th>
<th>AITL (n=27)</th>
<th>Alk- ALCL (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>20 (29)</td>
<td>8 (30)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>10 (14)</td>
<td>5 (19)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>PR</td>
<td>10 (14)</td>
<td>3 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>SD</td>
<td>16 (23)</td>
<td>9 (33)</td>
<td>5 (24)</td>
</tr>
</tbody>
</table>

Efficacy of Romidepsin in AITL

Responding Patients with AITL

- P: PR
- R: CR
- C: CR
- D: PD
- SC: T

Withdrawal by patient

Time to response
Duration of response
Duration of treatment

Patients who remain on treatment

- Standard dosing (3 x per cycle)
- Maintenance dosing (2 x per cycle)
- Maintenance dosing (1 x per cycle)

Pro et al. ASH 2014 abstract # 1742

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Targeted Therapy in ALCL

Targeting CD30
Targeting CD30
Brentuximab Vedotin
Pivotal Phase II Study Long-Term Follow-Up

Best Response (N=58)

<table>
<thead>
<tr>
<th></th>
<th>IRF*</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>50 (86)*</td>
<td>50 (86)</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission (CR)</td>
<td>34 (59)</td>
<td>38 (66)</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>16 (28)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>2 (3)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Histology ineligible (HI)</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not evaluable (NE)</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

* Primary endpoint

Future directions:
Role in CD30 + PTCL
Combination therapy in R/R setting
Maintenance vs retreatment
Frontline Therapy → ECHELON 2

Pro et al. ASH Dec 2014, Abstract 3095
Case study

- 48-year-old male, ALK+ sALCL
- Prior treatment:
  - CHOP
  - VAPEC B
  - ASCT
- Cycle 4 restaging: CR
- Patient experienced tumor lysis syndrome after first dose, recovered
- Patient received 8 cycles in total

# PFS and OS by cycle 4 PET status and ALK status

<table>
<thead>
<tr>
<th>Status</th>
<th>4-yr PFS (95% CI)</th>
<th>4-yr OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PET4 status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET+ (n=20)</td>
<td>16% (0%, 32%)</td>
<td>50% (28%, 72%)</td>
</tr>
<tr>
<td>PET- (n=28)</td>
<td>63% (44%, 83%)</td>
<td>86% (72%, 99%)</td>
</tr>
<tr>
<td><strong>ALK status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK+ (n=16)</td>
<td>37% (11%, 62%)</td>
<td>56% (32%, 81%)</td>
</tr>
<tr>
<td>ALK- (n=42)</td>
<td>38% (22%, 54%)</td>
<td>67% (52%, 81%)</td>
</tr>
</tbody>
</table>

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Targeted Therapy in ALCL
Targeting ALK

- 60% of ALCL associated with overexpression of the ALK protein = ALK⁺

typical t(2;5) (p23;35)

<table>
<thead>
<tr>
<th>NPM</th>
<th>ALK</th>
<th>NPM-ALK fusion protein</th>
<th>Variant ALK-fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>chr 5</td>
<td>chr 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALK protein expression
Crizotinib

- 11 ALK+ relapsed NHL patients (9 ALCL)
  - Median of 3 prior therapies
  - Clinical responses in 10 of 11
    - All 9 ALCL pts achieved complete remissions lasting 2-40+ months
    - Negative for NPM/ALK by PCR
    - 2 -yr PFS 64%
  - Non-cross resistant with brentuximab

Ongoing PHASE I-II study in combination with chemotherapy in untreated patients

Gambacorti Passerini et al. J. Natl. Cancer In:
Targeting PI3K
PI3K-δ and PI3K-γ Support the Growth and Survival of B-cell and T-cell Malignancies
Duvelisib (IPI-145) Phase 1 Study

MTD reached at 75 mg BID

- 2 dose limiting toxicities (DLTs) at 100 mg BID:
  - Gr 3 rash; Gr 3 ALT/AST elevation
  - Limited myelosuppression, rare pneumonitis

8 100 mg BID
n = 33

25 mg BID Expansion Cohorts
- R/R CLL/SLL, iNHL, MCL
- High-risk/Tx-naïve CLL

75 mg BID MTD Expansion Cohorts
- R/R CLL/SLL, iNHL, MCL
- T-cell lymphomas
- Aggressive B-cell lymphoma
- Myeloid neoplasms
- Acute lymphoblastic
Clinical Activity in TCL

<table>
<thead>
<tr>
<th>Population</th>
<th>Best Response, n (%)</th>
<th>Median Time to Response, months (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>CR</td>
</tr>
<tr>
<td>All TCL</td>
<td>33</td>
<td>2 (6)</td>
</tr>
<tr>
<td>PTCL</td>
<td>15</td>
<td>2 (13)</td>
</tr>
<tr>
<td>CTCL</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

- Clinical activity observed across PTCL and CTCL subtypes
  - PTCL: CRs in 1 EATCL and 1 PTCL NOS
    - PRs in 2 AITCL, 2 SPTCL, 1 PTCL NOS, 1 ALCL (ALK-negative)
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1

Horwitz S. et al, ASH 2014 Abs
Early Pharmacodynamic Response in PET Avid Disease May Predict Best Clinical Response

- Below: CT scans from a 71 year-old woman with relapsed AITCL. Prior therapies: rituximab (ITP), CHOP, pralatrexate, vorinostat, brentuximab vedotin

- 10 patients evaluated with PET (PET-CT) at Cycle 1 Day 22, 6 with a reduction in SUV, 4 with an increase in SUV

- 83% (5/6) with PET response had a subsequent clinical response (CR or PR)

- 100% (4/4) without PET response had disease progression

Horwitz S. et al, ASH 2014 Abstrac
Crizotinib

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  - Clinical responses in 10 of 11
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Gambacorti Passerini et al. J. Natl. Cancer In:

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Going Forward.....

Targeted Therapy in PTCL?

- Subtype-specific treatments
  - CD30+ → Brentuximab Vedotin
  - ALK+ ALCL → Alk inhibitors
  - ATLL → Mogamulizumab
  - NK-T → Asparaginase-based treatments, EBV directed cell therapy
  - PTCL-NOS → Pralatrexate, ? Others
  - AITL → HDACi, immunosuppressive therapy

- Combinations needed to improve CR rate for most subtypes

- Consolidation
  - If no transplant maintenance strategy?

6th International Workshop on PET in Lymphoma  Menton - September 20-21, 2016
The Value and Relevance of the T Cell Lymphoma Registries and International Collaborations: the Case of COMPLETE and the T-Cell Project

Monica Bellei¹ · Chadi Nabhan² · Emanuela Anna Pesce¹ · Luana Conte³ · Julie M. Vose⁴ · Francine Foss⁵ · Massimo Federico¹
Grazie !