Lymphoma Tumor Board

T-cell lymphomas

May 12, 2017
### WHO / Revised European American Lymphoma (REAL) Classification

<table>
<thead>
<tr>
<th>B-cell lymphomas (80% - 85%)</th>
<th>T-cell lymphomas (15% - 20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diffuse large B-cell lymphoma</td>
<td>• Precursor T-lymphoblastic lymphoma/leukemia</td>
</tr>
<tr>
<td>• Follicular lymphoma</td>
<td>• Peripheral T-cell lymphomas</td>
</tr>
<tr>
<td>• Chronic lymphocytic leukemia / small lymphocytic lymphoma</td>
<td>• Cutaneous T-cell lymphomas (mycosis fungoides, Sézary syndrome, and others)</td>
</tr>
<tr>
<td>• Mantle cell lymphoma</td>
<td>• Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>• Marginal zone B-cell lymphomas</td>
<td>• Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>• Burkitt lymphoma</td>
<td>• Extranodal natural killer/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>• Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)</td>
<td>• Enteropathy-associated intestinal T-cell lymphoma (EATL)</td>
</tr>
<tr>
<td>• Hairy cell leukemia</td>
<td>• Anaplastic large cell lymphoma (ALCL)</td>
</tr>
<tr>
<td>• Primary central nervous system (CNS) lymphoma</td>
<td>• Peripheral T-cell lymphoma, unspecified</td>
</tr>
</tbody>
</table>
Peripheral T-Cell Lymphomas – Incidence
Peripheral T-Cell Lymphomas

- T-cell lymphomas are rare and account for one in ten cases of non-Hodgkin lymphoma
- Can be associated with EBV and Human T-lymphotropic virus 1 (HTLV-1)
  - Only 1-5% of infected persons are thought to develop cancer as a result of infection with HTLV-1
- Peripheral T-cell non-Hodgkin lymphoma (PTCL), not otherwise specified (NOS), is the most common PTCL subtype, accounting for 25% of cases
- Four primary classes of T-cell lymphomas:
  - Extranodal T cell lymphoma
  - Cutaneous T cell lymphomas: Mycosis fungoides and Sézary syndrome
  - Anaplastic large cell lymphoma
  - Angioimmunoblastic T cell lymphoma
Karyotypic abnormalities in a patient with PTCL

Figure 42.7

Complex karyotype abnormalities observed in a patient with peripheral T-cell lymphoma.
Subsets of $T_h$ cells and corresponding T-cell lymphomas

- **$T_h1$**: IFN-$\gamma$
  - Subset of PTCL, NOS
  - **TBX 21**
  - **T-bet**

- **$T_h2$**: IL4, IL5, IL13
  - Subset of PTCL, NOS
  - Poor overall survival
  - **GATA3**

- **$T_{FH}$**: IL21, CXCL13
  - Angioimmunoblastic T-cell lymphoma
  - **BCL6**

- **$T_{reg}$**: TGF-$\beta$, IL10
  - Adult T-cell lymphoma/leukemia (HTLV1)
  - **FOXP3**
Cutaneous T cell lymphoma (CTCL)

• As malignant T cell migrate, they can form skin lesions that appear as rashes
• These lesions progress to plaques and can be itchy
• Subtypes of CTCL:
  • Mycosis fungoides
  • Pagetoid reticulosis
  • Sézary syndrome
  • Granulomatous slack skin
  • Lymphomatoid papulosis
  • Pityriasis lichenoides chronica
  • Pityriasis lichenoides et varioliformis acuta
  • CD30+ cutaneous T-cell lymphoma
  • Secondary cutaneous CD30+ large cell lymphoma
  • Non-mycosis fungoides CD30-cutaneous large T-cell lymphoma
  • Pleomorphic T-cell lymphoma
  • Lennert lymphoma
  • Subcutaneous T-cell lymphoma
  • Angiocentric lymphoma
  • Blastic NK-cell lymphoma
Cutaneous T cell lymphoma (CTCL) – (2)

- US FDA approved treatments:
  - (1999) Denileukin diftitox (Ontak)
  - (2000) Bexarotene (Targretin) a retinoid
  - (2006) Vorinostat (Zolinza), a hydroxymate histone deacetylase (HDAC) inhibitor
  - (2009) Romidepsin (Istodax), a cyclic peptide histone deacetylase (HDAC) inhibitor

Figure 10. Cutaneous CD8 epidermotropic T cell lymphoma. (A) Lymphoid infiltrate with marked epidermotropism; and (B) positivity for CD8.
Anaplastic large-cell lymphoma (ALCL)

- Encompasses at least 4 clinical entities that histologically have in common the presence of large pleomorphic cells that express CD30 and T-cell markers
- Out of the 4 types of ALCL, one subtype of systemic ALCL expresses the protein anaplastic lymphoma kinase (ALK); the other types of ALCL do not express ALK
- Greater than 90% of the cases contain a clonal rearrangement of a T cell receptor
- Morphologic variants include the following types:
  - Common (featuring a predominance of hallmark cells)
  - Small-cell (featuring smaller cells with the same immunophenotype as the hallmark cells)
  - Lymphohistiocytic
  - Sarcomatoid
  - Signet ring
- CHOP is currently the first line of treatment
- Radiation therapy as per institutional preference, but usually added for bulky disease

Anaplastic large cell lymphoma - cytology of tumor cells showing binucleated cells and ring-shaped nuclei
Angioimmunoblastic T-cell lymphoma

- Represents only 1-2% of all cases of NHL, and 1 in 5 cases of PTCL per yr.

- Early stage AITL is very uncommon and median age of diagnosis is 65

- Strong association with EBV

- Nearly 70% of patients will have bone marrow involvement

- 20-50% of patients will experience skin manifestations in the form of rashes and urticarial lesions to nodular tumors

- Cell of origin is the T follicular helper ($T_{FH}$) cell, which is an effector T-cell subset

- Karyotypic abnormalities are seen in 9 out 10 cases

### Table 1. Clinical and laboratory features of AITL

<table>
<thead>
<tr>
<th>Publication reviewed</th>
<th>1975 to 1999*</th>
<th>2007 to 2016*</th>
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<tbody>
<tr>
<td>ATIL cases reviewed</td>
<td>77</td>
<td>556</td>
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<tr>
<td>Males, %</td>
<td>42-48</td>
<td>56-74</td>
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<tr>
<td>Median age range</td>
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<td>62-65</td>
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<tr>
<td>General clinical features, %</td>
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<td></td>
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<tr>
<td>B-symptoms</td>
<td>29-85</td>
<td>55-77</td>
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<tr>
<td>Performance status &gt;1</td>
<td>57</td>
<td>37-50</td>
</tr>
<tr>
<td>LDH elevation</td>
<td>25-74</td>
<td>60-86</td>
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<tr>
<td>Advanced stage (III/IV)</td>
<td>94</td>
<td>81-92</td>
</tr>
<tr>
<td>Low-risk IPI (0-1)</td>
<td>No reported</td>
<td>11-21</td>
</tr>
<tr>
<td>Areas of involvement, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple nodal stations</td>
<td>97-100</td>
<td>76-99</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>61</td>
<td>28-70</td>
</tr>
<tr>
<td>Skin rash</td>
<td>38-48</td>
<td>31-45</td>
</tr>
<tr>
<td>Laboratory tests, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>40-83</td>
<td>33-65</td>
</tr>
<tr>
<td>Positive DAT (Coomb's)</td>
<td>43-57</td>
<td>13-75</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>20-31</td>
</tr>
<tr>
<td>Hypergammaglobulinemia</td>
<td>50-77</td>
<td>50-84</td>
</tr>
<tr>
<td>Hypereosinophilia</td>
<td>29-39</td>
<td>32-34</td>
</tr>
</tbody>
</table>

DAT, direct anti-globulin test; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

*Article referenced in reference section; not all parameters were recorded for all patients.
Angioimmunoblastic T-cell lymphoma expresses CXCL13. (a) A polymorphous paracortical infiltrate is seen in this case of angioimmunoblastic T-cell lymphoma (hematoxylin and eosin). (b) CD4-positive neoplastic T cells are clustered in the perifollicular area and extend into the paracortex (immunoperoxidase). (c) The neoplastic T cells show intense CD10 positivity (immunoperoxidase). (d) Strong cytoplasmic staining for CXCL13 is seen in the same cell population (inset, immunoperoxidase). (e) Increased numbers of CD20-positive B cells and immunoblasts are present in the paracortex (immunoperoxidase). (f) Immunoblasts are positive for EBV (in situ hybridization).
Extranodal NK/T-Cell Lymphoma

• Also known as nasal-type NK lymphoma and polymorphic/malignant midline reticulosis
• The nasal cavity, nasopharynx and upper aerodigestive tract are often involved, although extranasal presentations do occur (skin, gastrointestinal, eye, testis, lung, soft tissue)
• Strong association with EBV
• “The NCCN guidelines recommend either high-dose radiotherapy alone for stage I without high risk features, or concurrent chemoradiotherapy for stage I and II with either of two regimens”

Figure 6. A–C, Extranodal NK-cell/T-cell lymphoma, nasal type. A, H&E-stained section shows infiltration by atypical lymphocytes with necrosis and haemorrhage (case 32, Dr Goodlad, Western General Hospital & University of Edinburgh, UK). The patient, a 70-year-old Cau- casian man, presented with facial swelling and induration. The tumour involved paranasal sinuses, skin, and testis. B, Perforin-positive neo- plastic cells show prominent angioinvasive growth. C, Almost all tumour cells are EBER-positive.
Peripheral T-cell Lymphoma, not otherwise specified

- “With current immunophenotypic and molecular markers, about 30% to 50% of PTCL cases are not further classifiable and are categorized as PTCL-NOS”

- Genetic studies point to recurrent genetic abnormalities of the following genes:
  - TET2
  - IDH2
  - DNMT3A
  - RHOA
  - CD28
Normal T and NK cells, cell lines, and PTCL cases classified by unsupervised hierarchical clustering: Major entities of PTCL form tight clusters with cases of PTCL-NOS and other rare entities interspersed.

Gene expression–based molecular predictors of the major subgroups of PTCL

Estimating prognosis in patients with PTCL

Peripheral T-Cell Lymphomas

INTERNATIONAL PROGNOSTIC INDEXa

ALL PATIENTS:
• Age >60 years
• Serum LDH > normal
• Performance status 2-4
• Stage III or IV
• Extranodal involvement
>1 site

INTERNATIONAL INDEX, ALL PATIENTS:
• Low
• Low intermediate
• High intermediate
• High
0 or 1
2
3
4 or 5

PROGNOSTIC INDEX FOR PTCL-U (PIT)b

RISK FACTORS:
• Age >60 years
• Serum LDH > normal
• Performance status 2-4
• Bone marrow involvement

PROGNOSTIC RISK:
• Group 1
• Group 2
• Group 3
• Group 4
0
1
2
3 or 4

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEXa

PATIENTS ≤60 YEARS:
• Stage III or IV
• Serum LDH > normal
• Performance status 2-4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:
• Low
• Low/intermediate
• High/intermediate
• High
0
1
2
3


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Treatment overview – peripheral T cell lymphomas

Peripheral T-Cell Lymphomas

**INDUCTION THERAPY**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I, II</td>
<td>Multiagent chemotherapy[^h^] x 6 cycles ± RT (30-40 Gy to involved region) or Multiagent chemotherapy[^h^] x 3-4 cycles + RT (30-40 Gy to involved region)</td>
</tr>
<tr>
<td>Stage III, IV</td>
<td>Multiagent chemotherapy[^h^] x 6 cycles</td>
</tr>
</tbody>
</table>

**ALCL, ALK +**

- **PTCL, NOS**
- **ALCL, ALK**
- **AITL**
- **EATL**

![Flowchart](image)

- **Breast implant-associated ALCL**

  - Emerging entity described as development of ALCL around the implant (involving the fibrous capsule and/or seroma only). In this setting, the natural history of this entity appears generally favorable with surgical removal of the implant alone as adequate therapy for most patients.
  - However, rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALCL ALK.
  - Optimal treatment of these cases is not well defined and management should be individualized.

[^h^]: For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.

[^k^]: Localized areas can be irradiated before or after high-dose therapy.

[^i^]: See Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[^g^]: See Suggested Treatment Regimens (TCEL-B).

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Treatment of peripheral T-cell lymphomas - regimens

### Suggested Treatment Regimens

#### First-line Therapy:
- Clinical trial
- ALCL, ALK+ histology
  - CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  - CHOP-E (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- Other histologies (ALCL, ALK-; PTCL, NOS; AITL; EATL), regimens that can be used include:
  - CHOEP
  - CHOP-14
  - CHOP-21
  - CHOP followed by ICE (ifosfamide, carboplatin, etoposide)
  - CHOP followed by IVE (ifosfamide, etoposide, epirubicin)
  - Alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine

#### First-line Consolidation:
- Consider consolidation with high-dose therapy and stem cell rescue.
  (ALCL, ALK+ is a subtype with good prognosis and does not need consolidative transplant if in remission.)

#### Second-line Therapy (candidate for transplant):
- Clinical trial preferred
- Belinostat (category 2B)
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL (category 2B)
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- Dose-adjusted EPOCH
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine, oxaliplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- MINE (mesna, ifosfamide, mitoxantrone, etoposide)
- Pralatrexate
- Romidepsin

#### Second-line Therapy (non-candidate for transplant):
- Clinical trial preferred
- Alemtuzumab
- Belinostat (category 2B)
- Bortezomib
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL (category 2B)
- Cyclosporine for AITL only
- Dose-adjusted EPOCH
- Gemcitabine
- Pralatrexate
- Radiation therapy
- Romidepsin

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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Treatment of relapsed/refractory PTCL

Peripheral T-Cell Lymphomas

RELAPSE/REFRACTORY DISEASE

ADDITIONAL THERAPY

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

Candidate for transplant

Clinical trial (preferred) or Second-line therapy
See Suggested Regimens (TCEL-B)

Clinical trial or Second-line therapy
See Suggested Regimens (TCEL-B) or Palliative RT

No response

CONSOLIDATION/ADDITIONAL THERAPY

Complete response or Partial response

Clinical trial or Consider allogeneic stem cell transplant (non-myeloablative or ablative) or Consider high-dose therapy with autologous stem cell rescue

Clinical trial or Best supportive care or Palliative RT

RELAPSE #2 OR GREATER

Clinical trial

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
OS of patients with the common subtypes of PTCL


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**Table 2.** Comparison of IPI and PIT-calculated survival outcomes in four PTCL-NOS case series. Survival figures are given as percentages. IPI, International Prognostic Index; PIT, Prognostic Index for PTCL-NOS; OS, overall survival; FFS, failure-free survival; PFS, progression-free survival.

<table>
<thead>
<tr>
<th>Index</th>
<th>Score</th>
<th>Gallamini, 2004(^{21})</th>
<th>Weisenburger, 2011(^{24})</th>
<th>Ellin, 2014(^{25})</th>
<th>Xu, 2015(^{26})</th>
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<tr>
<td></td>
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<td>5-year OS</td>
<td>5-year OS</td>
<td>5-year FFS</td>
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<td>11</td>
<td>8</td>
<td>18</td>
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</tbody>
</table>

(*) Low-intermediate and high-intermediate risk patients according to IPI are grouped together as intermediate-risk patients.
References

- [https://www.slideshare.net/nohasalah/nhl-updates-2016-59716919](https://www.slideshare.net/nohasalah/nhl-updates-2016-59716919)
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- [http://asheducationbook.hematologylibrary.org/content/2008/1/491/F25.expansion](http://asheducationbook.hematologylibrary.org/content/2008/1/491/F25.expansion)
  - [http://topics.sciencedirect.com/topics/page/T_cell?](http://topics.sciencedirect.com/topics/page/T_cell?)