CLL: Update on Treatment and Side Effects Management

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Welcome and Introductions
Disclosures
John C. Byrd, MD does not have any relevant financial relationships with any commercial interests to disclose.

Kimberly A. Holt, BSN, RN, OCN® does not have any relevant financial relationships with any commercial interests to disclose.

Current CLL Therapy Landscape 2015

John C. Byrd M.D.
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Chronic Lymphocytic Leukemia

- The most prevalent type of adult leukemia
- Defined by < 5 x 10^9/L CD5, CD19, CD20, CD23, slg (dim)+ cells in blood
- < 5 x 10^9/L cells in blood without cytopenias or organomegaly is monoclonal B-cell lymphocytosis (MBL) with many of the same complications and 1-2% chance of progression to CLL/per year
- Median age of diagnosis of CLL is approximately 72, 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—no common gene

Initial Work-up of CLL Patients

- All patients at diagnosis:
  - Flow cytometry to confirm CLL diagnosis
- Informative for prognostic and/or therapy determination
  - Interphase cytogenetics looking for +12, del(13q), del(17)(p13.1) and del(11)(q22.3); del 17p and del 11q portend for more aggressive disease
  - Unmutated V_H gene status assessment (good lab)
  - ZAP-70 expression by flow cytometry is not recommended outside clinical trial
  - Beta-2-microglobulin
- No CT scan unless symptoms are present; PET scan can be helpful if Richter's suspected
- Bone marrow biopsy and aspirate not necessary in absence of cytopenias
Complications of CLL

- Infections
- Autoimmune complications
- Secondary cancers
- Richter’s transformation

When to Treat CLL Patients

- No advantage to treating CLL until symptoms develop irrespective of genomic features
- IWCLL 2008 criteria for treatment (primary and in relapse include)
  - 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 or doubling time not an indication for Rx *

*NCCN Guidelines for NHL 2014
How to Differentiate Patients for Treatment

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

- Genomic Features
  - Del(17p13.1) or not
  - Favorable markers (IgHV mutated with del(13q14) or +12)

CLL8 Study Design

817 Patients with untreated, active CLL and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Demographics similar between 2 treatment arms

Updated results of the 3rd analysis
Median observation time 5.9 years

Summary of German CLL8 Study

- Toxicity of FCR similar to FC except for more neutropenia
- FCR versus FC a better therapy for young CLL
  - Significantly improves ORR and CR
  - Significantly improves PFS (57 versus 33 months, at 5.9 yrs)
  - Significantly improves OS (69.2% vs 62.3% at 5.9 yrs)
- MRD status at end of therapy most predictive factor for long term PFS and OS
- Majority of genetic groups benefit from FCR therapy except for
  - Del(17p13.1)
  - Normal karyotype (using FISH probes only)


Recent Data to Consider Decisions

- Long-term follow up FCR data from MDA FCR300 series and German CLL VIII data (not shown) relative to “curability”
- CLL10 data from German CLL Group
- Ibrutinib data with del(17)(p13.1) and approval by FDA for initial use in symptomatic CLL
**FCR300: PFS by IGHV Mutation Status**

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<th>Events</th>
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<td>131</td>
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<td>87</td>
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Conclusion: Cure or long-term remission may be possible for low-risk but not high-risk IGHV unmutated patients.

**CLL10 Study: FCR vs BR in Front-line**

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

1:1 Randomization

FCR n = 100
BR n = 93

CLL10 Study: FCR vs BR in Front-line

Survival Functions

- Study Medication
  - FCR
  - BR
  - FCR-censored
  - BR-censored

<table>
<thead>
<tr>
<th>Survival Functions</th>
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<td>PFS (months)</td>
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(p=0.041)

- Median PFS
  - FCR: not reached
  - BR: 44.9 months

Cytopenias and infections increased with FCR; Rx related mortality similar

Conclusion: FCR appears to be better than BR if chemoimmunotherapy is choice of therapy

Ibrutinib: A Potent 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
- Once-daily dosing results in 24-hr sustained target inhibition

Honigberg et al: PNAS 2010; 107:13075-80
Progression-free Survival by Cytogenetics (FISH) in Relapsed/Refractory Population

Approaches to Consider in Elderly Population

- **Not** Fludarabine-based regimens

- **Bendamustine + rituximab**
  ‣ Slightly higher toxicity rate but feasible in this population

- **Chlorambucil + rituximab**
  ‣ ORR 82% (9% CR, 15% nPR) with median PFS of 23.5 months

- **High-dose methylprednisolone + rituximab**
  ‣ Lower steroid dose typically utilized; favored regimen for del(17p)

- **Obinutuzumab + chlorambucil**: A standard of care change
### CLL11: Study Design

- **Stage 1**, \( n = 590 \)
- Additional 190 patients in stage 2

**Randomized**

- GA101 + chlorambucil x 6 cycles
- Chlorambucil x 6 cycles (control arm)
- Rituximab + chlorambucil x 6 cycles

**GA101 + chlorambucil**
- Previously untreated CLL with comorbidities
- Total CIRS score > 6 and/or creatinine clearance < 70 mL/min
- Age ≥ 18 years
- \( N = 781 \)

**R-Clb vs Clb**

**Stage 1a**

**G-Clb vs Clb**

**Stage 1b**

**Stage 2**

G-Clb vs R-Clb

- Previous untreated CLL with comorbidities
- Total CIRS score > 6 and/or creatinine clearance < 70 mL/min
- Age ≥ 18 years
- \( N = 781 \)

**RA NDOM IZE**


### CLL11: Response and Toxicity

**Response**

- CLB 31% ORR, 0% CR
- CLB + Rituximab 65% ORR, 7% CR
- **CLB + Obinutuzumab 77% ORR, 22% CR**

**Toxicity**

- Grade 3 and 4 infusion related events
  - 20% with obinutuzumab versus 4% with rituximab
  - Infusion events with obinutuzumab early (day 1, within minutes of starting infusion sometime)
- Grade 3 and 4 neutropenia
  - 33% obinutuzumab versus 28% with rituximab
  - No increased risk in serious infections was noted in any arm

\[ p < 0.001 \]
MRD Comparison and Impact on Outcome

MRD negative patients (%)

No. of patients: 61/239 6/244

GA101 Rituximab

P<0.00001

25.5% 2.5%

G-Clb vs G-Clb: Progression-free Survival

The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute


R-Clb vs G-Clb: Progression-free Survival

The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

Stratified HR: 0.39
95% CI: 0.31-0.49
P<0.0001

No. at risk

G-Clb: 333 307 302 278 213 156 122 93 60 34 12 4 1 0
R-Clb: 330 317 309 259 163 114 72 49 31 14 5 2 0 0

Time (months)

Progression-free survival

0 3 6 9 12 15 18 21 24 27 30 33 36 39

15.2 26.7
My Approach for Patients > 70

- Repeat interphase cytogenetics, bone marrow
- Clinical trial with strong consideration of non-chemotherapy regimen with 2nd generation BTKi (ACP-196) or A041202 (randomized trial)
- Off trial
  - Del(17p13.1): Ibrutinib monotherapy
  - Other genetic features: Obinutuzumab + CLB or bendamustine + rituximab
- Do not use rituximab, alemtuzumab, CLB or rituximab maintenance

Considerations for Relapsed CLL

- Outcome of patients at time of relapse depend upon
  - Interphase cytogenetics, β2M, and stage
  - Prior therapy (i.e. monotherapy or chemoimmunotherapy)
  - Time of remission with last treatment
- Treat relapsed patients when symptomatic only
- 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
- Transplant evaluation (only) should be considered early in this pt population if any unfavorable features present
Past Salvage Regimens for CLL

- Fludarabine, cyclophosphamide, and rituximab (70% ORR, 24% CR, 30.4 m PFS)
- Bendamustine + rituximab (59% ORR, 9% CR, 14 m PFS)
- Lenalidomide + rituximab (66% ORR, 12% CR, 17 m PFS)
- Ofatumumab—50% response, 6m PFS and does not work in bulky del(17p13.1)
- High-dose methylprednisolone + rituximab-30-50% response, ≈12 m PFS but very immunosuppressive
- Alemtuzumab—33% ORR, 2% CR, ≈ 6-12m PFS
- Lymphoma salvage regimens (not effective)

Non-ablative Allogeneic Transplant

- Transplant with traditional ablative regimens carry a 40-50% 100 day mortality in CLL patients age 40-49 making application minimal in past
- Non-ablative approach significantly lowers 1-year mortality (10-20% at year 1)
- Non-ablative approach unique in
  - Pts with significant adenopathy (> 5 cm) have high relapse rate
  - Chronic graft-versus-host disease represents big problem in many patients (40-50%) with research now focused toward lowering this
- Role of transplant being redefined in new era or BTKi—still quite debated in young patients
Targeting BCR Signaling

Ibrutinib Pivotal Phase II Study

- 132 patients with CLL enrolled onto this study
  - 31 pts age > 65 years 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 and PFS (data therefore merged)
  - Early lymphocytosis frequently noted early in therapy but resolves with time

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.

Adverse Events Observed Over Time

**PCYC 1102 Best Overall Response**

![Bar chart showing response rates for PCYC 1102 study](image)

- **TN (n = 31)**
  - Median DOR in months (range): NR (0 to 35.0+)
  - Month 30 (95%CI): 100.0% (NE)

- **R/R (n = 101)**
  - Median DOR in months (range): NR (0 to 35.2+)
  - Month 30 (95%CI): 79.1% (64.2 to 88.4)

- **Total (N = 132)**
  - Median DOR in months (range): NR (0 to 35.2+)
  - Month 30 (95%CI): 85.3 (74.4 to 91.8)


**Ibrutinib Progression-free Survival**

![Graph showing progression-free survival](image)

- **Del17p**
  - 30-month PFS: 45.9%
  - Median PFS: 28.1 months

- **Del11q**
  - 30-month PFS: 74.2%
  - Median PFS: Not reached

- **No del17p/11q**
  - 30-month PFS: 89.0%
  - Median PFS: Not reached

Phase III Resonate Study in Relapsed/Refractory CLL

- 391 relapsed and refractory pts randomized 1:1 between ibrutinib and ofatumumab

- Outcome dramatically improved with ibrutinib
  - Response (42.1% versus 4%, p<0.001)
  - PFS (median NR versus 8 months; HR 0.22, p<0.001)
  - OS (12 m 90% versus 81%, HR 0.43, p<0.005)

- Toxicity differs between arms
  - Atrial fibrillation (6% versus 1%) > with ibrutinib
  - Grade 1/2 bleeding/ecchymosis (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 ecchymosis are noted frequently with ibrutinib but major bleeding uncommon provided
  - Coumadin® (warfarin) 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 at high risk for embolic disease (consider idelalisib)

- Arthralgias, panniculitis, and erythema nodosum associated with this can be managed with short course of steroids

- Benefit of rituximab to ibrutinib unclear at this time
Future Questions and Application of Ibrutinib in CLL

- Treatment of symptomatic, untreated CLL
- Treatment of early, asymptomatic, but previously untreated CLL with high-risk genomic features
- Combination strategies to increase CR rate, prevent resistance and allow cessation of therapy in a subset of patients
- Identification and treatment of ibrutinib resistant disease

Ibrutinib in Previously Untreated CLL

- Initial phase 2 study
  - 31 untreated patients > 65 yrs
  - ORR of 84%, with 23% attaining CR, 55% PR, and 6% PR-L.
  - PFS at 30 months—96%

- Ongoing phase 3 studies
  - CLB versus ibrutinib (age >65 yrs)
  - BR versus IR versus I (age >65 yrs)
  - FCR versus IR (age < 70 yrs)

- Early intervention trials for high-risk, asymptomatic pts ongoing
Combination Strategies in Ibrutinib

- **Goal:** Increase CR rate, PFS, and decrease development of resistance
  - Ibrutinib + BR (positive study as measured by PFS)
  - Ibrutinib + FCR (DFC)
  - Ibrutinib + CD20 antibody (rituximab, ofatumumab, and obinutuzumab) (MD Anderson, Company)
  - Ibrutinib + Lenalidomide (U Colorado, Stanford, OSU)
  - Ibrutinib + CC-122 (Company)
  - Ibrutinib + Venetoclax (MRC)
  - Ibrutinib + Venetoclax + Obinutuzumab (OSU)
  - Ibrutinib + immune checkpoint inhibitors

Management of Ibrutinib Resistant Disease

- **Richter's transformation**
  - Occurs most commonly during year 1, 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**
  - Occurs virtually always after year 1 of therapy
  - Virtually always associated with C481S BTK or PLCG2 mutation that can be assessed by genotyping blood
  - Therapy with ibrutinib should continue until initiating next therapy to avoid withdrawal tumor flare
  - Response after ibrutinib possible in this group, particularly with alternative targeted therapies (transplant should be considered)
Representative Male Patient on Ibrutinib Developing Resistance

Specific mutations allow for surveillance and the development of targeted agents and combinations to treat resistant disease.

Idelalisib (GS1101, CAL101) in CLL

- Idelalisib is an oral agent that targets PI3K-delta providing selectivity thereby allowing good target coverage.

- Ph I study in relapsed CLL/NHL with 54 CLL pts
  - Pt demographics median 5 prior Rx, 82%; 31% del(17p13.1)
  - Dose of 150 mg BID based upon Pk and PD
  - Response to therapy remarkable
    - 91% with node/spleen response
    - 24% ORR due to persistent lymphocytosis
    - Median PFS of 18 m; less durable in del(17p)
  - Toxicity modest but includes
    - Early grade 3-4 transaminitis
    - Late hypersensitivity pneumonitis, colitis/diarrhea, and rash

Study 116: Randomized, Double-blind, Placebo-controlled Trial

**Primary Study 116**
- Randomized Combination Therapy
- Single-Agent Therapy

**Extension Study 117**
- Extension Single-Agent Therapy

**Arm A (N=110)**
- Idelalisib (150 mg BID)
- Rituximab (6 months)

**Arm B (N=110)**
- Placebo (BID)
- Rituximab (6 months)

**81% PR**
- Disease Progression

**13% PR**

Eligibility
- Relapsed pts inappropriate for chemoimmunotherapy

R-Idelalisib for Relapsed CLL: Outcome

**Progression Free Survival**
- Idelalisib + Rituximab
- Placebo + Rituximab

Toxicity similar to phase 1 study

Overall Survival
- Idelalisib + Rituximab
- Placebo + Rituximab

All groups doing well including del(17p)

Furman R et al. NEJM 370:997-1007, 2014
Where Does Idelalisib Fall in CLL Therapy?

- Idelalisib + rituximab a reasonable therapy for previously treated CLL but many questions remain
  - Where in priority of therapy with ibrutinib
    - Unclear efficacy is similar, particularly in del(17p) pts
    - Need for dual therapy with rituximab raises cost and inconvenience as compared to monotherapy oral agent
    - Toxicity monitoring (LFTs early and colitis late) makes administration more challenging
    - Can be used in the setting of anticoagulation or higher bleeding risk

- My practice is to use idelalisib only when ibrutinib is contraindicated (need for warfarin) or not tolerated
  - Ibrutinib works in idelalisib refractory pts; reverse unknown
Outcome of CAR-T Cells

- Incredibly promising results in refractory pediatric and adult acute lymphoblastic leukemia (80-90% responses)
- Data in CLL somewhat limited
- Some responses in CLL but less than ALL and often only partial
- Major toxicities of CAR-T cells include
  - Cytokine release syndrome
  - Fever and infection
  - Prolonged suppression of normal B-cells (due to CAR-T cells)
  - Need for life-long immunoglobulin production
- Future application of CAR-T cells might include
  - Addition of ibrutinib
  - Use following CLL cytoreduction to lower frequency of cytokine release syndrome

Other Novel Agents in CLL

- Other small molecule inhibitors
  - Duvelisib (IPI-145, a p110δ and p110γ inhibitor)
  - 2nd generation BTK inhibitor (ACP-196, ONO-4059)
  - Selinexor (XPO1 inhibitor)
  - Venetoclax (bcl-2 but not bcl-xl antagonist)
  - Entospletinib (syk)
  - Many others

- Antibodies and biologic therapy
  - TRU-016—CD37 SMIP
  - MOR-208 (CD19 engineered antibody)
  - CD19 Chimeric antigen receptor t-cells
  - CC-122
  - Many others
Important Conclusions

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

- CD20-antibody chemoimmunotherapy offers a survival advantage for symptomatic CLL; in no patient should chemotherapy alone be considered

- Patients with del(17p13.1) who require therapy do not respond well to chemoimmunotherapy and should receive ibrutinib

- Kinase inhibitors such as ibrutinib have
  - Altered the recommended time for transplant
  - Have the potential to change treatment paradigm of CLL

Living Well With CLL
Kimberly Holt, BSN, RN, OCN
June 17, 2015

The James
OBJECTIVES

Managing Potential Side Effects of Treatment

Aiding Patient/Caregiver In Treatment Adherence

Tips on The Survivorship Challenges of CLL

Common Side Effects of Newer CLL Therapies

- **IBRUTINIB** - increased risk of bleeding, arthralgias and myalgias, fatigue, hand and foot cramping, bruising, rash, mouth sores, diarrhea, upper respiratory infections and A-fib. Due to the increased risk for bleeding, Ibrutinib should be held 3 to 7 days prior to procedures, hold time depending on complexity of procedure.
- **ACP 196** - headaches, infrequent nausea
- **LENALIDOMIDE** - rash
- **ABT-199** - tumor lysis syndrome, low blood counts
- **ZYDELIG** - diarrhea, pneumonitis, colitis
- **IPI-145** - diarrhea
- **KPT** - anorexia and weight loss

**Educate the patient on potential side effects and how they should expect to feel**

**Teach the patient to monitor their temperature and s/sx of infection**

**Upon starting any new therapy, the patient should be instructed to call their physician if they notice any new symptoms that occur while on treatment**
Aiding Patient/Caregiver In Treatment Adherence

- Consider the cost of medications to the patient; inquire if they are able to afford this; educate patients on MAPs
- The patient should be thoroughly educated on the purpose of each medication in their treatment regimen (including preventives)
- The patient should be taught that even if they ‘feel well’ to still take their medication regimen as prescribed and to discuss any suggested changes with their physician before altering regimen
- Educate the patient to call their physician’s office when running low (2 week supply or less) on specially ordered meds

Tips on Survivorship Challenges of CLL

Because CLL is a chronic condition, survivors must continually monitor and treat the disease.  

- Survivorship is a joint effort between patient, caregiver, and healthcare team
- When seeing a CLL or hematology/oncology specialized physician, patients should be encouraged to maintain a good relationship with their local oncologist and/or PCP as well
- The healthcare team should be easily accessible to the patient (clearly communicate best contact person and numbers, and where applicable, information on email/myChart)
- Encourage the patient to connect with other CLL/cancer survivors (i.e survivorship programs, support groups, blogs, and events such as LLS Light The Night® and Pelotonia®)
**Tips on Survivorship Challenges of CLL**

- Maintain health and wellness
  - Keeping follow-up appointments with your hematologist/oncologist
  - Preventative health screening (PSA, colonoscopy, dermatology, etc)
  - Annual flu vaccination and pneumonia vaccination every five years; NO LIVE VACCINES

- Aim to avoid contact with persons who have known infections until the infection is resolved. Having CLL puts a patient at greater risk for infection

- Good nutrition, staying active/exercise, and getting plenty of rest

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**CLL Resources**

- **Your Specialized Healthcare Team**
  - Hematologist/oncologist, nurse, social worker, clinical research coordinator

- **Leukemia and Lymphoma Society:** [www.LLS.org](http://www.LLS.org)
  - Blood Cancer Information and Support
  - Copay Assistance Program: (877) 557-2672
  - Telephone/Web Education Programs
  - Education Videos
  - Online Discussion Boards and Chats
  - Consult with an Information Specialist: (800) 955-4572
  - Clinical Trials Information: (800) 955-4572
  - Information for Veterans: (800) 749-8387
  - Other Helpful Organizations: [www.LLS.org/resourcedirectory](http://www.LLS.org/resourcedirectory)

- **Air Charity Network (Flights to Medical Appts.)**
  - [www.airlifethope.org](http://www.airlifethope.org)
  - [www.lifelinepilots.org](http://www.lifelinepilots.org)
  - [www.angelflight.com](http://www.angelflight.com)
CLL Resources

- Lodging Assistance
  - American Cancer Society: 800-227-2345
  - Hope Hollow: www.hopehollow.com

- Cancer Information and Support
  - The James Cancer Hospital and Solove Research Institute: http://cancer.osu.edu
  - The American Cancer Society: www.cancer.org
  - The National Cancer Institute: www.cancer.gov
  - www.chemocare.com
    (Patient friendly chemo education; great instructions on managing side effects)

Medication Assistance Programs

- Imbruvica®: You and I Access Program
  www.youandiaccess.com, 1-877-877-3536
  - Assistance with copays if eligibility criteria met and connection with other resources for the uninsured

- Zydelig®: AccessConnect Patient Support Program
  www.zydeligaccessconnect.com, 1-844-622-2377
  - Financial support for uninsured and copay assistance for those who meet eligibility criteria

- Patient Access Network Foundation
  www.panfoundation.org, 1-866-316-PANF
  - Assistance with medications for patients who have insurance coverage, income must be below 500% of the federal poverty level

- LLS Copay Assistance
  www.LLS.org/copay

Questions?

References

Thank You

To learn more about Ohio State's cancer program, please visit cancer.osu.edu or follow us in social media:

[Social media icons]

CLL: Update on Treatment and Side Effects Management

Question & Answer Session

The speakers’ slides are available for download at www.LLS.org/CE
Resources to make informed treatment decisions

Resources from The Leukemia & Lymphoma Society (LLS):

- For more information about blood cancers, other LLS programs, and support for your patients please contact an LLS Information Specialist.
  - TOLL-FREE PHONE: (800) 955-4572
  - EMAIL: infocenter@LLS.org
  - Continuing education programs: www.LLS.org/CE
  - CLL information and resources: www.LLS.org/leukemia
- Free publications ranging from disease specific information to health insurance options and resources to help patients and families.
  - WEBSITE: www.LLS.org/publications