Diagnosis and Management of Lymphoma in Head and Neck

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Objectives

1. To address the diagnostic challenges and new molecular tests of lymphoma

2. To understand the role of local management of lymphoma in head and neck

3. To learn the new targeted therapies in CLL/SLL
Epidemiology

- 4% increase each year 1950s-1990s. The rate of increase has decreased within last a few years
- 65,000 new cases in US
Etiology

**Infectious Agent**
- Epstein-Barr virus
- HTLV-I
- HIV
- Hepatitis C virus
- *Helicobacter pylori*
- Human herpes virus 8

**Inherited immunodeficiency disease**

**Acquired immunodeficiency diseases**

**Autoimmune disease**

**Chemical or drug exposures**
Diagnosis
Relative frequency of lymphoid malignancies. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; MALT, mucosa-associated lymphoid tissue.

From: Hematology and Oncology
Harrison's Manual of Medicine, 18e, 2014
WHO Classification of Lymphoma

- Lymphoid development: progenitors, mature lymphocytes, plasma cell
- T- cells or B- cells (including plasma cells)

I. Indolent or aggressive is not included in the classification
II. Leukemia vs. Lymphoma
### WHO classification of the non-Hodgkin lymphomas (subclassified according to clinical aggressiveness*)

<table>
<thead>
<tr>
<th>The indolent lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell neoplasms</strong></td>
</tr>
<tr>
<td>Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma (+ Waldenstrom's macroglobulinemia)</td>
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<tr>
<td>Plasma cell myeloma/plasmacytoma</td>
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<tr>
<td>Hairy cell leukemia</td>
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<tr>
<td>Follicular lymphoma (grade I and II)</td>
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<tr>
<td>Marginal zone B-cell lymphoma</td>
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<td>Mantle cell lymphoma</td>
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<tr>
<td><strong>T-cell neoplasms</strong></td>
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<tr>
<td>T-cell large granular lymphocyte leukemia</td>
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<tr>
<td>Mycosis fungoides</td>
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<tr>
<td>T-cell prolymphocytic leukemia</td>
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<table>
<thead>
<tr>
<th>Natural killer cell neoplasms</th>
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<tbody>
<tr>
<td>Natural killer cell large granular lymphocyte leukemia</td>
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### The aggressive lymphomas

<table>
<thead>
<tr>
<th><strong>B-cell neoplasms</strong></th>
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<tbody>
<tr>
<td>Follicular lymphoma (grade III)</td>
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<tr>
<td>Diffuse large B-cell lymphoma</td>
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<tr>
<td>Mantle cell lymphoma</td>
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</tbody>
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<tr>
<th><strong>T-cell neoplasms</strong></th>
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<tbody>
<tr>
<td>Peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, T/null cell</td>
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</table>

### The highly aggressive lymphomas

<table>
<thead>
<tr>
<th><strong>B-cell neoplasms</strong></th>
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<tbody>
<tr>
<td>Burkitt's lymphoma</td>
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<tr>
<td>Precursor B lymphoblastic leukemia/lymphoma</td>
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<tbody>
<tr>
<td>Adult T-cell lymphoma/leukemia</td>
</tr>
<tr>
<td>Precursor T lymphoblastic leukemia/lymphoma</td>
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* Editor's note: The WHO classification system of non-Hodgkin lymphoma (NHL) is presented here, subclassified according to the degree of clinical aggressiveness (ie, indolent, aggressive, highly aggressive) shown by each variant. Mantle cell lymphoma can behave clinically as either an indolent or an aggressive disorder. Adapted from Harris, NL, Jaffe, ES, Diebold, J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee meeting-Ann Arbor, November 1997. J Clin Oncol 1999; 17:3995.
Cytogenetic Translocation and Associated Oncogenes Often Seen in Lymphoid Malignancies

- **Precursor B cell acute lymphoid leukemia**
  - t(9;22)(q34;q11) BCR/ABL

- **Mantle cell lymphoma**
  - t(11;14)(q13;q32) BCL-1, IgH

- **Follicular lymphoma**
  - t(14;18)(q32;q21) BCL-2, IgH

- **Burkitt's lymphoma, Burkitt's leukemia**
  - t(8;)(q24;)- C-MYC

- **CD30+ Anaplastic large cell lymphoma**
  - t(2;5)(p23;q35) ALK

- **Lymphoplasmacytoid lymphoma**
  - t(9;14)(p13;q32) PAX5, IgH
“Double-hit lymphomas”

- High-grade B-cell lymphomas
- Dual chromosomal rearrangements
  - MYC
  - BCL2 or BCL6
- Poor outcome: OS: 34 months

- Risk-adapted therapy: DA-EPOCH-R, Bone Marrow Transplant
- Bcl2 inhibitor ABT-199: downregulate Bcl2 and resensitize patients to chemotherapy
Clinical course is highly variable
Asymptomatic patients
Treatment related morbidity and mortality
Withhold therapy until CLL/SLL related:
  - Symptoms: fatigue, WT loss, Enlarged spleen and lymph node
  - Complications: impaired bone marrow or immune function
  - Clear evidence of disease progression
Clinical Difference in Common FISH Detected Cytogenetic Abnormalities

- **17p- p53 mutation**
  - Resistant to chemotherapy but sensitive to mAbs, Lenalidomide, BCL-2 inhibitors, BCR antagonists or allo-transplant

- **11q- ATM deletion and DNA repair defect**
  - High CR rate but shot remissions

- **Trisomy12**
  - High CD-20 expression

- **13q- MiR-15/16 deletion**
  - High response rate
FDA Approved Drugs for Treatment of Patients with CLL

- **Glucocorticoids**
- **Conventional Chemotherapy**
  - *Alkylating agents*
    1. Chlorambucil
    2. Cyclophosphamide
    3. Bendamustine
  - *Purine Analogs*
    1. Fludarabine
    2. Pentostatin
    3. Cladribine
- **Kinase Inhibitors**
  - Ibrutinib
  - Idelalisib (w/ Rituximab)
- **Monoclonal Abs (mAb)**
  - Alemtuzumab
  - Ofatumumab
  - Rituximab
  - Obinutuzumab (Gazyva) (Rituximab with an attitude)
Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia
Byrd, J.C. NEJM 370:997 2014

A Progression-free Survival

B Overall Survival

No. at Risk (events)

Idelalisib

Placebo
Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

Byrd, J.C. NEJM, 371:213

A

Progression-free Survival (%)

Hazard ratio for progression or death, 0.22 (95% CI, 0.15–0.32)
P=0.001 by log-rank test

Months

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Ofatumumab</th>
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<tbody>
<tr>
<td>195</td>
<td>183</td>
<td>116</td>
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<tr>
<td>38</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
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B

Overall Survival (%)

Hazard ratio for death, 0.43 (95% CI, 0.24–0.79)
P=0.005 by log-rank test

Months

No. at Risk

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<td>115</td>
</tr>
<tr>
<td>88</td>
<td>31</td>
<td>3</td>
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Lymphoma-like Disorders

- Drug reaction: Phenytoin or Carbamazepine
- Immune disorders
- Viral infection: EBV, CMV
- Bacterial infections: Cat-scratch disease

Without definitive diagnosis of lymphoma: follow up, repeat biopsy instead of instituting therapy
“Significant” Lymph Node(s)

Size:
- 1.5cm x 1.5 cm
- <1 cm
- 1-1.5 cm

Location:
- Supraclavicular: 75-90%
- Cervical and axillary: 60-70%
- Inguinal: 30-40%

Context
- >3 groups of enlarged LNs
- B symptoms
- Abnormal chest imaging
- *fluctuation of size of lymph node is nature of indolent or less aggressive lymphoma
Types of Biopsies

- **FNA: screening test**
  - Suggesting lymphoma
  - Impossible for accurate diagnosis of lymphoma

- **FNA + Flow cytometry**
  - Reactive vs mature B cell lymphoma

- **Excisional biopsy of an intact lymph node**
  - Standard biopsy for lymphoma diagnosis
Diagnosis of Lymphoma

- Histology

- Immunophenotype

- Genetic studies:
  - Ig gene rearrangement  Positive in 85% of B cell lymphoma
  - TCR PCR Positive in 90% of T cell lymphoma
Lymphoma Treated Surgically or With Radiation Alone

1. MZL of parotid gland
2. Cutaneous B cell lymphoma
3. Follicular lymphoma of eye lid