Chronic Lymphocytic Leukemia: Prognostic Factors, Supportive Care Issues and Therapeutic Advances

John C. Byrd, MD
D Warren Brown Chair of Leukemia Research
Distinguished University Professor of Medicine, Medicinal Chemistry, and Pharmaceutics
Director, Division of Hematology
The Ohio State University Comprehensive Cancer Center
Presenter Disclosure Information

Dr. Byrd is an unpaid consultant for Pharmacyclics, Acerta, and Genentech.
Chronic Lymphocytic Leukemia

• The most prevalent type of adult leukemia
• Defined by $> 5 \times 10^9/L$ CD5, CD19, CD20, CD23, sIg (dim) cells in blood
• $< 5 \times 10^9/L$ cells in blood without cytopenias or organomegaly is monoclonal B-cell lymphocytosis (MBL):
  • Prognostic factors of CLL not valuable for this
  • 1-2% chance of progression to CLL per year
  • Infections and secondary cancers more common than healthy individuals
• Median age of diagnosis of CLL is 72 (only 10% of patients < 50 yrs); 2:1 male: female 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 - no common gene
The Big Question at Diagnosis in Asymptomatic Patient

How will this “bad” leukemia influence my quality of life and life expectancy?

• Stage not helpful to the individual with CLL
• Many retrospective biomarkers predicting time to first treatment
# CLL Outcome From Diagnosis by Fluorescence In Situ Hybridization (FISH) Interphase Chromosomal Abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>% Pts</th>
<th>Median Time to Treatment (mo)</th>
<th>Median Overall Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(17)(p13.1)</td>
<td>7</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>del (11)(q22.3)</td>
<td>18</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>16</td>
<td>33</td>
<td>114</td>
</tr>
<tr>
<td>del(13)(q14)</td>
<td>55</td>
<td>49</td>
<td>133</td>
</tr>
<tr>
<td>None Detected</td>
<td>18</td>
<td>92</td>
<td>111</td>
</tr>
</tbody>
</table>

Survival: IGHV Gene Mutation Status and CD38 Expression as a Surrogate for This

Other New Prognostic Factors

• Stimulated karyotype (not regular type)
  « Complexity (> 3 abnormalities) associated with short TFS and poor response to therapy (including transplant and BTK inhibitors)

• Additional interphase abnormalities
  « add 2p - increased risk of Richter’s transformation
  « +8 or amplification of myc - short TFS and OS

• ZAP-70 methylation (more reproducible than ZAP-70 protein expression, and correlates with favorable outcome)

• Select mutations associated with rapid progression to treatment
  « p53
  « NOTCH1
  « SF3B1
  « BIRC3

All associated with IGHV unmutated disease
My Initial Workup of CLL

- All patients at diagnosis:
  - Flow cytometry to confirm CLL diagnosis

- Informative for prognostic prediction if patients want to know:
  - Interphase cytogenetics: del 17p, del 11q, add 2p portend aggressive disease; t(11;14) to rule out mantle cell lymphoma
  - IGHV gene mutational status
  - ZAP-70 methylation (<20% unfavorable) if available
  - Beta-2-microglobulin (B₂M)
  - CLL gene mutation panel of uncertain value outside of p53 mutation (be careful)

- No CT scan unless symptoms are present; PET scan can be helpful if Richter’s suspected

- Bone marrow biopsy not necessary in absence of cytopenias
My Approach to Common Symptoms at Diagnosis

• Anxiety over diagnosis—most common in younger males
  • Time, education, and reassurance during first visit
• Fatigue in early stage patients—very common
  • If onset time of diagnosis, follow for 2-3 months to see if with extensive education and
    assurance this resolves
  • Other causes - sleep apnea, cardiac, metabolic (thyroid, testosterone, menopause, vitamin D
    deficiency); depression
  • Ritalin can sometimes help
• Night sweats
  • Richter’s, viral reactivation (EBV, CMV), hormonal
Autoimmune Cytopenias of CLL

- Autoimmune hemolytic anemia and thrombocytopenia common in CLL (10-25%); often when disease is active
- Anemia or thrombocytopenia due to autoimmune complication does not impact staging survival
- AIHA and ITP treatment: prednisone (1 mg/kg/day) followed by slow taper (~70% response, but taper often unsuccessful); rituximab should be added at this time
  - IVIG
  - Cyclosporin
  - Rituximab, cyclophosphamide, dexamethasone
  - Splenectomy (durable response generally not seen)
  - Romiplostim (Nplate)-ITP
  - Ibrutinib (for chronic relapsing patients once disease is controlled)
Infections in CLL

- Most common cause of morbidity and mortality in CLL with bacterial, viral and later opportunistic infections being problematic

- Preventative strategies should include:
  - Pneumococcal vaccine (Prevnar 13) at diagnosis and Q5 years
  - Influenza vaccine yearly (poor response) and prophylaxis if exposed
  - No live vaccine (Including varicella zoster vaccine)
  - Viral and PCP prophylaxis for fludarabine-based combinations or idelalisib

- IVIG use:
  - Although expensive, this is very effective to augment treatment of recurrent infections not cleared with multiple antibiotic courses
  - Post influenza if serum IgG low
Other CLL Related Complications

• Secondary cancers:
  • Solid tumors more common in CLL; routine screening important
  • therapy-related myeloid neoplasms (trMN) common (3-10%) after FCR treatment

• Richter’s Transformation:
  • Pathology can be large cell lymphoma or Hodgkin’s Disease
  • Seen most commonly in previously treated patients with high risk features (IGHV unmutated, IGHV 4-39 stereotype, 2p+, TP53 and NOTCH1 mutated, del(17p), complex karyotype)
  • PET scans can be useful in deciding nodal region to biopsy
  • Outcome of these patients poor unless
    • diagnosed prior to therapy
    • Clonally unrelated to CLL
    • Hodgkin’s transformation in absence of prior fludarabine treatment
When to Treat CLL Patients

• No advantage to treating CLL until symptoms develop, irrespective of genomic features

• NCCN criteria for treatment (primary and in relapse)
  • 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 count < 300 x 10^9/L not an indication for Rx

• Lymphocyte doubling time < 6 months or 50% increase over a 2-month time period is NOT an indication for Rx
Decision Tree to Decide on Therapy

• Age or Functional Status
  • Age 65-70 often used in US
  • CIRS score + creatinine clearance < 60 ml/min used in Europe

• Patient characteristics and preferences
  • Need for long-term anticoagulation with warfarin
  • Comfort with being on continuous therapy for life
  • Outpatient insurance coverage

• Genomic Features
  • Del(17p13.1) or not
  • Favorable markers (IGHV mutated with del(13q14) or +12)
• FCR versus FC a better therapy for young CLL:
  • significantly improves ORR and CR
  • significantly improves PFS (57 versus 33 months, at 5.9 years)
  • significantly improves OS (69.2% vs 62.3% at 5.9 yrs)
• MRD-negative status by 4-color flow cytometry at end of therapy best predictor of long term PFS and OS
• Majority of genetic groups benefit from FCR therapy except:
  • del(17p13.1)
  • Normal karyotype (using FISH probes only)
• Toxicity of FCR similar to FC except for more neutropenia

PFS and OS of German CLL8 Study


FCR (N=408) vs. FC (N=409)

**A**

Probability of Progression-Free Survival

- **PFS**
  - Months on Study
  - Number at risk:
    - FCR: 408, 358, 310, 261, 222, 178, 76, 18, 1
    - FC: 409, 360, 232, 297, 262, 220, 100, 33, 1

**B**

Probability of Overall Survival

- Months on Study
- Number at risk:
  - FCR: 408, 384, 363, 342, 318, 290, 134, 41, 2
  - FC: 409, 360, 232, 297, 262, 220, 100, 33, 1

*p = 0.001 by log-rank test*
Long Term Follow up with FCR and Cure?

Median F/U 12.8 years

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Median PFS:
- FCR: 55.7 months
- BR: 41.2 months

Cytopenias and infections increased with FCR; Rx related mortality similar

No IGHV mutated survival plateau with BR

Ibrutinib: A Potent and Irreversible BTK Inhibitor

- Forms a specific and irreversible bond with cysteine-481 in BTK
- Potent and irreversible BTK inhibition with IC_{50} = 0.5 nM
- Blocks BCR signaling; active in canine model of spontaneous lymphoma
- Orally bioavailable with short half-life
- Alternative irreversible targets could include EGFR, ERB2, ERB4, BMX, ITK, TEC, BLK, and JAK3
- Many reversible targets

Honigberg et al., *PNAS* 2010; 107:13075-80
Ibrutinib: Phase 1b/2 Studies in Untreated CLL

• Phase 1b study (Byrd et al., Blood 125: 2497, 2015; O’Brien et al., ASH 2016)
  • 31 pts age >65
  • Early lymphocytosis common, but resolves
  • Major toxicities: diarrhea, rash, bruising, and heartburn
  • 84% ORR (27% CR and going up); 1 pt with PD
  • 92% PFS and OS at 60 months

• NHLBI Phase 2 study (Farooqui et al., Lancet Oncol. 16:169, 2015)
  • 50 pts age > 65 with prior treatment or del(17p) untreated
  • Toxicities similar except more myalgias, nail ridging, fatigue
  • Response noted in 45 (88%); 5 (10%) attaining CR (4 untreated)
  • PFS at 24 months is 82% for all pts; 8 (16%) of pts have died (5 with PD, 2 infection, 1 sudden death)

• Surprise in both studies: Remarkable immune recovery over time!
Ibrutinib versus Chlorambucil (RESONATE 2)

• Phase 3 study in symptomatic, untreated CLL/SLL patients of ibrutinib versus chlorambucil (crossover allowed)

• Eligibility criteria including 65 years of age, ANC $1 \times 10^9/L$, platelets $50 \times 10^{12}/L$ and no del(17p13.1)

• Patient demographics: median age 73 years ($70\% \geq 70$), 45% advanced Rai stage, 20% del(11q22;q23)

• Response: ibrutinib 86% (4% CR) vs. chlorambucil 36% (2% CR)

• Significant PFS and OS with ibrutinib (despite crossover)

• Toxicity similar between except diarrhea and atrial fibrillation (ibrutinib)

Progression-Free Survival: RESONATE 2 Trial

Overall Survival: RESONATE 2 Trial

Hazard ratio, 0.16 (95% CI, 0.05–0.56)
P=0.001 by log-rank test

My Approach for Patients < 70

- IGHV mutated
  - Extensive discussion about curability with FCR, risks of this therapy, and desire for long-term therapy
  - FCR or ibrutinib

- IGHV unmutated, no del(17p)/complex karyotype
  - Discussion of desire to be on chronic therapy
  - Ibrutinib (my strong preference) or FCR

- IGHV unmutated, del(17p)/complex karyotype
  - Ibrutinib and referral for transplant evaluation
  - Time to proceed to allogeneic transplant controversial

- Do not use PCR, BR, CD20 Ab monotherapy or maintenance, idelalisib, or chlorambucil
Approaches to Consider in Elderly Population

- **Not** fludarabine-based regimens (Eichhorst et al., Blood 2009, Woyach et al., J Clin Oncol 2012)
- Bendamustine + rituximab OK, but more side effects
- German CLL 11 Study: A standard of care change:
  
  **Responses**
  
  - CLB 31% ORR: 0% CR  \[ p<0.001 \]
  - CLB + rituximab: 65% ORR, 7% CR  \[ p<0.001 \]
  - CLB + obinutuzumab: 77% ORR, 22% CR

  **Side effects**
  
  - Grade 3-4 infusion reactions 20% with obinutuzumab (early) vs. 4% with rituximab
  - Neutropenia slightly increased (33% versus 26%) with obinutuzumab vs. rituximab
Obinutuzumab + CLB versus CLB Alone

Obinutuzumab PFS superior to rituximab (17 vs. 27 months)

My Approach for Patients > 70

• Repeat interphase cytogenetics, bone marrow

• Off trial:
  • Majority of patients: ibrutinib monotherapy
  • Need for anticoagulation: obinutuzumab + CLB
  • Too costly: obinutuzumab + CLB or consider trial

• Do not use bendamustine, CD20 antibody monotherapy or maintenance, alemtuzumab, or chlorambucil
Considerations for Relapsed CLL

• Outcome of patients at time of relapse depend upon:
  • Interphase cytogenetics, age, and stage
  • Prior therapy given for CLL and other cancers
  • Time of remission with last treatment for CLL

• Interphase cytogenetics should be repeated prior to initiating salvage therapy

• All patients with cytopenias should have repeat bone marrow to assess for MDS if prior FCR given

• Do not use chemotherapy regimens here, with very rare exceptions

• Transplant evaluation (only) should be considered early in this population if any unfavorable features are present or progression on ibrutinib is noted
Past Salvage Regimens for CLL

- Fludarabine, cyclophosphamide, and rituximab: 70% ORR, 24% CR, 30.4 mo. PFS
- Bendamustine + rituximab: 59% ORR, 9% CR, 14 mo. PFS. Does not work for del(17p)
- Lenalidomide ± rituximab: 66% ORR, 12% CR, 17 mo. PFS
- Ofatumumab: 50% response, 6 mo. PFS. Does not work in bulky del(17p13.1)
- High-dose methylprednisolone + rituximab: 30-50% response, ~12 mo. PFS but very immunosuppressive
- Alemtuzumab: 33% ORR, 2% CR, ~6-12 mo. PFS
- Lymphoma salvage regimens: not effective
Ibrutinib Pivotal Phase 2 Study

- 132 CLL patients enrolled
- 31 pts age > 65 with symptomatic disease but no prior therapy
- 101 pts of any age with relapsed/refractory disease
  - Median 4 prior therapies
  - 57% Advanced (Stage 3 or 4) disease
  - 35% Del(17)(p13.1)
  - Dosed at 420 mg or 840 mg dose Qd with similar response (86%) therefore merged
- Early lymphocytosis noted, but resolves with time

Byrd et al., Blood 125:2497-506, 2015
O’Brien et al., ASH 2016
Adverse Events Observed in ≥ 15% of Patients

Diarrhea (TN 68%, R/R 53%), fatigue, and upper respiratory tract infection were the most common adverse events.
Survival Outcomes by Chromosomal Abnormalities Detected by FISH in Relapsed/Refractory Patients

O’Brien et al., ASH 2016

<table>
<thead>
<tr>
<th>Chromosomal Abnormality</th>
<th>Median OS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 17p (n=34)</td>
<td>57 mo</td>
<td>32%</td>
</tr>
<tr>
<td>Del 11q (n=28)</td>
<td>NR</td>
<td>61%</td>
</tr>
<tr>
<td>Trisomy 12 (n=5)</td>
<td>NR</td>
<td>80%</td>
</tr>
<tr>
<td>Del 13q (n=13)</td>
<td>NR</td>
<td>91%</td>
</tr>
<tr>
<td>No abnormality** (n=16)</td>
<td>NR</td>
<td>83%</td>
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</table>

<table>
<thead>
<tr>
<th>Chromosomal Abnormality</th>
<th>Median PFS</th>
<th>5-year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 17p (n=34)</td>
<td>26 mo</td>
<td>19%</td>
</tr>
<tr>
<td>Del 11q (n=28)</td>
<td>55 mo</td>
<td>33%</td>
</tr>
<tr>
<td>Trisomy 12 (n=5)</td>
<td>NR</td>
<td>80%</td>
</tr>
<tr>
<td>Del 13q (n=13)</td>
<td>NR</td>
<td>91%</td>
</tr>
<tr>
<td>No abnormality** (n=16)</td>
<td>NR</td>
<td>66%</td>
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</table>
Phase 3 RESONATE Study in Relapsed/Refractory CLL

- 391 relapsed and refractory pts randomized 1:1 between ibrutinib and ofatumumab
- Outcome dramatically improved with ibrutinib:
  - Response (42% versus 4%, p<0.001)
  - PFS (median NR vs. 8 months; HR 0.22, p<0.001)
  - OS (12 months 90% vs. 81%, HR 0.43, p<0.005)
- Toxicity differs between arms:
  - Atrial fibrillation (6% versus 1%) > with ibrutinib
  - Grade 1-2 bleeding/echymosis (44% versus 12%) > with ibrutinib
  - Rash (8% versus 4%) > with ibrutinib
  - Blurred vision (10% versus 4%) > with ibrutinib
  - Peripheral neuropathy (4% versus 13%) > with ofatumumab
  - Infusion events (0 versus 28%) > with ofatumumab

Important Management Points About Ibrutinib

- Early lymphocytosis is expected and unless other signs of progression present, therapy should be continued
- Bruising and echymosis are noted frequently with ibrutinib, but major bleeding uncommon provided:
  - coumadin therapy is avoided
  - ibrutinib is held 3-7 days before and after major surgeries
- Management of atrial fibrillation should avoid warfarin and substitute ASA unless high risk for embolic disease (consider idelalisib)
- Arthralgias, paniculitis, and erythema nodosum associated with this can be managed with short course of steroids
- Benefit of adding rituximab to ibrutinib unclear at this time
Ibrutinib Failure: What is the Pattern

Woyach et al., J Clin Oncol 2017 (online)
Management of Ibrutinib Resistant Disease

• Intolerance
  • Alternative BTK inhibitor (acalabrutinib); idelalisib or venetoclax

• Richter’s transformation
  • Withdrawal of ibrutinib can mimic this early due to tumor flare
  • Molecular aberrations uncertain in this patient group
  • Clinical trial or continue ibrutinib with DLBCL regimen
  • Outcome extremely poor, ability of transplant to salvage uncertain

• CLL
  • Rarely observed until after at least 1 year of therapy
  • 85% associated with BTK C481S or PLCG2 mutation
  • Therapy with ibrutinib should continue until initiating next therapy
  • Alternative therapies effective in this group (venetoclax)
Idelalisib (GS1101, CAL101) in CLL

• Targets PI3K delta, providing selectivity and thereby allowing good target coverage

• Phase 1 study in relapsed CLL/NHL with 54 CLL patients:
  • Median 5 prior treatments, 82%; 31% del(17p13.1)
  • Dose of 150 mg BID based upon PK and PD
  • 91% with node response; 24% ORR due to persistent lymphocytosis
  • Median PFS 18 months with shorter response in del(17p13.1)
  • Toxicity modest but includes early Grade 3-4 transaminitis and late hypersensitivity pneumonitis, colitis/diarrhea, and rash

• Confirmatory pivotal study in relapsed CLL pts inappropriate for chemotherapy:
  • rituximab + idelalisib (150 mg BID) or placebo; crossover at progression
  • 81% PR + PR-L with combination versus 13% PR with rituximab

Brown et al., Blood 123:3390-7 2014
Furman et al., NEJM 370:997-1007, 2014
- Toxicity similar to Phase 1 study
- All groups doing well including del(17p)

Furman et al. NEJM 370:997-1007, 2014
Idelalisib + rituximab is a reasonable therapy for previously treated CLL, but not widely used for several reasons:

- Toxicity profile in untreated patients problematic (More LFT abnormalities, pneumonitis, and autoimmune complications)
- Unclear if efficacy is comparable to ibrutinib, particularly in del(17p13.1) patients
- Marketing indication with rituximab raises cost and inconvenience compared to monotherapy oral agent
- Ability to administer therapy as long-term continuous therapy is challenging due to late onset toxicity

- My practice is to use idelalisib initially when ibrutinib is contraindicated (need for warfarin) or BTK inhibitors are not tolerated
Venetoclax in Relapsed/Refractory CLL/SLL

- Second-generation selective BCL2 BH3 domain inhibition
- 116 previously-treated patients treated in Phase 1 dose escalation (n=56) or expansion (n=60)
- Toxicity included mainly diarrhea (mild), nausea, and neutropenia (responsive to G-CSF); tumor lysis syndrome manageable
- 79% ORR with 20% CR (5% MRD-negative by flow cytometry) with 15 month PFS of 69% for patients dosed at 400 mg/m²; remissions shorter for del(17p13.1)
- PFS curve does not appear to have plateau in any group; combination potential of venetoclax appears excellent
- Approved for del(17p13.1) patients with one prior therapy; active in ibrutinib-resistant disease

Jones et al., ASH 2016
Other Novel Agents in CLL

Other small molecule inhibitors:

- Acalabrutinib (more selective irreversible BTK inhibitor)
- Entospletinib (GS9973; Syk inhibitor)
- Duvelisib (IPI-145; PI3K-delta and -gamma inhibitor)
- TGR-1202 (safer PI3K-delta inhibitor?)
- Selinexor (XPO1 inhibitor)
- Reversible BTK inhibitors (for BTK C481S-mutated CLL)

Antibodies and Biologic Therapies:

- MOR-208 (CD19 engineered antibody)
- CD19 Chimeric Antigen Receptor (CAR) T-cells (with ibrutinib)
- CC-122
- PD1 antibodies (Richter’s transformation)
Important Conclusions

• Select genomic studies can assist in risk stratification of newly diagnosed patients

• Education of patients early in diagnosis of CLL can improve their coping with the disease

• CD20 antibody chemo-immunotherapy offers a survival advantage for symptomatic CLL and may cure a subset of patients with IGHV mutated disease

• Ibrutinib extends PFS and OS in untreated and treated CLL and represents a new standard of care

• CLL is rapidly moving toward a chemotherapy-free approach except for IGHV mutated patients
Thank you for attending this Master Class for Oncologists

Questions?
A 68 year old man with CLL and del(17)(p13.1) has been treated with ibrutinib for 3 years and now presents with a rising lymphocyte count, new adenopathy and anemia. His LDH is 400 (ULN 170). Appropriate management includes all of the following except:

a. Obtain a PET scan and bone marrow biopsy
b. Put through prescription authorization for venetoclax
c. Obtain a hemolytic anemia work-up
d. Refer for transplant evaluation
e. Discontinue ibrutinib in anticipation of next therapy