What’s on the Horizon for Chronic Lymphocytic Leukemia?

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Harvard Medical School
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Disclosures
Matthew S. Davids, MD, MMSc has affiliations with: AbbVie, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, Janssen, MEI, Merck, Pharmacyclics, Surface Oncology, and TG Therapeutics.
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Associate Director | CLL Center
Dana-Farber Cancer Institute

May 8, 2018

Disclosures for Matthew S. Davids, MD, MMSc

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<td>Employment</td>
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<td>Consultancy/Advisory Committee</td>
<td>Janssen, Genentech, Pharmacyclicas, Abbvie, Roche, TG Therapeutics, Merck, Astra-Zeneca, MEI Pharma, Verastem, InCyte</td>
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<td>Equity Ownership</td>
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<td>Research Funding</td>
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<td>Honoraria</td>
<td>None</td>
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<td>Patents &amp; Royalties</td>
<td>None</td>
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<tr>
<td>Speakers Bureau</td>
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<tr>
<td>Other</td>
<td>None</td>
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<tr>
<td>Presentation includes a description of the following off-label use of a drug or medical device</td>
<td>Venetoclax, lenalidomide</td>
</tr>
</tbody>
</table>
### The Big Picture

**NHL**

- **T-cell** (15%)
  - PTCL-NOS
  - ALCL
  - AITL
  - CTCL
- **B-cell** (85%)
  - **Indolent** (30%-40%)
    - SLL/CLL (19,000/yr)
    - Follicular
    - Marginal zone
    - LPL
  - **Aggressive** (60%-70%)
    - DLBCL
    - Mantle cell
    - Burkitt

### CLL | Fast Facts

- Median age at diagnosis is 72
- Patients often diagnosed on routine blood work
- Powerful biologic predictors of response
- Early stage patients without symptoms observed
- Advanced stage, symptomatic patients treated with chemoimmunotherapy
- Highly treatable, but historically most therapies not curative
- Bone marrow transplant may lead to long term survival
- Novel oral agents have begun to revolutionize the field
CLL | Diagnosis

- Peripheral blood flow cytometry:
  - ABC ct. >5,000 (CD5+CD23+CD19+dimCD20+dimIg+)
  - N.B. ABC ct. <5,000, same markers = monoclonal B cell lymphocytosis (MBL)
- Lymph node biopsy (excisional or core) (SLL)
- Bone marrow biopsy (rarely)

**Key point:** small lymphocytic lymphoma (SLL) is part of the same disease continuum as CLL

CLL | Pathology

Courtesy of the Ohio State University CLL Center
CLL | Staging

Clinical staging systems (Rai)*

- Stage 0 (elevated lymphocyte count)
- Stage I (enlarged lymph nodes)
- Stage II (enlarged spleen or liver)
- Stages III (anemia) and IV (low platelets)

*Bone marrow biopsy and CT not required

Rai et al., Blood, 1975

Key Prognostic Factors

- Beta-2 microglobulin
- Cytogenetic abnormalities (FISH)
- Immunoglobulin gene mutation (IGHV)
- Somatic mutations (TP53, SF3B1, NOTCH1)
- ZAP-70
- CD38
**CLL | Prognostic Factors: Cytogenetics**

"Routine Karyotype"

<table>
<thead>
<tr>
<th>Cytogenetic Abnormality</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q deletion</td>
<td>178 (55)</td>
</tr>
<tr>
<td>11q deletion</td>
<td>58 (18)</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>53 (18)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>23 (7)</td>
</tr>
<tr>
<td>6q deletion</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Normal</td>
<td>57 (18)</td>
</tr>
</tbody>
</table>

Döhner, et al., *NEJM*, 2000

**CLL | Prognostic Factors: IGHV**

**IGHV mutation status**

Reviewed in Chiorazzi et al., *NEJM*, 2005
CLL | Prognostic Factors: Somatic Mutations

Treatment

“Why can’t you just cut it out, doc?”
**CLL | When to Treat**

- **Indications for treatment**
  - Low blood counts
  - Bulky or rapidly enlarging lymph nodes or spleen
  - Symptoms (fevers, night sweats, unintentional weight loss, fatigue, pain)
  - Refractory autoimmune conditions
  - +/- LDT <6 months

If none of the above... → **OBSERVATION**

---

### CLL Trialists’ Group Meta-analysis, JNCI, 1999

<table>
<thead>
<tr>
<th>Start year</th>
<th>Study name</th>
<th>Treatment</th>
<th>Deaths/Patients</th>
<th>Immediate</th>
<th>Deferred</th>
<th>Ratio of annual death rates</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>CALGB</td>
<td>CHI</td>
<td>7/32</td>
<td>0/26</td>
<td>0.5</td>
<td>2.7</td>
<td>Immediate better</td>
</tr>
<tr>
<td>1978</td>
<td>MRC-CLL-1</td>
<td>CHI</td>
<td>31/397</td>
<td>32/41</td>
<td>3.7</td>
<td>15.1</td>
<td>Deferred better</td>
</tr>
<tr>
<td>1990</td>
<td>FRE-CLL-80</td>
<td>CHI</td>
<td>175/300</td>
<td>169/307</td>
<td>10.1</td>
<td>86.6</td>
<td>Immediate better</td>
</tr>
<tr>
<td>1984</td>
<td>MRC-CLL-2</td>
<td>CHI</td>
<td>76/121</td>
<td>73/118</td>
<td>5.2</td>
<td>36.6</td>
<td>Deferred better</td>
</tr>
<tr>
<td>1986</td>
<td>FRE-CLL-80</td>
<td>CH/P</td>
<td>122/407</td>
<td>128/462</td>
<td>2.0</td>
<td>62.0</td>
<td>Immediate better</td>
</tr>
<tr>
<td>1986</td>
<td>PHEMA</td>
<td>CH/P</td>
<td>21/77</td>
<td>21/81</td>
<td>0.5</td>
<td>10.4</td>
<td>Deferred better</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>432/1014</td>
<td>430/1034</td>
<td>16.8</td>
<td>212.3</td>
<td>Immediate better</td>
</tr>
</tbody>
</table>

- 99% or <95% confidence intervals
- Heterogeneity between 8 trials: $X^2 = 1.7; P > 0.1; NS$
Revisiting early intervention in the modern era

**CLL7 Trial**

- Diagnosed within 1 year
- No prior treatment
- Planned enrollment ~ 600

- 17p-, 11q- deletion, trisomy 12
- Unmutated IGHV, TK > 10 U/L
- Predicted LDT < 12 months

- ≥ 2 risk factors
- Planned n = 150

- Some serious side effects such as infections seen in FCR arm

- NO DIFFERENCE IN OS

**COHORT I**
FCR x 6

**COHORT II**
Watch & wait

Schweighofer et al., ASH, 2013

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**CLL12 is the first study of ibrutinib for high risk watch/wait patients**

- Screening phase (within 30 days before randomization)
- Risk stratification
  - Low
  - Intermediate
  - High
  - Very high

- 1:1 randomization
  - Treatment starts within 28 days
  - n=126

- Watch and wait
- Placebo 420 mg
- Ibrutinib 420 mg

- Disease progression or treatment discontinuation
- Follow-up phase

Primary endpoint: EFS

Langerbeins et al., Future Oncol, 2015
“What can I do to slow this down?”

Polyphenon E: The Mayo Clinic Study

Shanafelt et al., Cancer, 2013

CLL | Initial Treatment

1960s
- Alkylating agents
  - Chlorambucil
  - Cytoxan
  5% CR

1970s
- Purine nucleosides
  - Fludarabine
  - Pentostatin
  - Cladribine
  5%-20% CR

1980s
- Purine nucleosides and alkylators
  30% CR

1990s
- Alemtuzumab monotherapy
  24% CR
  - Bendamustine
  30% CR
  - Chemo-immunotherapy (CIT)
  41%-70% CR

2000s
- obinutuzumab
- ibrutinib
- idelalisib
- venetoclax
- next generation molecules
  %CR: variable

2010s

%CR: variable
FCR

- Fludarabine (days 1-3)
- Cyclophosphamide (days 1-3)
- Rituximab (day 1)

Plus Neulasta on day 4

-- above given in 6 monthly cycles --

**FCR has curative potential in mutated IGHV CLL**

**MDACC – FCR**

**GCLLSG – CLL8**

Thompson et al., Blood 2016

Fischer et al., Blood 2016
- **Bendamustine** (days 1-2)
- **Rituximab** (day 1)

Plus Neulasta on day 3

-- above given in 6 monthly cycles --

**CLL10 Study: FCR vs. BR in Frontline**

**Progression free survival**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FCR</strong></td>
<td>55.2 months</td>
<td></td>
</tr>
<tr>
<td><strong>BR</strong></td>
<td>41.7 months</td>
<td></td>
</tr>
</tbody>
</table>

**Overall survival**

<table>
<thead>
<tr>
<th></th>
<th>OS at 36 months:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FCR</strong></td>
<td>90.6%</td>
</tr>
<tr>
<td><strong>BR</strong></td>
<td>92.2%</td>
</tr>
</tbody>
</table>

- $P < 0.001$
- $HR = 1.626 = > 1.388$

Eichhorst et al., ASH, 2014
CLL10 Study: FCR vs. BR Frontline Side Effects

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (%)</th>
<th>BR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>84.2</td>
<td>59.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.6</td>
<td>10.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5</td>
<td>14.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Infection</td>
<td>39.1</td>
<td>26.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All infections in patients ≤ 65 years</td>
<td>35.2</td>
<td>27.5</td>
<td>0.1</td>
</tr>
<tr>
<td>All infections in patients &gt; 65 years</td>
<td>47.7</td>
<td>20.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sec Neoplasm*</td>
<td>6.1</td>
<td>3.6</td>
<td>0.244</td>
</tr>
<tr>
<td>TRM</td>
<td>4.6</td>
<td>2.1</td>
<td>0.107</td>
</tr>
</tbody>
</table>

*AML/MDS: FCR=6, BR = 1

Eichhorst et al., ASH, 2014

Can We do Better than Rituximab in CLL?

GA101: Mechanisms of action

- Increased Direct Cell Death
  - Type II versus Type I antibody
- Enhanced ADCC
  - Glycoengineering for increased affinity to FcγR IIa
  - Lower CDC
  - Type II versus Type I antibody

ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
Missonnet E. et al. J Immunol 2010; 185:4325-4402
**Obinutuzumab is Highly Active in CLL**

Goede et al., NEJM, 2014
Goede et al., Leukemia, 2015

**Toxicities of note:** infusion reactions, neutropenia, infection

**Time to next treatment:** 42.7 mo.

---

**CLL | Treatment of Relapsed/Refractory Disease**

**“Refractory” definition:**
- < 24 mo. response to chemoimmunotherapy

**“Relapsed” definition**
- Achieved >24 mo. response but then disease came back

**Further evaluation:**
- Recheck peripheral blood FISH to rule out clonal evolution
- No need to recheck IGHV status (stable marker)
Older Agents

- Ofatumumab (Arzerra)
- Rituximab
- Lenalidomide (Revlimid)
- Alemtuzumab (Campath)
- High-dose methylprednisolone (HDMP)

Hematopoietic Cell Transplantation

The Allogeneic Transplant Process

1. Collection
   Stem cells are collected from the patient’s bone marrow or blood.

2. Processing
   Bone marrow or peripheral blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the transplant.

3. Cryopreservation
   Bone marrow or blood is frozen to keep the stem cells alive until they are infused into the patient’s bloodstream.

4. Chemotherapy
   High-dose chemotherapy and/or radiation therapy is given to the patient.

5. Infusion
   Stem cells are infused into the patient.
Transplant guidelines are in flux given the novel agents

Factors influencing the decision to undergo allo HCT in the era of CLL novel agents

<table>
<thead>
<tr>
<th>Favorable transplant risk</th>
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</thead>
<tbody>
<tr>
<td>Younger, fit, well-matched donor, experienced transplant center</td>
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</table>

<table>
<thead>
<tr>
<th>High risk CLL</th>
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</thead>
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<td>Del(17p), TP53 mut, possibly del(11q), NOTCH1 mut</td>
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</table>

<table>
<thead>
<tr>
<th>Unfavorable transplant risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older, comorbid, mismatched donor, low-volume transplant center</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low risk CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable cytogenetics, mutated IGHV, not CIT-refractory</td>
</tr>
</tbody>
</table>


Immune-based Therapies: CARs (‘Serial Killers’)

- 24 patients treated with CD19 CAR-T
- ORR 71%, CR 21%, 88% with marrow clearance
- 83% CRS
- 33% neurotoxicity (reversible in all but 1 case)
- Median PFS 8.5 mo., median OS not reached

Turtle et al., *J Clin Oncol*, 2017
“Hide and seek”

Reviewed in Davids and Brown, *Leuk & Lymph*, 2012
The BTK inhibitor ibutinib leads to comparable PFS/OS regardless of IGHV status (PCYC-1102 study)

Ibrutinib leads to durable response in most FISH subgroups
**Frontline ibrutinib is effective even in pts with TP53 dysfunction**

**RESONATE-2: no del(17p)**

**NIH: Del(17p)/TP53 mut**

Toxicities of note: diarrhea, bruising, bleeding, hypertension, atrial fibrillation, infection


Farooqui et al., *Lancet Oncol*, 2015

---

**Why not use indefinite ibrutinib monotherapy?**

- Achievement of CR is rare
- Duration of response in del(17p)/del(11q)/ complex karyotype is shorter
- Resistance mutations already described
- Long term adherence issues
- Cost

O’Brien et al., *ASH Annual Meeting*, 2016

Woyach et al., *NEJM*, 2014
Novel Targeted Agents

Reviewed in Davids and Brown, Leuk & Lymph, 2012

PI3K Inhibitor: Idelalisib (GS1101/CAL-101) -δ-specific

Best Lymph Node Response

Lymphocyte and Nodal Response

Presence of del17p or TP53 mutation

Common side effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>30%</td>
</tr>
<tr>
<td>Elevated liver function tests</td>
<td>24%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22%</td>
</tr>
</tbody>
</table>

Brown et al., ASCO, 2013
The PI3K-δ inhibitor idelalisib is active in R/R CLL, including those with TP53 dysfunction

![Graphs showing progression-free survival and median PFS with del17p/TP53mut present vs not present]

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDELA + R</td>
<td>19.4 mo (16.6, –)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PBO + R</td>
<td>7.3 mo (5.5, 8.5)</td>
<td></td>
</tr>
</tbody>
</table>

Sharman et al., ASH Annual Meeting 2014

Novel Targeted Agents

![Diagram showing targeted agents and their interactions]

Reviewed in Davids and Brown, Leuk & Lymph, 2012
Venetoclax causes profound disease reduction even in pts with TP53 dysfunction, with some risk of TLS
Venetoclax dosing: follow the directions!

Impact of MRD levels on long-term outcomes in CLL

(courtesy of Peter Hillmen)
Diverse mechanisms allow for many possible combinations

- **NA + CIT**
- **NA + CD20 mAb**
- **NA-NA combos**

**Ibrutinib + FCR (iFCR) is a promising new frontline approach for young, fit CLL patients**

- Best BM MRD neg: 83%, higher than any prior CIT or NA regimen for 1L CLL therapy
- Response deepens over time in both *IGHV* mutated and unmutated patients with ibrutinib maintenance
- Ibrutinib discontinuation after 2 years of maintenance now being explored in patients who are BM MRD neg.

Davids et al., ASH Annual Meeting, 2017
Venetoclax + rituximab is highly active in R/R CLL

- Phase 1b: CR rate 51%, marrow MRD-neg. (57%)
  - MRD neg. pts who discontinued venetoclax have not recurred a median of 9.7 mo. after discontinuation
- Phase 3 (MURANO): CR rate 27%, peripheral blood MRD-neg. (84%)
  - This positive registrational study is likely to lead to full approval in R/R CLL

Venetoclax + obinutuzumab is safe and active in frontline CLL

- All 32 patients responded
- CR/Cri: 56%
- BM MRD-neg: 62.5%
- No clinical TLS observed
- 56% rate of infusion reactions

<table>
<thead>
<tr>
<th>Overall response rate (%)</th>
<th>(N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>58</td>
</tr>
<tr>
<td>Partial response</td>
<td>42</td>
</tr>
<tr>
<td>Minimal residual disease in peripheral blood (%)</td>
<td>(N=11)</td>
</tr>
<tr>
<td>Negative (&lt;10^-4)</td>
<td>91</td>
</tr>
<tr>
<td>Intermediate (≥10^-4 and &lt;10^-2)</td>
<td>9</td>
</tr>
</tbody>
</table>
A PI3K-δ/BTK doublet has shown promising efficacy and safety in R/R CLL

A phase I/ib study of umbralisib (TGR-1202) plus ibrutinib in R/R CLL and MCL

- ORR: 16/18 (89%)
  - PR or PR-L: 15/18 (83%)
  - IW-CLL CR: 1/18 (6%), radiographic CR: 4/18 (22%)
  - 1 year PFS and OS: 94%


• Davids et al., IW-CLL, 2017

Several ongoing studies of ibrutinib + venetoclax have shown early promising data

**CLARITY study**

- Bone marrow examinations
- VEN and IBR stop at 14 months if 8 month BM is MRD negative
- VEN and IBR stop at 26 months if 14 month BM is MRD negative
- IBR alone continues if 26 month BM is MRD positive

Hillmen et al. ASH 2017; Abst 428
QUESTION

What new and emerging therapies are you most excited about:

a) CAR T-cell Therapy
b) Novel targeted monotherapy (ibrutinib, idelalisib, venetoclax)
c) Combing existing and novel targeted therapies
d) Combining novel targeted therapies with each other

Ongoing randomized trials may define a new standard of care for frontline CLL treatment
### Treatment Summary: TP53 dysfunction

<table>
<thead>
<tr>
<th>Current Treatment Options</th>
<th>Frontline</th>
<th>CLL Patients with TP53 Dysfunction</th>
<th>Relapsed/refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP53 dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ibrutinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- older regimens (HDMP, alemtuzumab)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If no prior ibrutinib:

- ibrutinib
- venetoclax
- idelalisib + rituximab
- alloHCT

### Possible Future Treatment Options

- ibrutinib +/- CD20 mAb
- venetoclax +/- CD20 mAb
- ibrutinib + venetoclax +/- CD20 mAb
- 2nd generation NA combinations

### Treatment Summary: TP53 intact

<table>
<thead>
<tr>
<th>Current Treatment Options</th>
<th>Frontline</th>
<th>CLL Patients with Intact TP53</th>
<th>Relapsed/refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP53 intact</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Young, fit**

- FCR
- ibrutinib

**Older, frail**

- BR
- CHI + anti-CD20 mAb
- ibrutinib

### Possible Future Treatment Options

**Young, fit**

- ibrutinib + FCR
- ibrutinib + CD20 mAb
- venetoclax + CD20 mAb
- ibrutinib + venetoclax +/- CD20 mAb
- 2nd generation NA combinations

**Older, frail**

- BR (IGHV mutated only)
- ibrutinib +/- CD20 mAb
- venetoclax + CD20 mAb
- ibrutinib + venetoclax +/- CD20 mAb
- 2nd generation NA combinations

If no prior ibrutinib:

- ibrutinib
- venetoclax
- idelalisib + rituximab
- alloHCT

### Possible Future Treatment Options

- ibrutinib +/- CD20 mAb
- venetoclax +/- CD20 mAb
- idelalisib +/- rituximab
- ibrutinib + BR
- idelalisib + BR
- 2nd generation NA combinations
- CAR-T
Conclusions

• We have reached the end of the beginning of the NA era

• We now have a powerful toolkit of NAs, with more coming

• Sequencing should be guided by patient characteristics, prognostic markers, and response to prior therapy

• NA monotherapy may be appropriate for frail patients

• Fit patients (especially those with high risk markers) should consider combination therapy

• Active participation in clinical trials is critical

Adapted from DeVita and Chu, Cancer Res, 2008

Combination chemotherapy can cure hematologic malignancies

Adapted from DeVita and Chu, Cancer Res, 2008
What’s on the Horizon for Chronic Lymphocytic Leukemia?

Q&A Session
The Leukemia & Lymphoma Society Offers:

- **Information Specialists**: Master’s level oncology professionals available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - TOLL-FREE PHONE: 1-800-955-4572
  - EMAIL: infocenter@LLS.org

- **Free Education Booklets**: [www.LLS.org/booklets](http://www.LLS.org/booklets)

- **Free Telephone/Web Programs**: [www.LLS.org/programs](http://www.LLS.org/programs)

- **Live, weekly Online Chats**: [www.LLS.org/chat](http://www.LLS.org/chat)

The Leukemia & Lymphoma Society Offers:

- **LLS Podcast, The Bloodline with LLS**: Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.LLS.org/thebloodline](http://www.LLS.org/thebloodline)

- **Education Video**: Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)

- **Information on leukemia**: For information about chronic lymphocytic leukemia, visit [www.LLS.org/leukemia](http://www.LLS.org/leukemia)

- **Patti Robinson Kaufmann First Connection Program**: Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)

- **Free Nutrition Consults**: Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)

- **What to ask**: Questions to ask your treatment team: [www.LLS.org/whatsask](http://www.LLS.org/whatsask)

- **Support Resources**: LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)
We have one goal: A world without blood cancers