Update on Diagnosis and Treatment of Lymphoma

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Cancer Incidence

New Cancer Cases
- Lymphoma: 63,000
- NHL: 53,600
- HL: 79,000

Cancer Death
- Lymphoma: 25,280
- NHL: 23,800
- HL: 1,480

Outline
- Diagnostic approach to lymphoma
- Advances in treatment of follicular lymphoma
- Monitor long-term treatment toxicities in survivors of Hodgkin’s lymphoma
- Monitors patients with newly diagnosed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Primary cutaneous lymphoma

CA Cancer J Clin 1997
Case 1: “I have a new lump”

- 64 yo male developed a 2 cm painless soft tissue mass in the right neck 4 weeks prior. No recent h/o URI. Otherwise normal physical exam. The pt received a trial of antibiotics, but the node was growing.

What do you do next?
1. Observe
2. Antibiotics
3. Fine needle aspiration
4. Excisional biopsy

What do you do next?
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2. Antibiotics
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Case 1: cont’d

- A fine needle aspiration was performed.
- The cytology report:
  Mature-looking lymphocytes, expressing CD20, CD10, without co-expression of CD5 and CD23. The morphology and immunostaining support the diagnosis of follicular lymphoma, but can not exclude diffuse large B cell lymphoma. Recommend excisional biopsy.
B cell Lymphoma Classification

- Highly aggressive: Rapid growing, highly curable
  - Burkitt lymphoma
- Aggressive lymphoma: Curable
  - diffuse large B cell lymphoma
- Indolent lymphoma: incurable
  - follicular lymphoma: grade 1-3

Gold Standard for Diagnosis of Lymphoma

- Excisional biopsy
- Core biopsy
- FNA is inadequate in most cases

Lymphoma Staging

- Limited Stage: Stage 1 and stage 2
- Advanced stage: Stage 3, 4
- Imaging studies: CT versus PET/CT
- Bone marrow biopsy
- Lumbar puncture in selected cases
Case 1: cont’d

- Now your pt is most likely has a new diagnosis of lymphoma, while he is waiting for an oncology consult, what else you can do?
  1. An excisional biopsy of the lymph node
  2. CT with IV contrast C/A/P
  3. Whole body PET/CT
  4. 1+2
  5. 1+3

What else can you do?

1. An excisional biopsy of the lymph node
2. CT with IV contrast C/A/P
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Follicular Lymphoma: Clinical Features

- Median age of diagnosis: 64 yo
- Incurable with standard therapy
- Asymptomatic pts do not require treatment
- High response rate to initial therapy
- Continued relapse over the years
- Survival has improved in the past decade from 10 yrs to 18 yrs
- Can transform to more aggressive lymphoma, after which, survival is < 1 year
Treatment of Follicular Lymphoma

- Limited Stage:
  - Standard of care: Radiotherapy
- Advanced Stage:
  - Watchful waiting for asymptomatic pts
  - Rituximab alone
  - Rituximab-containing chemotherapy

Rituximab

- Anti-CD20 Antibody
- Targeted therapy: CD20 is expressed on malignant as well as benign B cells
- The single most important therapeutic advancement in lymphoma in the past 30 years

Rituximab: Randomized trials

Rituximab + chemotherapy versus chemotherapy alone

Rituximab plus chemotherapy is superior to chemotherapy alone in response rate, duration of response and overall survival, without added toxicity
New in 2009 for follicular Lymphoma: The StiL trial

- Rituximab + Bendamustine is equivalent to Rituximab + CHOP in efficacy, but with less toxicity
- A new standard first-line therapy for follicular lymphoma?

Rummel MJ et al., ASH 2009, Abstract 405

Summary: Follicular Lymphoma

- Diagnosis: excisional or core biopsy
- Staging: whole body PET/CT or CT plus bone marrow biopsy
- Treatment: Rituximab
  - Early stage: XRT can generate long term remission
  - Advanced Stage and require treatment: no standard first line therapy, rituximab +/- chemo
- Overall survival: 18 years from diagnosis
- Transformation: very poor outcome

Case 2: Asymptomatic Lymphocytosis

- 65 yo male was found to have lymphocytosis on a routine annual physical exam. His WBC 13.5, Absolute lymphocytes are mildly elevated to 7500. Absolute neutrophils, Hb, Platelets are all within normal limits. He is otherwise healthy with well controlled HTN.
- What would you do?
Case 2: cont’d

1. Watch and wait
2. Request a review of the blood smear by a hematopathologist
3. Repeat the CBC in one week
4. Request a heme consult

Case 2: cont’d

- The hematopathologist told you that it does not look like acute leukemia. You repeated the blood counts in 3 months, WBC is still elevated at 15 (from 13.5), absolute lymphocytes increased from 7500 to 8000. Now what would you like to do?

What would you do?

1. Watch and wait
2. Request a review of the blood smear by a hematopathologist
3. Repeat the CBC in one week
4. Request a heme consult
DDx: Lymphocytosis

- Reactive:
  - Infectious:
    - Viral: EBV, CMV, influenza, hepatitis, etc
    - Bacterial: Pertussis, cat scratch, toxo,…
  - Non-infectious:
    - Hypersensitivity
    - Stress-induced
    - Persistent polyclonal B-cell lymphocytosis

- Malignant and pre-malignant:
  - Acute leukemia
  - Chronic leukemia
  - Lymphoproliferative disease of large granular lymphocytes
  - Thymoma

Determine the Clonality of Lymphocytes: Flow Cytometry

- What does flow cytometry do?
  - Examine the surface marker expression at a single cell level
  - Determine if the lymphocytosis is caused by T or B lymphocytes
  - Determine the clonality of B cells
  - T cell clonality can only be determined by PCR
Case 2: CLL

- Now you decided to send peripheral blood for flow cytometry analysis:
- Result:
  Kappa restricted B cell lymphoproliferative disease, expressing CD19, weak CD20, CD5 and CD23, consistent with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

CLL

- A disease of elderly: median age 70
- More common in men than women
- Strongest risk factor: family h/o lymphoid malignancies
- Median age for familial cases: 58 yo
- Incurable with standard therapy
- No survival benefit to treat asymptomatic pts
- Indolent clinical course
- Can transform to more aggressive lymphoma

New Concept: Monoclonal B Cell Lymphocytosis (MBL)

- Definition:
  - Clonal B cell population in the blood with the phenotype of CLL or other B cell malignancies
  - Absolute lymphocyte count < 5,000
  - No other features of a lymphoproliferative disorder or autoimmune disease
  - A pre-malignant condition for CLL
  - Almost all CLLs are preceded by MBL
  - Prevalence: 4% general population >40 yo
  - Annual risk of MBL converting to CLL that requires treatment is 1-2%

Staging for CLL

<table>
<thead>
<tr>
<th>Rai Stage</th>
<th>Definition</th>
<th>Survival, yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (low risk)</td>
<td>Lymphocytosis in blood and marrow only</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>II and III (intermediate risk)</td>
<td>Lymphadenopathy, splenomegaly +/- hepatomegaly</td>
<td>7</td>
</tr>
<tr>
<td>IV (high risk)</td>
<td>Anemia, thrombocytopenia</td>
<td>0.75 - 4</td>
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Prognostic Factors:
- CD38 status
- IGHV mutation status
- ZAP-70 expression
- β2-microglobulin
- Cytogenetic abnormalities

Cytogenetic Abnormalities in CLL

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Frequency, %</th>
<th>Median Survival, mos</th>
<th>Time to Treatment, mos</th>
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<tbody>
<tr>
<td>trisomy 12</td>
<td>39</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>17</td>
<td>72</td>
<td>15</td>
</tr>
<tr>
<td>t(14;18) + other</td>
<td>14</td>
<td>114</td>
<td>38</td>
</tr>
<tr>
<td>Normal Karyotype</td>
<td>16</td>
<td>111</td>
<td>48</td>
</tr>
<tr>
<td>trisomy 12 only</td>
<td>36</td>
<td>113</td>
<td>82</td>
</tr>
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N = 325

Dohner et al., NEJM, 2000
### FAQ for Newly Diagnosed CLL

<table>
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<tr>
<th>How to follow?</th>
<th>When to treat?</th>
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<tbody>
<tr>
<td>1. H&amp;P, CBC every 3 months initially</td>
<td>1. Lymphocyte doubling time &lt;6 mos</td>
</tr>
<tr>
<td>2. Look for signs of transformation: B symptoms, progressive adenopathy at one site, elevated LDH</td>
<td>2. Bulky progressive adenopathy</td>
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<td>3. Cytopenias from packed marrow</td>
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<td>4. B symptoms</td>
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<td>5. Frequent infections</td>
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### Non-myeloablative Allogeneic Transplant for Refractory CLL

- Allogeneic bone marrow transplant is the only potentially curative treatment for CLL
- Take advantage of graft-versus-leukemia effect
- Can be performed in pts up to 75 yo
- Treatment related mortality: 10-20%
- Relapse free: 50-60% at 5 years
- Overall survival: 70-80% at 5 years
- Biggest non-relapse risk: graft-versus-host-dz
  - Acute GVH: 10-20%
  - Chronic GVH: up to 50%

Montserrat et al., 2006

### Summary: CLL

- Most common leukemia in the West
- Proceed by Monoclonal B Cell Lymphocytosis
- No survival advantage to treat asymptomatic pts
- Generally indolent and incurable by standard treatment
- Reduced-intensity allogeneic bone marrow transplant is high risk, but is potentially curative for CLL pts
- The age cut-off for reduced-intensity allogeneic transplant is 75 yo
Case 3: “I have a cough that does not go away”
- 25 yo female with a progressive dry cough for 2 months, no other URI symptoms, no B symptoms
- A CXR showed

Anterior Mediastinal Masse

DDX: Anterior Mediastinal Masses
- Thymomas
- Germ cell tumors
- Non-Hodgkin's lymphoma
  - Primary med diffuse large cell lymphoma
- Hodgkin's lymphoma
- Congenital cysts
- Intrathoracic thyroid tissue
- Parathyroid lesions
Diagnostic Procedures

- Mediastinoscopy
- Path showed classical Hodgkin’s lymphoma

Hodgkin’s Lymphoma

- One of the most curable cancers
- Bimodal age distribution: 15-35, 65
- Associated with EBV infection
- Subclassification:
  - Classical HL: 95%
  - Lymphocyte predominant HL: 5%

Dr. Thomas Hodgkin 1798 - 1866

Treatment of Hodgkin’s Lymphoma: A risk-adapted approach

- Favorable early stage: chemo + XRT
- Unfavorable early stage: chemo + XRT
- Advanced stage: chemo +/- XRT
Research Focus for HL

Minimize long term treatment toxicity while maintain the high cure rate

New in 2009:
Favorable Early Stage HL

- Decrease radiation from 30 Gy to 20 Gy; decrease chemotherapy from 4 cycles to 2 cycles
- New standard: 2 cycles of ABVD followed by 20 Gy radiation
- Still maintained cure rate of above 90% for early favorable HL


Case 3 cont’d

- The pt was diagnosed with unfavorable Stage II A/E Hodgkin’s lymphoma with elevated ESR and bone invasion from the mediastinal mass
- She was treated with ABVD x 4 followed by radiotherapy to the neck and chest, yielding a complete remission
- How do we follow this pt in the years to come?
Post-remission Followup for Hodgkin’s Survivors: Risks

- Relapsed disease:
  - 80% relapses occur during the first 2 years of remission
- Potential risks from having received radiotherapy:
  - Hypothyroidism
  - Early cardiovascular disease
  - Second cancers
- Reproductive health

Post-remission Followup: The first 5 years

- Followup with oncologist:
  - Every 2 months first year
  - Every 3-4 months second year
  - Every 6 months 3-5 yrs
  - Annually after 5 yrs
- Scans: controversial
  - CT every 6 months for the first 2 years
- Labs: CBC with diff, Chem 7, LFTs, TFTs, ESR
- Reproductive health: UCSF fertility research for pts with heme malignancies

Post-remission Followup: Monitoring Late Effects after 5 Years

- Annual H&P:
  - Cardiovascular: aggressively manage BP, baseline ECHO/stress test at 10 y
  - Vaccination: annual flu, pneumococcal re-vaccination after 5 y if had splenectomy/XRT.
    Meningococcal and H-flu in selected cases
- Annual Labs: CBC, chem 7, Lipids, TFTs
- Annual breast screening: begins 8-10 y after therapy or reaches age 40
- Annual chest imaging in high risk pts

NCCN Guidelines 2010
Summary: Hodgkin’s Lymphoma
- Mostly occurs in young patients
- Highly curable
- Treatment is based on a risk-adapted approach: chemo+/- radiation
- Monitoring for late toxicity is paramount

Primary Cutaneous Lymphomas
- Rare disease: representing 2% of lymphomas
- Very heterogeneous group of diseases

UCSF Multidisciplinary Cutaneous Lymphoma Clinic
- Dermatologist
- Oncologist
- Dermatopathologist
- Radiation oncologist

Clinical Course of Mycosis Fungoides
- Disease progression:
  - Patch -> Plaque -> Tumor -> Lymph Node
  - Blood /visceral
- Staging:
  - Skin, the area of skin involvement, lymph node, blood and visceral
- Prognosis: based on staging
Survival of Mycosis Fungoides

Kim, et al., Arch Dermatol. 2003

Treatment: A Stage-based Approach

- Skin directed therapy:
  - Topical steroids
  - Topical chemo
  - UV light therapy
- Systemic Therapy:
  - Oral methotrexate
  - Biologic modifiers
  - Photopheresis
- Radiotherapy: spot radiation and total skin radiation
- Chemotherapy
- Allogeneic Transplant

Summary:
Primary Cutaneous Lymphoma

- Rare disease
- Generally indolent
- Incurable, generally require life-long treatment
- Early stage disease is life-changing, advanced disease is life-threatening
- Significantly expanded therapeutic options available now
Thank you!