UPDATE on CLL

Welcome & Introductions

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CLL Update on Diagnosis and Treatment

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Chronic Lymphocytic Leukemia

- Most prevalent type of adult leukemia
- Defined by select flow cytometry markers on leukemia cells (CD5, CD19, CD20, CD23, slg).
- Median age of diagnosis of CLL is 72 years, with only 10% of patients under age 50.
- More common in men than women (2:1 ratio)
- Environmental predisposition uncertain, although Vietnam Veterans with Agent Orange exposure warrant “service-connected status”
- Genetic predisposition present, with approximately 10% of patients having a first-generation relative with CLL however no common gene has been identified
Critical Decision Times for CLL Patients

- **Diagnosis***
  - Learning about disease and impact on life
  - Working through stress of having a blood cancer and likely not doing anything (watch and wait versus watch and worry)

- **At time of first treatment***
  - Appropriate tests and choice of initial therapy
  - Consideration of clinical trials with non-chemotherapy based treatment

- **Relapse disease***
  - Appropriate tests and choice of and consideration of clinical trials/transplant

*All junctures, in particular relapse are ideal times to see a CLL specialist who can work with your local doctor*

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**Diagnosis and Evaluation of CLL**

- Immunophenotype of blood to confirm diagnosis
- Physical exam and labs to confirm Rai stage
  - Rai 0 just lymphocytosis
  - Rai 1 lymph node enlargement
  - Rai 2 spleen enlargement
  - Rai 3 anemia (hemoglobin < 11 in absence of AIHA)
  - Rai 4 low platelets (<100 in absence of ITP)
- Bone marrow biopsy and CT scans not needed
- Prognostic factors
  - FISH—del(17p) and del(11q22.3) less favorable
  - IVGH mutational status—un-mutated less favorable
  - B2M—higher less favorable
  - Lymphocyte doubling time < 1 year—higher less favorable
  - Other prognostic factors include CD38, ZAP-70 and others
Typical Discussion Following Testing

- Asymptomatic low risk disease (Stage 1-2)
  - No therapy or consideration of early intervention as part of clinical trial
  - Follow up Q3 months for 1 year and than Q6m
- Asymptomatic high risk disease (Stage 1-2)
  - No therapy outside of trial but consideration of early intervention with non-chemotherapy approach in clinical trial
  - Follow up Q3m indefinitely
- Symptomatic low or high risk disease or Stage 3-4
  - Consider treatment based upon genetic findings
- Discussion of complications of disease

Autoimmune Cytopenias of CLL

- Autoimmune hemolytic anemia and thrombocytopenia common in CLL (10-25%) and often presents when disease is active
- Anemia or thrombocytopenia due to autoimmune complication does not impact survival and should not be used for staging
- Approach of AIHA and ITP requires assessment of secondary causes and relationship to disease or therapy
- AIHA and ITP treatment are quite similar with prednisone ± rituximab
Infections in CLL

- Most common cause of morbidity and mortality in CLL
- Preventative strategies include
  - Prevnar 13 at diagnosis and Q5 years
  - Influenza vaccine yearly and prophylaxis if exposed
  - No live vaccine (Including varicella zoster vaccine)
  - Viral and PCP prophylaxis with fludarabine or bendamustine
- IVIG use
  - Although expensive, it is effective prevent recurrent infections not cleared with multiple antibiotic courses
  - Consider giving for 1-2 months post influenza if IgG low

Other CLL Related Complications

- Secondary cancers
  - more common in CLL and related to immune suppression-
    regular screening should be considered for these
  - Bone marrow damage (MDS) more common after FCR
- Richter's Transformation
  - Pathology can be large cell lymphoma or Hodgkin’s Disease
  - PET scans can be extremely useful in deciding nodal region
to biopsy
  - Outcome of these patients poor and transplant should be
    considered
- Hypersensitivity to insects
When to Treat CLL Patients

- No advantage to treating CLL until symptoms develop irrespective of genomic features
- IWCLL 2008 criteria for treatment
  - Enlarging, symptomatic lymph nodes (> 10 cm)
  - Enlarging, symptomatic spleen (> 6 cm)
  - Cytopenias due to CLL (hemoglobin < 11, platelets < 100)
  - Constitutional symptoms due to disease (fatigue, B-symptoms)
  - Poorly controlled AIHA or ITP
  - Lymphocyte doubling time < 6 months or increase of 50% over a 2-month time period (weakest criteria)
- Lymphocyte count < 300 x 10^9/L not an indication for Rx


History of CLL Therapy: 1970-2013

- Chlorambucil: well tolerated oral agent but low response
- Fludarabine: higher response, longer remission but no major impact on survival; not beneficial to age >65 years
- Fludarabine/cyclophosphamide: higher response, longer remission, but no major impact on survival; MDS
- Antibody rituximab: well tolerated with low response
- Rituximab addition to fludarabine ± cyclophosphamide (FCR): higher response, longer remission and overall survival
  - FCR currently standard therapy for younger CLL patients
  - Bendamustine + Rituximab often substituted for FCR
Complications of FCR Therapy

- More common in patients > age 65
- Early
  - More neutropenia with rituximab; thrombocytopenia, and infection are similar
- Late
  - More Neutropenia with rituximab
  - Richter’s Transformation risk lowered with rituximab
  - Myelodysplasia (3%)
  - Secondary cancer 8-9%

Alternative Regimens for CLL Therapy

- Bendamustine/rituximab (Fischer et al, JCO 2012)
  - 117 pt phase II study of untreated pts, 30 > age 70
  - 88% ORR, 23% CR
  - 34 month PFS
  - less effective in del(17p) pts (35% PR)
  - Toxicity includes cytopenias, infections and rash with overall 3.4% mortality; ? Less than FCR
  - Phase III study testing this versus FCR
- High Dose Methylprednisolone + Rituximab
- Chlorambucil + Rituximab
- Lenalidomide
Therapy Approach for Patients < age 65

- Repeat interphase cytogenetics, perform a bone marrow biopsy to rule out non-CLL problem
- Clinical trial offered with strong consideration of non-chemotherapy bridge therapy
- Off trial
  - Del(17p13.1): rituximab + high dose solumedrol or FCR followed by non-myeloablative allogeneic stem cell transplant
  - Del(11q22.3): FCR, BR
  - Other genetic features: FR, BR
- Do not use PCR, rituximab, alemtuzumab, CLB or rituximab maintenance

Therapy Approach in Older Population (> 65 yrs)

- Not Fludarabine-based regimens irrespective of functional status; can consider
  - Bendamustine + Rituximab
  - Chlorambucil + Rituximab
- Infirmed patients: chlorambucil or rituximab
- New options: lenalidomide (approved by NCCN but insurance sometimes does not pay for)
  - Immune modulating agent
  - Reverses hypogammaglobulinemia seen in disease
  - Diminished infections as compared to other chemotherapy approaches
  - 64% progression free at 3-years
Considerations for Relapsed CLL

- Outcome of pts at time of relapse depend upon
  - Interphase cytogenetics, β₂M, and stage
  - Prior therapy (i.e. monotherapy or chemoimmunotherapy)
  - Time of remission with last treatment

- Interphase cytogenetics should be repeated prior to initiating salvage therapy

- All pts with cytopenias should have repeat bone marrow biopsy to assess for MDS if prior FCR given

- Transplant evaluation should be considered early in this pt population if any unfavorable features present

Salvage Regimens for CLL

- Fludarabine, Cyclophosphamide, and Rituximab
- Bendamustine + Rituximab-59% response and 14 m PFS with significant immune suppression
- High dose Solumedrol + Rituximab-30-50% response but very immunosuppressive
- Lenalidomide ± Rituximab-66% response and 24 m PFS
- Ofatumumab—50% response but short PFS and does not work in bulky del(17p13.1)
- Lymphoma salvage regimens (not effective except for Richters transformation
Our Goal in CLL Therapy: CML in 2012

86% 8-year OS in era of imatinib


Targeting BCR Signaling in CLL

B-cell antigen receptor (BCR) signaling is active in proliferation centers (LN, spleen, bone marrow)

High risk CLL patients with over-expression of ZAP-70 have more BCR signaling

Targeting BCR pharmacologically is now possible
GS-1101 (CAL-101) in CLL

- GS-1101 is an oral agent that targets PI3K-delta
- Ph I study in relapsed CLL/NHL with 54 CLL pts
- Pts had a median 5 prior Rx, 82%; 31% del(17p13.1)
- Response to therapy remarkable
  - 91% with node/spleen response that was rapid concomitant with early increase in lymphocytosis
  - 24% response overall due to persistent lymphocytosis
  - Remissions durable except in del(17p13.) with median PFS of 18 m
- Toxicity modest (LFT abnormalities, pneumonia)


GS-1101 Response and Outcome Summary

PFS -- Overall and by Response Category

PFS -- Overall and by 17p Deletion

Changes in Lymph Node Area and Blood ALC

Mean ALC and BLM (10,000)

Hemoglobin and Platelet Counts

GS1101 Current Direction

- Ongoing studies in CLL
  - Phase III Bendamustine/Rituximab ± GS-1101 in relapsed CLL
  - Phase III Ofatumumab ± GS-1101 in relapsed CLL
  - Phase III Rituximab ± GS-1101 in elderly, refractory CLL
  - Phase II Rituximab + GS1101 in untreated CLL (done)—to be reported at ASCO
  - Phase II Ofatumumab + GS110 in untreated CLL

Ibrutinib (PCI32765) in CLL

- Ibrutinib irreversibly inhibits of Bruton’s tyrosine kinase
- Phase Ib/II study to assess efficacy
  - 85 relapsed CLL pts Rx with 420 mg (n=51) or 840 mg n=34) dose; median 4 prior Rx, 65% advanced Rai, 35% del(17p13.1)
  - 31 elderly (age ≥65) with no prior Rx; 48% advanced Rai

  Response similar between two doses in relapsed pts
  - 92% with node/spleen response
  - 71% ORR/2% CR in previously Rx and 67% ORR/10% CR due to transient lymphocytosis produced by this class of drugs
  - PFS at 26 months 75% in previously Rx and 96% in unRx

  Toxicity profile modest (loose stools, arthralgia, fatigue dyspepsia, rash) with minimal myelosuppression

Ibrutinib Remissions Are Durable

R/R + High-Risk R/R (n=85)
Est. PFS at 26 mo is 75%
Treatment Naïve (n=31)
Est. PFS at 26 mo is 96%

Progression Free Survival by Genomic Feature

Relapsed/Refractory including High-Risk R/R
del(17p13.1)/del(11q22.3) Status
- del17p (n=28)
  Est. PFS at 26 mo is 57%
- del11q (n=23)
  Est. PFS at 26 mo is 73%
- No del17p or del11q (n=29)
  Est. PFS at 26 mo is 93%

IgVH Status
- Mutated (n=12)
  Est. PFS at 26 mo is 83%
- Unmutated (n=69)
  Est. PFS at 26 mo is 72%

Logrank p=0.0437
Logrank p=0.6732
Combination Studies with Ibrutinib

- PCYC 1109: Ibrutinib + Ofatumumab in relapsed CLL/SLL (completed, OSU)
- PCYC 1108: Ibrutinib + BR or FCR in relapsed CLL/SLL (completed, multicenter)
- IIT: Ibrutinib + Rituximab in high-risk CLL (completed, MDA)
- CTEP: Ibrutinib + Lenalidomide (U Col and OSU)

Summation of Results: Higher response rate and no obvious added toxicity

- Planned Intergroup Phase III studies
  - FCR vs Ibrutinib + Rituximab (< 70 yrs)
  - BR vs Ibrutinib + Rituximab vs Ibrutinib (> 65 yrs)

Where are BTK Inhibitors Going?

- Ibrutinib in relapsed phase III studies in CLL
  - Ibrutinib versus Ofatumumab (relapsed)
  - Ibrutinib + BR versus BR (relapsed)
  - Ibrutinib in relapsed del(17p) CLL

- Ibrutinib in untreated CLL - minimal development
  - Phase III study of Ibrutinib versus CLB in elderly CLL
  - Phase II of Ibrutinib in elderly CLL (MDA)

- Alternative agents
  - AVL292 (Does not appear as active as ibrutinib to date)
  - ONO-WG-307
  - HM71224
  - Others with improved features
Chimeric Antigen Receptor (CAR) T-Cells in CLL

- CAR contains an extracellular domain targeting CD19 and internal CD3 zeta chain, and costimulatory domain containing 4-1BB or CD28
- N=10 pts; Median age 66
- Chemotherapy 4-7 days pre-infusion
- 3 CR, 4 PR, 2 NR, 1 NE due to being too early


Other New Drugs (Before BCR antagonists)

- IPI-145—second generation PI3-kinase delta inhibitor
- Dinaciclib and Flavopiridol—active in CLL including del(17p)*
- ABT263 and ABT199—active in CLL including del(17p13.1)*
- Xm5574—CD19 engineered antibody active in CLL*
- GA101—CD20 engineered antibody active in CLL
- Tru-016—CD37 SMIP active in CLL*
- KPT330—XPO1 inhibitor—early activity in B-cell malignancies*

*supported by LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers
Important Conclusions

- Select genomic studies can assist in risk stratification of newly diagnosed patients.
- Rituximab chemoimmunotherapy offers a survival advantage for symptomatic CLL.
- Patients with del(17p13.1) who require therapy have very poor outcomes with traditional therapies.
- BTK inhibitor ibrutinib is very active in symptomatic untreated and treated CLL including those with del(17p) and yields very durable remissions.
- CAR-T cells are promising alternative to allo SCT.

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UPDATE on CLL

Question and Answer Session
Dr. Byrd’s slides are available for download at www.LLS.org/programs
The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified CLL patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

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

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

- **TOLL-FREE PHONE:** (800) 955-4572
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