Disclosures

Consulting advice:

Teva, Gilead, Juno, Celgene, Kite, Genmab, Nanostring, Biotest, Regeneron, Abbvie, Sutro, Sunesis, BMS
How does lymphoma present itself?

- Feel or see a lump (lymph nodes)
  - Patient, family, doctor
  - Get a scan for another reason
- Abnormal lab test
  - Blood counts, chemistry, other
- Symptoms
  - Pain
  - Fatigue
  - Fever, weight loss
  - Location-related issue (e.g. bowel issue)
  - Other
Making the diagnosis

- Biopsy
  - Lymph node, bone marrow, other
  - Excisional, core needle, fine needle
  - More is better
- Sometimes appropriate to rebiopsy
- Pathology second opinions can be helpful
What does the pathologist do?

- Look at the material directly
  - Cell characteristics under the microscope
- Immunophenotype or “markers” (CD)
- Molecular studies
  - Clonality
  - Cytogenetics
  - FISH
Staging tests

- Perhaps less important than in other tumors

- Physical examination

- Laboratory tests

- Bone marrow aspirate and biopsy

- Radiology tests (varies)
  - CT scan
  - PET scan
  - MRI

- Lumbar puncture – sometimes

- Other tests as appropriate (e.g. colonoscopy, eye exam)
Lymphoma staging

Most patients have stage III or IV

Less important than other cancers
Lymphoma is complicated

- Over 100 different types (confusing)
  - Classifications keep changing
  - Making an accurate diagnosis is key
- Different types have different treatments
  - Vary dramatically
- Expected goals of therapy can differ widely
  - Curing the disease
  - long term management ("chronic disease")
  - New ways to understand the disease are continually evolving
- Novel treatments keep coming – CLINICAL TRIALS !!
# NHL: Facts and Figures

Hematologic malignancies: Estimated new cases in 2010

<table>
<thead>
<tr>
<th>Type</th>
<th>Estimated New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphoma</strong></td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>8,490</td>
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<tr>
<td><strong>Non-Hodgkin lymphoma</strong></td>
<td>65,540</td>
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<tr>
<td><strong>Myeloma</strong></td>
<td>20,180</td>
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<tr>
<td><strong>Leukemia</strong></td>
<td>43,050</td>
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<tr>
<td>Acute lymphocytic leukemia</td>
<td>5,330</td>
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<tr>
<td>Chronic lymphocytic leukemia</td>
<td>14,990</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>12,330</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>4,870</td>
</tr>
<tr>
<td>Other leukemia</td>
<td>5,530</td>
</tr>
</tbody>
</table>

Incidence of NHL has increased over recent eras

NHL=non-Hodgkin lymphoma; SEER=Surveillance, Epidemiology, and End Results.

Emerging potential contributors to lymphoma development

- Tumor cell genetic abnormalities
- Host factors
  - tumor microenvironment – “immune response”
  - angiogenesis
  - host genetic polymorphisms
- Infectious agents
  - bacterial, viral
- Immune dysregulation
  - autoimmunity, immunosuppression
- Other environmental exposures
What features determine prognosis?
What is the plan?

- Multiple factors, that interact with each other
- Type of lymphoma
- Age
- Fitness of the patient
- Stage
- Lots of areas of involvement outside of nodes
  - Depends on type
- Blood tests
- Other special tests depending on type
Major types of lymphoma

- Hodgkin’s lymphoma
  - “Classical”
  - Other (Lymphocyte Predominant)
- T cell non-Hodgkin’s lymphoma (10-15%)
  - Cutaneous
  - Large cell (aggressive)
  - Other
- B cell non-Hodgkin’s lymphoma (85-90%)
Therapy summary – HL and T cell

- Hodgkin’s lymphoma
  - ABVD chemotherapy, other regimens
  - Radiation
  - Stem cell transplantation (some relapsed patients)
  - Brentuximab vedotin

- T cell non-Hodgkin’s lymphoma (10-15%)
  - Cutaneous
    - UV light, chemotherapy, biologic agents, radiation, new treatments
  - Large T cell (aggressive)
    - Similar to large B cell, chemotherapy, stem cell transplantation
B cell non Hodgkin’s Lymphoma
Prognosis and Treatment

- **Indolent** (follicular, CLL/SLL, marginal zone) – 30%
  - Goal: Disease control over many years
  - Observe, chemotherapy, rituximab, radioimmunotherapy, combinations, stem cell transplant
  - Can “transform” to more aggressive type

- **Mantle cell lymphoma** – 10%
  - Goal: Disease control over years
  - Chemotherapy, rituximab, stem cell transplant

- **Aggressive** (diffuse large B cell, Burkitts) – 35%
  - Goal: Curable with chemotherapy + rituximab
  - CHOP-R standard, radiation, other chemotherapy, stem cell
If on watch and wait for indolent or mantle cell, when to start treatment?

- Large lymph nodes
- Many sites
- Rapid change over time
- Symptoms
- Blood count or lab problems
Commonly used treatment options as first line treatment for lymphoma

- Rituximab (indolent)
- Bendamustine + Rituximab (indolent)
- CHOP-R (indolent or aggressive)
- EPOCH-R (aggressive)
- R-HyperCVAD, R-CODOX-M (mantle cell, highly aggressive)
- Combinations in clinical trials
- Novel agents/approaches
Antibody targets on B cell malignancies

Cheson and Leonard, NEJM 2008
Antibody Structure

Human

Murine

Chimeric
Main mechanisms of monoclonal antibody action in lymphoma

Cheson and Leonard, NEJM 2008
New directions in monoclonal antibody therapy

- New versions of rituximab (novel anti-CD20)
  - Ofatumumab, obinutuximab
  - Generally given with higher/more doses

- Other antibodies against different targets

- Combinations of antibodies

- Adding an “immune stimulant” to rituximab or other antibodies

- Radioactive antibodies

- Toxin-linked antibodies
Brentuximab vedotin (SGN-35)

- Chimeric SGN-30 antibody linked to Monomethyl Auristatin E (MMAE)
  - MMAE is analogue of anti-mitotic agent dolastatin 10
- Highly potent (low nM), 100-1000-fold greater than doxorubicin
- Inhibits tubulin polymerization

Francisco et al, Blood 2003
Brentuximab vedotin (SGN-35) Mechanism of action

Younes et al, NEJM 2010
Pembrolizumab and Nivolumumab
Immune checkpoint inhibitors

- PD-1 is present on immune (T) cells
- Its ligands/partners, PD-L1 and PD-L2, are present on certain tumor cells
- Binding of PD-1 to PD-L1/2 inhibits immune T-cell activation, allowing tumors to evade the immune response
- P and N are anti-PD-1 antibodies
IMIDs in lymphoid malignancies

- IMID effects
  - Inhibits TNFα
  - Inhibits angiogenesis
    - (bFGF, VEGF)
  - Stimulates T cells (CD8+)
  - Inhibits IL-12
  - Induces apoptosis
  - Alters cytokines
  - Affects stromal cells
  - Inhibits pro-survival factors (Akt)

Lenalidomide in NHL

- FDA approved in myeloma, myelodysplasia
- Related to thalidomide
  - Modulates immune system, direct tumor effects, blood vessel formation
- Pill, given 3 weeks on, one off
- Main side effects are on blood counts
- Responses seen in most lymphoma subtypes
  - 20-50% of relapsed patients
- Several studies in various NHL types
- Combinations with rituximab and chemotherapy
B-cell receptor signaling and inhibition in B cell malignancies

Modified from Stevenson F K et al. Blood 2011;118:4313-4320
Ibrutinib in NHL

- FDA approved in mantle cell, CLL, marginal zone
- Bruton’s Tyrosine Kinase Inhibitor
- Main side effects are on blood counts, GI, fatigue
- Responses seen in most CLL and MCL patients
- Several studies in various NHL types
- Combinations with rituximab and chemotherapy
Idelalisib in NHL

- FDA approved in follicular lymphoma, CLL
- PI3 kinase Inhibitor
- Main side effects are on blood counts, liver enzymes, sometimes colitis
- Responses seen in most CLL and follicular NHL patients
- Several studies in various NHL types
- Combinations with rituximab and chemotherapy have been associated with infections in some settings
Stem cell transplantation

- **Autologous stem cell transplant**
  - Basically way to administer higher doses of chemotherapy
  - More common in relapsed aggressive lymphoma and relapsed Hodgkin’s disease

- **Allogeneic stem cell transplant**
  - Another donor, “matched”
  - More toxic, but adds immune anti-tumor effects
  - Less commonly used in lymphoma
  - New versions under study - “mini allo”
CAR-T cell therapy

1. Leukapheresis
2. T-cell activation/transduction
3. Modified T-cell expansion
4. Chemotherapy
5. Modified T-cell infusion

Antibody-coated beads
Bead removal
Early clinical trial data with CAR-T cells

- Studies are small, with varied patient characteristics and regimens
- Time in preparing the T cells creates some biases
- Significant responses have been seen (some extending 1-2 years +) in ALL, CLL and NHL of various types with refractory disease
- Toxicity (cytokine release) involving transient mental status changes and ICU stays can occur
- Promising, awaiting more data with longer followup and comparative studies with larger patient numbers
How can we use imaging to guide lymphoma therapy?

- CT scans give size of masses
- PET scans include an injection of radioactive glucose
  - Taken up more in aggressive lymphoma
  - Less in indolent lymphomas, MCL
  - Also taken up in infection, inflammation
- Use of PET scans generally
  - Recommended in aggressive, hodgkins
  - Not recommended in indolent, MCL
    - Unless looking for transformation
PET scans in AGGRESSIVE LYMPHOMA (DLBCL) and HODGKINS

- Early negative PET scan is a good sign
- May allow us to limit radiation in some settings or eventually limit # of chemotherapy cycles

- BUT
  - Remember different with indolent and MCL
  - Lots of controversy about this (work in progress)
  - Lots of variability in what is positive and negative
  - Some studies suggest lots of false positive (inaccurate scans)

- Increasing discussion about doing FEWER scans in a general sense
The good news for our patients...

- Survival is improving in lymphoma
- Lots of new agents
  - Enhance standard regimens
  - Provide less toxic alternatives
  - Can be useful in relapsed/refractory settings
- New prognostic tools
  - Tailor treatment to the patient (slow progress)
- New insights into biology
  - Novel potential targets and biomarkers
- Lymphoma remains an active area of interest for researchers and pharma/biotech
Still room for improvement …

- Too many patients die from or with lymphoma
- Morbidity from disease and treatment
- Use of prognostic markers to guide treatment is rudimentary
- Information remains limited in how best to combine or sequence agents (indolent NHL)
- Patients rarely participate in clinical trials
  - Phase III trials particularly challenging
- Decreasing research funding
“One type” of tumor seems uniform
“One type” of tumor is very diverse
“One size fits all” treatment
“Precision” treatment

Rx A
Rx B
Rx C
Rx D
Rx A + W
Rx B + X
Rx C + Y
Rx D + Z
Rx A + X
Rx B + W
Rx C + Z
Rx D + Y
What does the future hold in lymphoma therapy?

- Additional causes or risk factors will be identified
- Patient subsets will be clarified with respect to prognosis and optimal therapy
- New agents will substitute for or be added to standard regimens
- Novel treatment options will emerge
- Better short- and long-term outcomes will result
What is advice for a newly diagnosed patient?

- Make sure the diagnosis is as clear as possible
- Get educated about lymphoma, clinical trials
- Develop relationships with a strong care team
  - MDs, nurses, PA/NP, social work, other support
  - Expertise, "good fit", clinical trials access
  - Family and friends
- Establish expectations of therapy
  - Is treatment necessary?
  - Cure vs long term management, "dictatorship vs negotiation"
- Chart and carry out plan but be prepared to change it
- Continue to live your life as best you can
What is advice for a patient in remission?

- Establish expectations about what the disease is likely to do
- Determine if there are steps to be taken that can reduce the chance of or delay relapse and whether they are worth the tradeoffs
- Don’t go crazy worrying about relapse
  - Generally think hard about doing scans if you are otherwise well
- Remain educated about what is new in lymphoma
- Do what they can to support lymphoma research, support and progress
- Enjoy being in remission and try to live well
What is advice for a patient who has relapsed?

- Make sure it is truly a relapse before acting
- Consider reassessing the lymphoma (rebiopsy)
- Decide if you need to broaden your care team (more complicated)
- Carefully determine the implications of the relapse
  - Do you need to act?
  - What does it mean for my big picture?
- Review treatment options, pros/cons and expectations
  - Make sure your list is complete and thoroughly analyzed
- Consider clinical trials
- Remember that it is usually not “the end of the world”