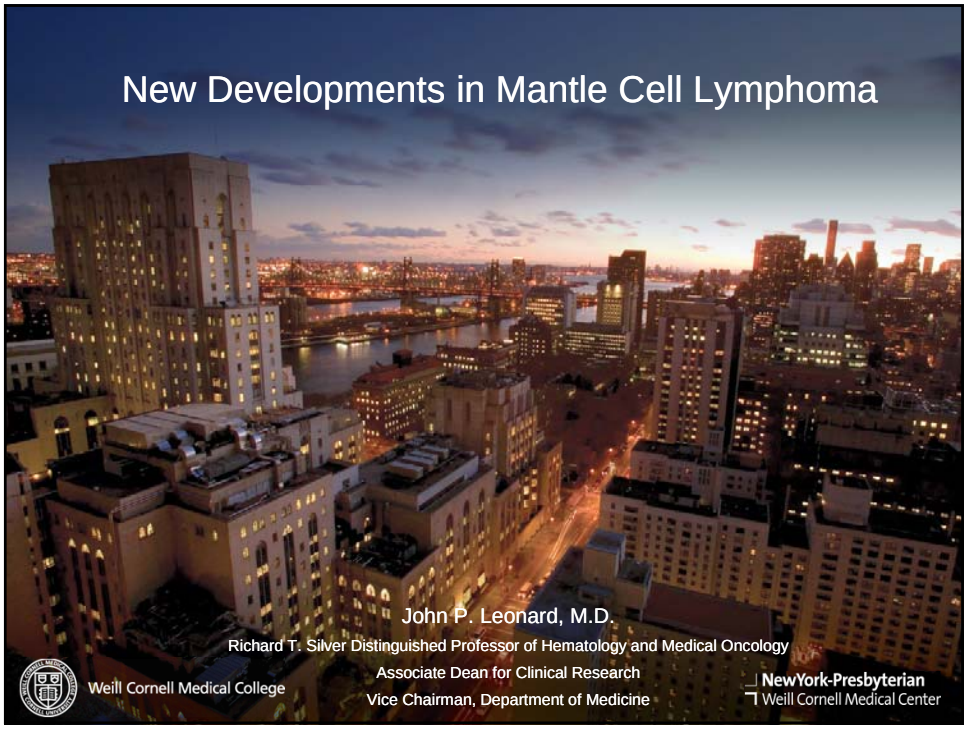
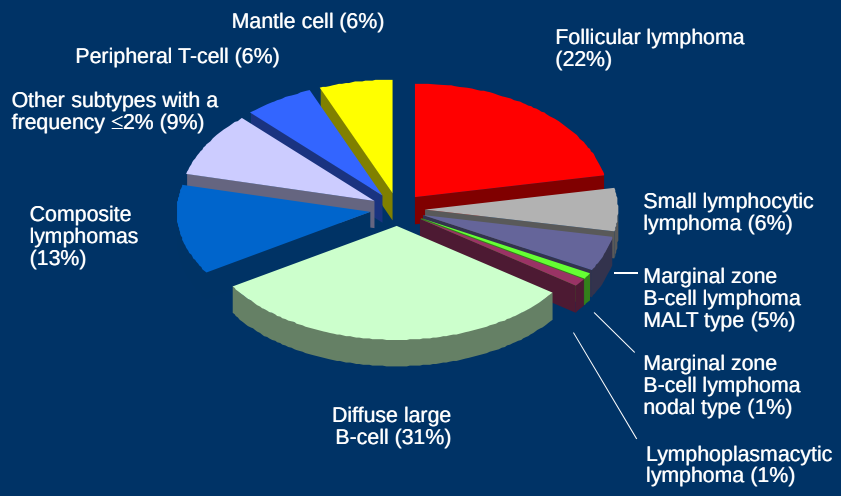


Lymphoma is Complicated

- Over 60 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 !!

Frequency of NHL Subtypes in Adults



Armitage JO and Weisenberger DD. *J Clin Oncol*. 1998;16:2780–2795.

What features determine prognosis?

- 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

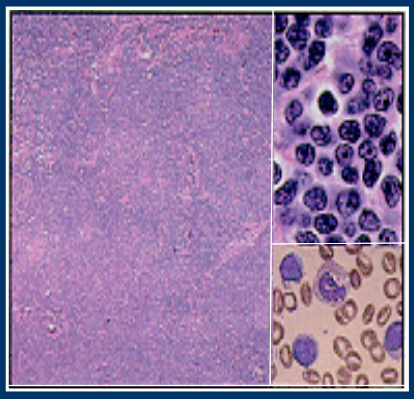
B-cell non-Hodgkin Lymphoma

Prognosis and Treatment

- Indolent (follicular, CLL/SLL, marginal zone) – 30%
  - Goal: Disease control over many years
  - Observe, chemotherapy, rituximab (Rituxan®, 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, new drugs
- Aggressive (diffuse large B-cell, Burkitt's) – 35%
  - Goal: Curable with chemotherapy + rituximab
  - CHOP-R standard, radiation, other chemotherapy, stem cell

Mantle Cell Lymphoma (MCL)

- 5-10% of B-cell NHL
- 74% male
- Median age 63 yrs
- Broad array of treatment options
- Clinical course can be variable
- Characterized by specific genetic lesions (11;14)



Fisher et al, *Blood.* 1995.
Available at: https://www.moffitt.usf.edu/pubs/ccj/v3n2/dept3.html.

MCL Initial Treatment Options

Observation
R-CHOP
Modified R-HyperCVAD
R-CHOP/RIT
R-Bendamustine

Less intensive

vs

R-CHOP/ASCT
R-HyperCVAD/MTX/Ara-C
R-HyperCVAD/MTX/Ara-C/ASCT
Nordic

More intensive

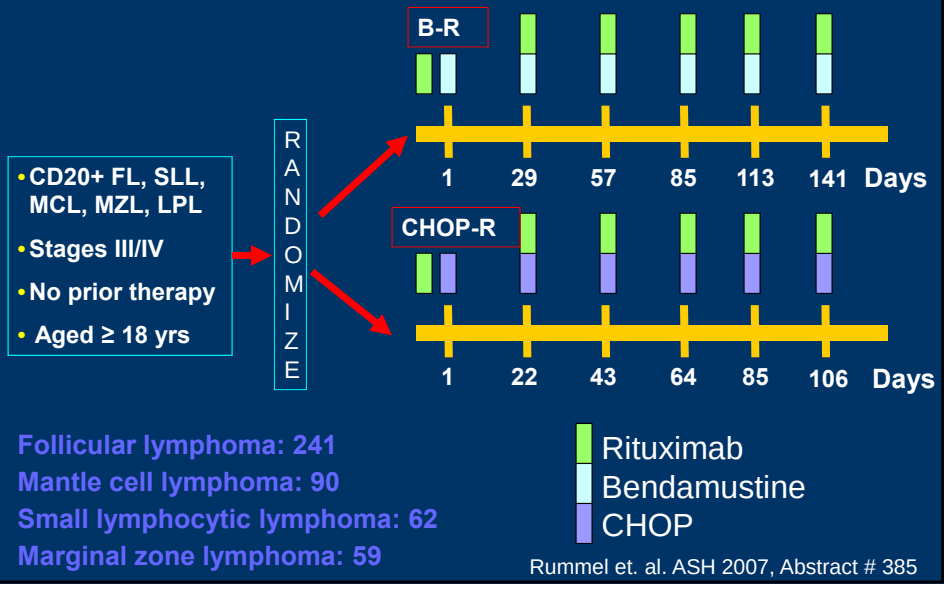
If on "watch and wait," when to start treatment?

- Large lymph nodes
- Many sites
- Rapid change over time
- Symptoms
- Blood count or lab problems

Rituximab Chimeric Anti-CD20 Monoclonal Antibody

- Binds to CD20 receptor on B-cells
- Administered weekly x 4 infusions
- Approximately 50% response rate in indolent NHL lasting roughly 12 months
  - Higher in follicular lymphoma
  - Lower in SLL/CLL and in aggressive lymphomas
  - Lower in bulky disease
- 40% response rate to retreatment
- Maintenance improves efficacy (? Particularly in MCL)
- Fc receptor status may correlate with outcome
- Generally well tolerated
- Many combinations with chemotherapy

Randomized Phase III Study of First-Line B-R versus CHOP-R in Indolent NHL



Rummel et. al. ASH 2007, Abstract # 385

Bendamustine + Rituximab vs CHOP + Rituximab

- B-R without hair loss, less blood count toxicity, fewer infections
- Response rate about 90%, 50% CR in both
- Durations of about 2-3 years (ongoing f/u), longer with B-R

Rummel et. al. ASH 2007, Abstract # 385

Issues in Treatment of MCL in Older or Less Fit Patients

- Role for “watch and wait” in asymptomatic patients
- Bendamustine-Rituximab vs CHOP-R
- Role of rituximab maintenance
- Can we use chemotherapy-free regimens?
- Clinical trial options

Issues in Treatment of MCL in Younger or More Fit Patients

- Role for "watch and wait" in asymptomatic patients
- Are more intensive treatments better?
  - Longer remissions, less clear survival
- Can we use chemotherapy-free regimens?
- Clinical trial options

Stem Cell Transplantation

- Autologous stem cell transplant
  - From "self", fancy way to give more chemotherapy
  - More common in MCL, relapsed aggressive lymphoma and relapsed Hodgkin disease
- Allogeneic stem cell transplant
  - From another person – "matched"
  - More toxic, but adds immune anti-tumor effects
  - Less commonly used in lymphoma
  - New versions under study – "mini allo"
- Other new drugs

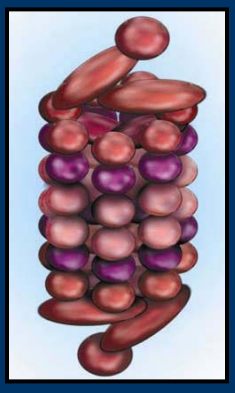
2 Opposite MCL Management Approaches

- Aggressive strategies
  - Objective of treatment – long period of remission extended survival
  - CHOP-R + SCT, hyperCVAD
  - Hoping that more intensive strategy will pay off
  - Downside – more toxicity
- Gentler strategies
  - Objective of treatment – disease control, less toxicity
  - Less intensive treatments, new drugs
  - Hoping that less intensity will improve quality of life
  - Downside – is it less effective in long term?

Biological Effects of Bortezomib (Velcade®)

Proteasome inhibition has several effects:

- Affects cell growth regulatory proteins
- Interferes with blood vessel formation
- Directly kills cells
- Different mechanisms
- Cancer cells may be more sensitive to effects



Bortezomib (Velcade®) in NHL

- FDA approved for recurrent MCL
- Given IV (few min) or SQ d 1, 4, 8, 11 every 3 weeks
- Main side effects: neuropathy, fatigue, platelets
- Responses in 1/3 of patients, usually 6-12 months, some patients longer

- Also active and under study in other NHL
- Combinations with rituximab and chemotherapy

Lenalidomide (Revlimid®) in NHL

- FDA approved in myeloma, myelodysplasia and MCL
- Cousin of thalidomide
  - Modulates immune system, direct tumor effects, blood vessel formation
- Pill, given 3 weeks on, 1 off
- Main side effects are on blood counts, rash, fatigue
- Responses seen in most lymphoma subtypes
  - 20-50% of relapsed patients, about 1/3 of MCL pts

- Several studies in various NHL types
- Combinations with rituximab and chemotherapy

Key New Drugs in MCL in Clinical Trials

- Ibrutinib (Bruton's tyrosine kinase inhibitor)
  - Oral agent, active, well tolerated, numerous ongoing studies
- Idelalisib (PI3 Kinase inhibitor)
  - Oral agent, active, well tolerated, some ongoing studies
- Palbociclib (Cell cycle inhibitor)
  - Oral agent, some combination studies
- ABT-199 (Apoptosis inhibitor)
  - Small MCL experience promising

So what is a newly diagnosed patient to do….?

- 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

So what is a patient in remission to do….?

- 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 you can to support lymphoma research, support and progress
- Enjoy being in remission and try to live well

So what is a patient who has relapsed to do….?

- Make sure it is truly a relapse before acting
- 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"

The good news…

- Survival is improving in lymphoma (including MCL)
- 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
- Patients rarely participate in clinical trials
  - Phase III trials particularly challenging
- Decreasing research funding

Conclusions

- Lots of progress happening – be encouraged
- Support participation in clinical trials
  - All I have presented stems directly from patient participation in clinical trials
  - Opportunity for access to new agents and approaches

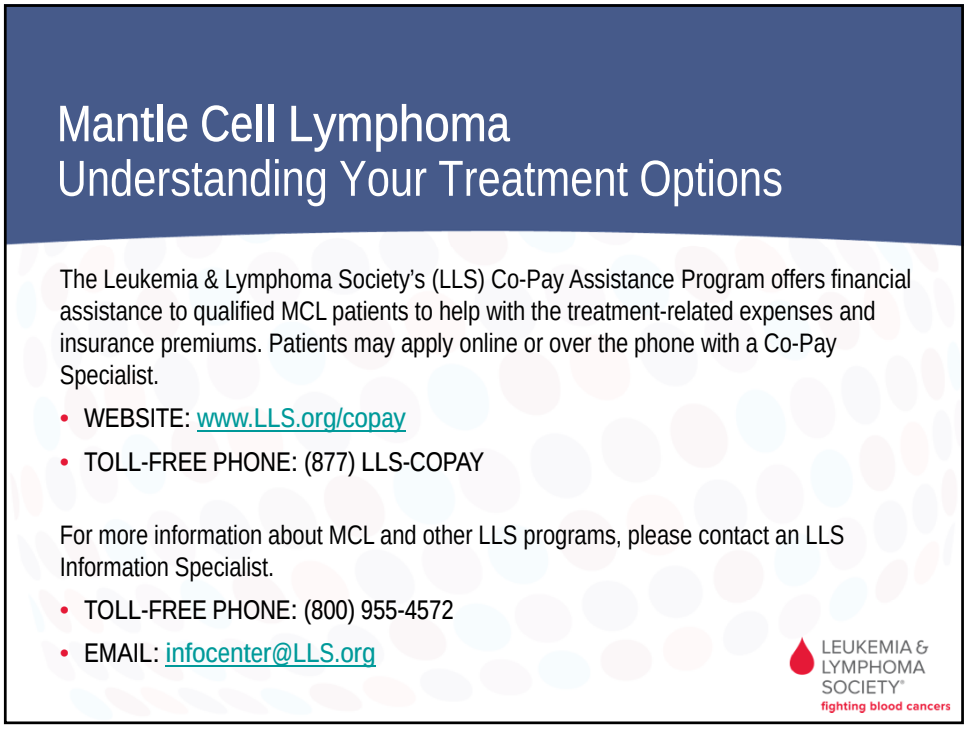
Mantle Cell Lymphoma
Understanding Your Treatment Options

Question and Answer Session

Dr. Leonard's slides are available for download at

www.LLS.org/programs

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers



Mantle Cell Lymphoma
Understanding Your Treatment Options

The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified MCL patients to help with the treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- WEBSITE: www.LLS.org/copay
- TOLL-FREE PHONE: (877) LLS-COPAY

For more information about MCL and other LLS programs, please contact an LLS Information Specialist.

- TOLL-FREE PHONE: (800) 955-4572
- EMAIL: infocenter@LLS.org

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