20TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

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Treatment Landscape in CLL

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20TH ULTMANN
CHICAGO LYMPHOMA SYMPOSIUM

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

Disclosures

Abbvie – Speaker's Bureau for venetoclax

Objectives

1. Review NCCN guidelines for the treatment of CLL:
   - Frontline
   - Relapsed/Refractory

2. Discuss considerations for BTK-I and BCL-2 + anti-CD20 monoclonal antibody therapies

3. Reflect on the past vs. present landscapes of CLL treatment

NCCN Preferred Treatment: First line, without *TP53 mutation*

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

NCCN Guidelines Index
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Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Acalabrutinib[f] ± obinutuzumab (category 1) • Venetoclax[f,g] + obinutuzumab (category 1) • Zanubrutinib[f] (category 1)	• Ibrutinib (category 1)[f,h] • Bendamustine[i] + anti-CD20 mAb[d,j,k] • Chlorambucil + obinutuzumab[l] • Obinutuzumab[l] • High-dose methylprednisolone (HDMP) + rituximab or obinutuzumab (category 2B; category 3 for patients <65 y without significant comorbidities) • Ibrutinib[f] + obinutuzumab[l] (category 2B) • Ibrutinib[f] + rituximab[p] (category 2B) • Ibrutinib + venetoclax[f,g] (category 2B)	(consider for IGHV-mutated CLL in patients age <65 y without significant comorbidities) • FCR (fludarabine, cyclophosphamide, rituximab)[m,n,o]

NCCN Preferred Treatment Regimens: Relapsed/Refractory

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SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation

SECOND-LINE THERAPY OR THIRD-LINE THERAPY		
Preferred regimens • BTKi ▸ Acalabrutinib[f,q] (category 1) ▸ Zanubrutinib[f,q] • BCL-2 inhibitor ▸ Venetoclax[f,g] + rituximab[e] (category 1)	**Other recommended regimen** • Ibrutinib (category 1)[f,h] • Venetoclax[f,g]	**Useful in certain circumstances** (for relapse after a period of remission if previously used as first line therapy) • Retreatment with venetoclax[f,g] + obinutuzumab

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi-AND VENETOCLAX-BASED REGIMENS[e]
Other recommended regimens • PI3K inhibitors[f] (alphabetical order) ▸ Duvelisib ▸ Idelalisib ± rituximab • CIT or Immunotherapy ▸ Bendamustine + rituximab[k] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) ▸ FCR[n,o,p] ▸ Lenalidomide ± rituximab ▸ Obinutuzumab ▸ HDMP + rituximab or obinutuzumab (category 2B)

NCCN Preferred Treatment Regimens: TP53 Mutated

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CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by category)
CIT is not recommended since del(17p)/*TP53* mutation is associated with low response rates.

FIRST-LINE THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f] ± obinutuzumab • Venetoclax[f,g] + obinutuzumab • Zanubrutinib[f]	• Alemtuzumab[r] ± rituximab • HDMP + rituximab • Ibrutinib[f,h] • Obinutuzumab • Ibrutinib + venetoclax[f,g] (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f,q] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Venetoclax[f,g] • Zanubrutinib[f,q]	• Ibrutinib[f,h] (category 1) Alemtuzumab[r] ± rituximab • Duvelisib[f] • HDMP + rituximab • Idelalisib[f] ± rituximab[s] • Lenalidomide[t] ± rituximab

Treatment Regimens

Frontline

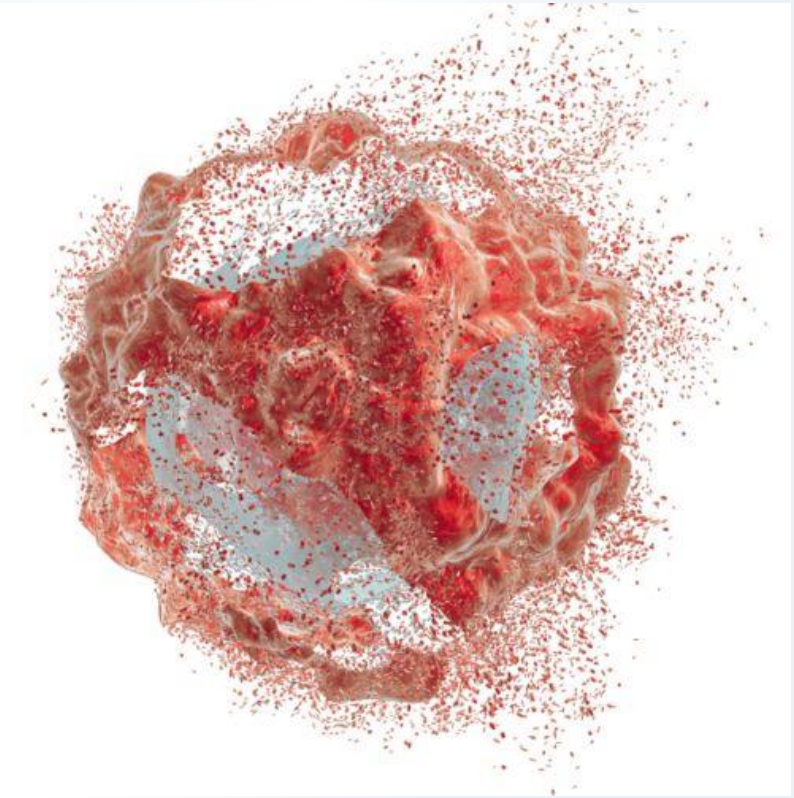
BTK Inhibitors - indefinite therapy

First generation: ibrutinib

Second generation: acalabrutinib (+/- obinutuzumab), zanubrutinib

Anti-CD20 monoclonal antibody + BCL2 inhibitor

Obinutuzumab + venetoclax for 1 year



https://together.stjude.org/en-us/diagnosis-treatment/side-effects/tumor-lysis-syndrome.html

Rai, K.R., Stilgenbauer, S. "Overview of the treatment of chronic lymphocytic leukemia." *Up to Date*, 01 February 2022

Relapsed/Refractory:

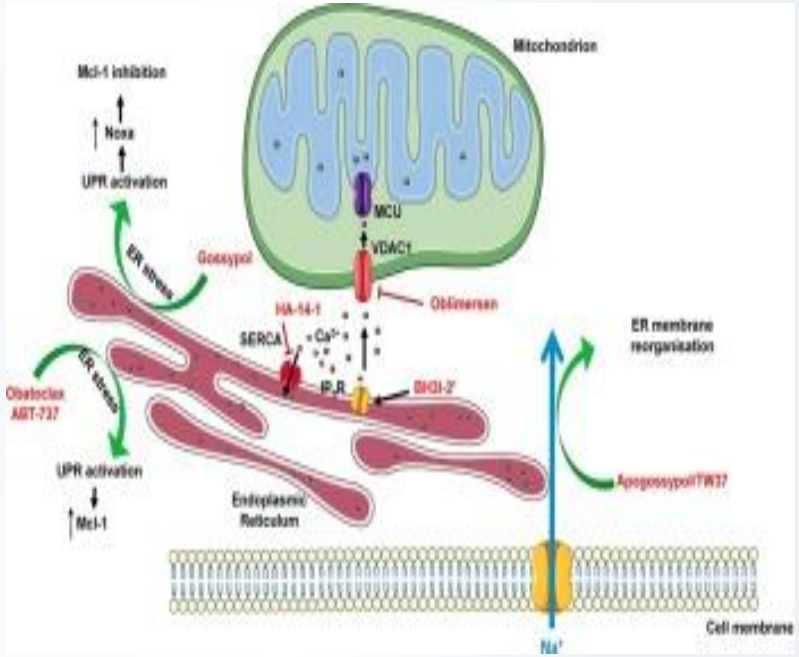
BTK Inhibitors - indefinite therapy

First generation: ibrutinib

Second generation: acalabrutinib, zanubrutinib

BCL2 inhibitor + Anti-CD20 monoclonal antibody

Venetoclax + rituximab for 2 years



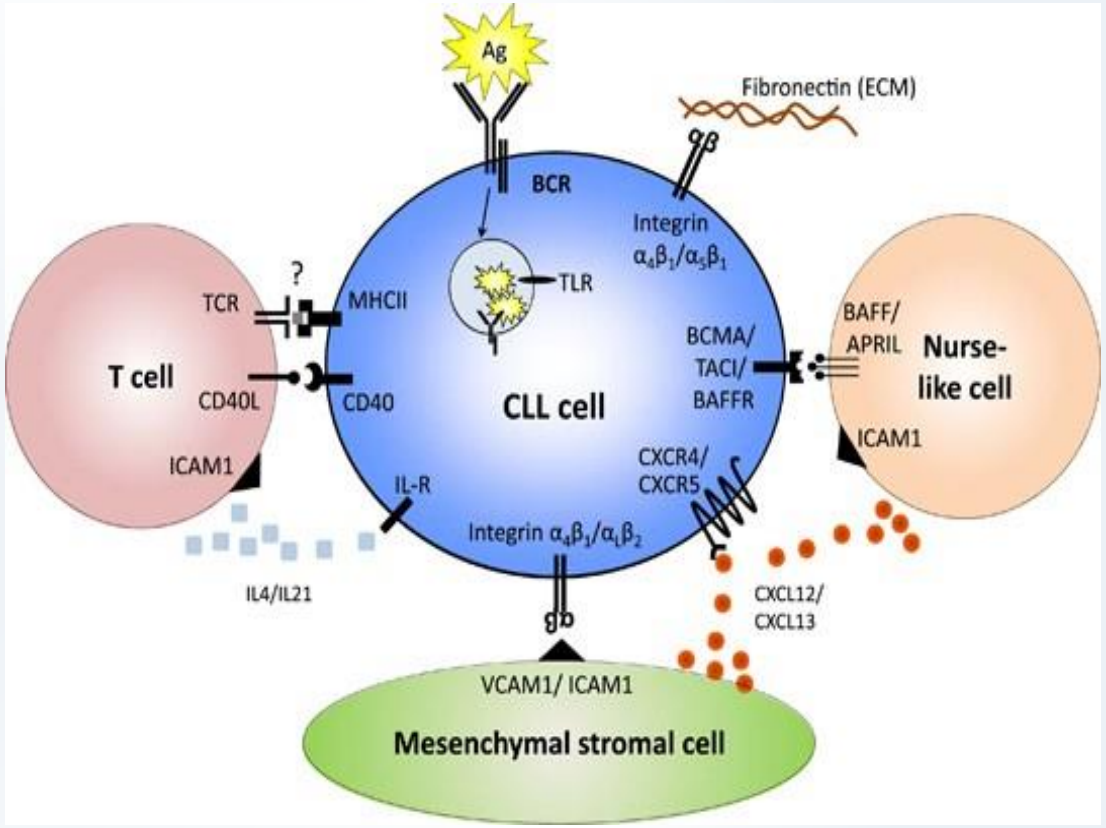
Rai, K.R., Stilgenbauer, S. "Overview of the treatment of chronic lymphocytic leukemia." *Up to Date*, 01 February 2022.

Considerations: BTK-inhibitors

- **Treatment-related lymphocytosis:** expected initially, typically decreases over the first several months of treatment
- **Rash:** identify drug rash early, consult dermatology

- **Atrial fibrillation & other cardiac risk factors:** screen prior to initiation; d/c ibrutinib if occurs
- **Bleeding:** must hold for invasive procedures
- **HTN:** consult to manage BP

- **Headache** (acalabrutinib): acetaminophen + caffeine, typically resolves after first few weeks of treatment
- **Myalgias**
- **Fatigue**
- **Diarrhea** (transient): loperamide, infectious workup



Rai, K.R., Stilgenbauer, S. "Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia." *Up to Date*, 06 July 2022.

Considerations: venetoclax

Upon initiation of treatment:

Tumor lysis syndrome (TLS) ramp up protocol

Antiuricemic

Reinforce hydration

Adverse events:

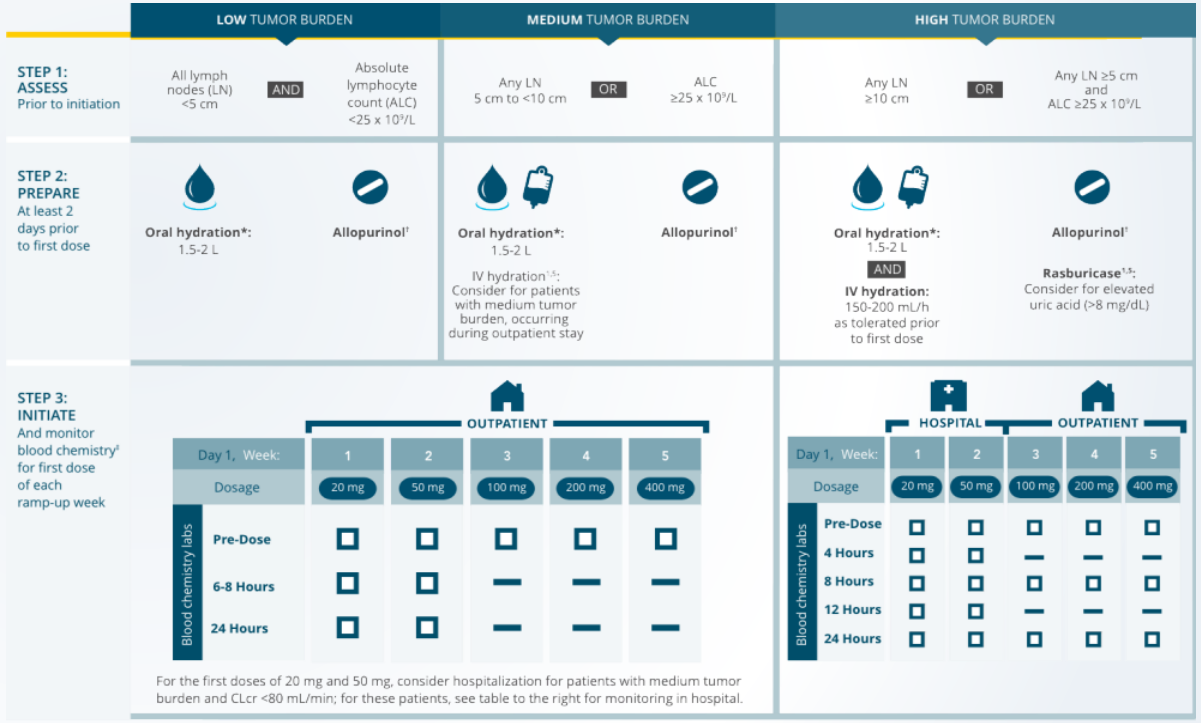
TLS (during ramp up)

Cytopenias - mostly neutropenia

Infection (URI)

Diarrhea

Fatigue



VENCLEXTA® (venetoclax tablets) | Risk Assessment for CLL/SLL (venclextahcp.com)

Rai, K.R., Stilgenbauer, S. "Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia." *Up to Date*, 06 July 2022.

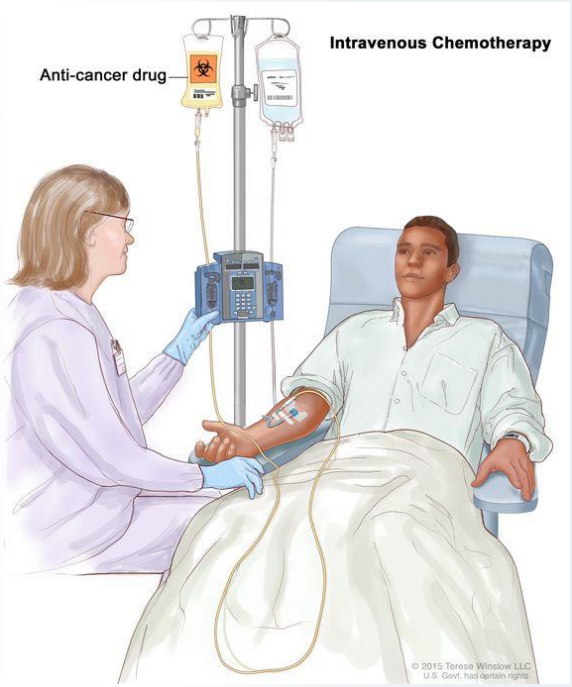
Chemotherapy and Immunotherapy – No Longer Preferred

Regimens:

Bendamustine + anti-CD20 monoclonal antibody

Chlorambucil + obinutuzumab

Past: FCR = fludarabine, cyclophosphamide, rituximab



Chemoimmunotherapy is not recommended for those with del(17p)/TP53 mutation because it's associated with low response rates

Rai, K.R., Stilgenbauer, S. "Overview of the treatment of chronic lymphocytic leukemia." *Up to Date*, 01 February 2022.

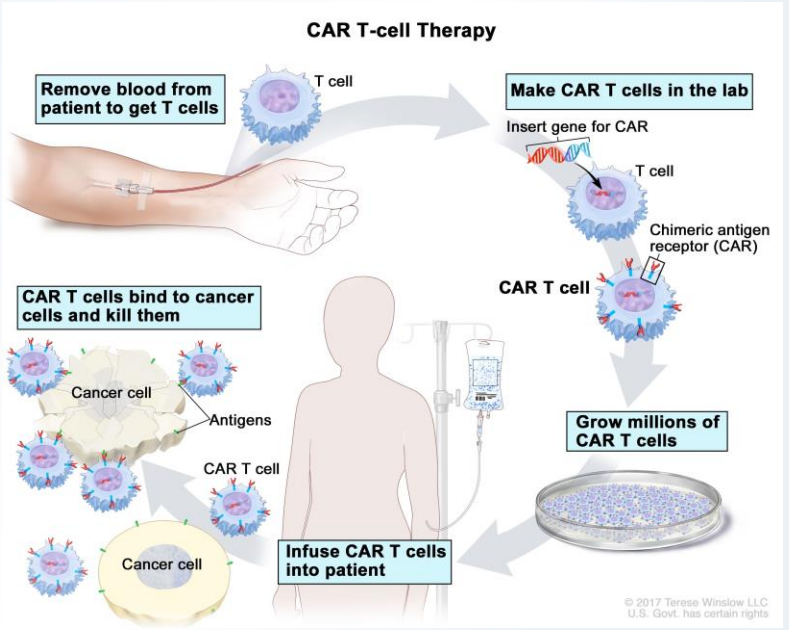
HSCT & CAR T

Stem Cell transplant

- Should be done via clinical trial
- Candidacy: CLL patients are typically elderly due to the slowly progressive nature of the disease
- However, this criteria is changing due to the advent of targeted therapies and genetic testing

CAR T-cell therapy

- Investigational
- AEs can be serious: neurotox, CRS
- Future: “off the shelf” CAR-NK



Rai, K.R., Stilgenbauer, S. “Hematopoietic cell transplantation in chronic lymphocytic leukemia.” *Up to Date*, 06 July 2022. PFS = progression-free survival. OS = overall survival. HCT = hematopoietic cell transplantation.

Rai, K.R., Stilgenbauer, S. “Treatment of relapsed or refractory chronic lymphocytic leukemia.” *Up to Date*, 02 Sep 2022