Treatment Strategies for Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

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Disclosures

I have nothing to disclose.

Objectives

- Evaluate recent literature to assess treatment strategies for patients with newly diagnosed CLL.
- Compare safety profiles of bruton tyrosine kinase (BTK) inhibitors including management of adverse events.
- Review barriers to oral oncology therapies as they relate to medication adherence.
- Discuss approaches to minimize financial toxicity in CLL.

Audience Participation Question #1

True or False: CLL is an aggressive disease that often impacts the elderly.

A. True
B. False

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Text **ONCEDSPEC** to **22333** once to join

Which chromosomal abnormality is associated with worse prognosis and is used to guide therapy options?

A. Mutated IGHV
B. Del(17p)
C. Trisomy 12
D. ZAP-70

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Patient Case

MS is a 67 year old male with newly diagnosed CLL. He has a past medical history of hypertension, atrial fibrillation, and peptic ulcer disease. His current medications include lisinopril 20 mg daily, apixaban 5 mg twice daily, pantoprazole 20 mg daily, and vitamin D 1000 IU daily. He presents to your clinic to discuss treatment options.

Epidemiology

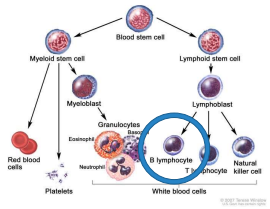
Incidence
- Most common leukemia in adults
- Men > women

Elderly
- Average age at diagnosis: 70 years

Indolent
- 5-year survival rate: 87.9%

Cancer Stat Facts: chronic lymphocytic leukemia. National Cancer Institute. Accessed September 9, 2022. seer.cancer.gov/statfacts/html/clyl.html
NCCN Clinical Practice Guidelines in Oncology for CLL/SLL. V.1.2023

Pathophysiology and Presentation



- Asymptomatic
- Symptomatic
  - Painful adenopathy
  - B-symptoms: fever, night sweats, weight loss, fatigue
  - Cytopenias: neutropenia, thrombocytopenia, anemia
  - Organ dysfunction: splenomegaly

N Engl J Med 2000; 343:1910-1916
NCCN Clinical Practice Guidelines in Oncology for CLL/SLL. V.1.2023

Rai Staging System

Stage	Description	Risk Status	Treatment
0	Lymphocytosis • Blood: >5x10^9 • Bone marrow: >40%	Low	Surveillance
I	+ lymphadenopathy	Intermediate	Consider treatment
II	+ either splenomegaly or hepatomegaly		
III	+ hemoglobin <11 g/dL	High	Treatment
IV	+ platelets <100,000/mm^3		

Blood 2018; 131:2745-2760
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Prognostic Factors

Interphase Cytogenetics (FISH)	• Identifies chromosomal abnormalities • Present in >80% of patients • Examples: del(13q), del(11q), trisomy 12, **del(17p)**, del(6q)
DNA Sequencing	• Identifies mutations in specific genes • Examples: IGHV, VH3-21, **TP53**
CpG-metaphase karyotype	• Profile of the chromosome found in CLL cells • Complex karyotype: ≥ 3 abnormalities

N Engl J Med 2000; 343:1910-1916 | Cancer 2015; 131:3612-3621
Leukemia 2005; 19:850-758| NCCN Clinical Practice Guidelines in Oncology for CLL/SLL. V.1.2023

Prognosis

Chromosomal Abnormality	Frequency	Median OS	Risk Category
Del(17p)	7%	2.7 years	Unfavorable
Del(11q)	18%	6.6 years	Unfavorable
Trisomy 12q	16%	9.5 years	Intermediate
Del(13q)	55%	11.1 years	Favorable

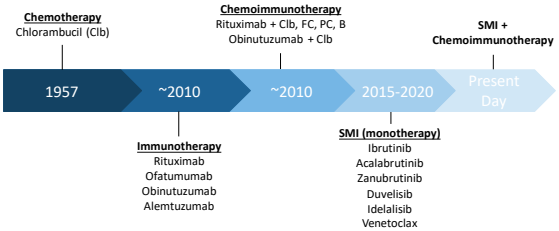
TP53
- Del(17q): loss of TP53 tumor suppressor gene is associated with mutations in TP53
- Worse outcomes

IGHV
- Unmutated IGHV: decreased survival with conventional chemoimmunotherapy

IGHV: immunoglobulin heavy chain | OS: overall survival

N Engl J Med 2000; 343:1910-1916 | Cancer 2015; 131:3612-3621
Leukemia 2005; 19:850-758| NCCN Clinical Practice Guidelines in Oncology for CLL/SLL. V.1.2023

Treatment History

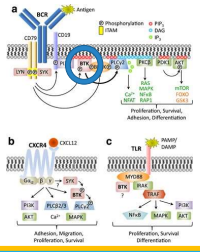


FC: fludarabine + cyclophosphamide | PC: pentostatin + cyclophosphamide
B: bendamustine | SMI: small molecule inhibitor

J Hematol Oncol 2021; 14: 69| NCCN Clinical Practice Guidelines in Oncology for CLL/SLL. V.1.2023

BTK Inhibitors

- Mechanism of Action
  - BTK plays a role in the B-cell receptor and cytokine receptor pathway
    - Involved with downstream signaling of B-cell proliferation, trafficking, chemotaxis, and cell adhesion
  - Parent drug and active metabolites form bonds with cysteine residue I active BTK site to inhibit enzyme activity
  - Results in decreased malignant B-cell proliferation and survival
- Agents: ibrutinib, acalabrutinib, zanubrutinib



Oncogene 2015; 34: 2426-2436

BTK Inhibitors: Adverse Events

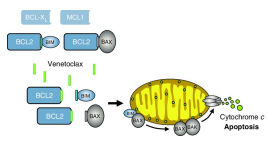
Class Toxicities (Grade 3 or 4)				
Toxicity	**Description**	**Ibrutinib**	**Acalabrutinib**	**Zanubrutinib**
Cardiac	Atrial Fibrillation, HTN	4%, 19% (8%)	≤ 3%, 5%	2%, 14% (9%)
Infection	Bacterial Viral Fungal	13-34% (24%)	65% (14%)	11-39% (23%)
Gastrointestinal	Diarrhea	36-59%	31%	20-23%
Myelosuppression	Neutropenia Thrombocytopenia	22-53% (23%) 33-69% (8%)	23% (13%) 32% (3.4%)	38% (15-27%) 27% (5-10%)
Hemorrhage	Bleeding	39% (4%)	8% (0.8%)	50% (2%)
Lymphocytosis	ALC ≥ 400,000	21-33%	16% (15%)	41% (16%)
Secondary malignancy	Non-melanoma skin cancer	6%	12%	9%

HTN: hypertension | ALC: absolute lymphocyte count

Ibrutinib (Imbruvica). Prescribing Information. Pharmacyclics LLC, December 2020
Acalabrutinib (Calquence). Prescribing Information. AstraZeneca, November 2019
Zanubrutinib (Brukinsa). Prescribing Information. BeiGene, September 2021

Venetoclax

- Mechanism of Action: BCL-2 inhibitor
  - BCL-2 is an anti-apoptotic protein that is overexpressed in CLL cells
  - Involved with tumor cell survival and chemotherapy resistance
  - Venetoclax selectively inhibits BCL-2
    - BIM (pro-apoptotic protein) is displaced
    - Mitochondrial membrane becomes permeable
    - Apoptosis
- Administered with obinutuzumab



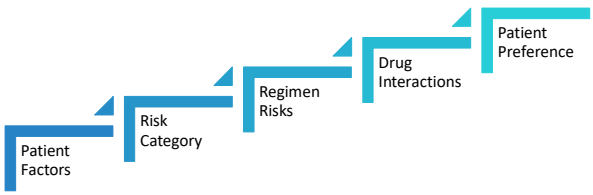
Venetoclax (Venclexta). Prescribing Information. AbbVie Inc, December 2021

Treatment Considerations

- Chemoimmunotherapy has a limited role in treating CLL
  - Useful for those with mutated IGHV
  - Reserved for younger, fit patients
- Novel agents have many advantages over traditional chemotherapy
  - Improved outcomes
  - Convenience
  - Adverse events are more tolerable

Hematology Am Soc Hematol Educ Program 2013:158-167

Therapy Selection



Blood 2009; 114: 957-964 | CA Cancer J Clin 2016; 66: 271-289
NCCN Clinical Practice Guidelines in Oncology for CLL/SLL V.1.2023

Pivotal Studies in First Line Therapy

Ibrutinib (Imbruvica®)

Study	Patient Population	Interventions	Outcomes
RESONATE-2 (n=269)	▪ Treatment naïve CLL ▪ ≥ 65 years ▪ No del(17p)	Ibrutinib vs chlorambucil	▪ mPFS: NR vs 15 mo (p<0.0001) ▪ mPFS at 8 years: NR vs 15 mo ▪ OS at 7 years: 59% favoring ibrutinib ▪ ADE: Afib, PNA, palpitations
ECOG-ACRIN (n=529)	▪ Treatment naïve CLL ▪ ≤ 70 years ▪ No del(17p)	▪ Ibrutinib + rituximab ▪ Standard chemotherapy: FCR	▪ 3-year PFS: 89.4% vs 72.9% (p<0.001) ▪ **Unmutated IGHV**: 90.7% vs 62.5% (p<0.001) ▪ Mutated IGHV : 87.7% vs 88% ▪ ADE: Afib, hypertension
iLLUMINATE (n=229)	▪ Treatment naïve CLL ▪ ≥ 65 years OR <65 years with comorbidities	▪ Ibrutinib + obinutuzumab ▪ Chlorambucil + obinutuzumab	▪ mPFS: NR vs 19 mo (p<0.0001) ▪ 30-month PFS: 79% vs 31% ▪ ADE: neutropenia, thrombocytopenia
Alliance (n=547)	▪ Treatment naïve CLL ▪ ≥ 65 years	▪ Ibrutinib monotherapy ▪ Ibrutinib + rituximab (IR) ▪ Standard chemotherapy: BR	2-year PFS ▪ Ibrutinib only: 87% vs 74% (p<0.001) ▪ IR: 88% vs. 74% (p<0.001) ▪ **Ibrutinib vs IR: no difference (p=0.49)** ▪ ADE: neutropenia/thrombocytopenia (BR) and Afib/hypertension (ibrutinib containing)

PFS: progression free survival | NR: not reached | OS: overall survival | ADE: adverse drug event | Afib: atrial fibrillation
PNA: pneumonia | FCR: fludarabine + cyclophosphamide + rituximab | BR: bendamustine + rituximab

N Engl J Med 2018; 379:2517-2528 | N Engl J Med 2019; 381:432-443
Lancet Oncol 2019; 20:43-56 | Blood 2022; 140:112-120

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RESONATE-2 (n=269)	▪ Treatment naïve CLL ▪ ≥ 65 years	Ibrutinib vs chlorambucil	▪ mPFS: NR vs 15 mo (p<0.0001) ▪ mPFS at 8 years: NR vs 15 mo ▪ ibrutinib
ECOG-ACRIN (n=529)			p<0.001) 62.5% (p<0.001)
iLLUMINATE (n=229)			1) cytopenia
Alliance (n=547)	▪ Treatment naïve CLL ▪ ≥ 65 years	▪ Ibrutinib + rituximab (IR) ▪ Standard chemotherapy: BR	(p<0.001) ▪ IR: 88% vs. 74% (p<0.001) ▪ Ibrutinib vs IR: no difference (p=0.49) ▪ ADE: neutropenia/thrombocytopenia (BR) and Afib/hypertension (ibrutinib containing)

Conclusions
- Ibrutinib is associated with a longer time to progression compared to conventional chemotherapy
- The addition of rituximab to ibrutinib does not improve PFS
- Ibrutinib reduced hematologic ADE but increases rates of non-hematologic ADE

PFS: progression free survival | NR: not reached | OS: overall survival | ADE: adverse drug event | Afib: atrial fibrillation
PNA: pneumonia | FCR: fludarabine + cyclophosphamide + rituximab | BR: bendamustine + rituximab

N Engl J Med 2018; 379:2517-2528 | N Engl J Med 2019; 381:432-443
Lancet Oncol 2019; 20:43-56 | Blood 2022; 140:112-120

Acalabrutinib (Calquence®)

Study Design	Patient Population	Interventions	Outcomes
ELEVATE-TN RCT, multicenter (n=535)	▪ Treatment naïve CLL ▪ ≥ 65 years or <65 years with comorbidities ▪ ECOG ≤2	▪ Group 1: acalabrutinib ± obin ▪ Group 2: chlorambucil + obin	▪ Median PFS: NR vs 22.6 months ▪ PFS at 24 mo: 93% vs. 87% vs. 47% ▪ Most common ADE: neutropenia, infections

Conclusions:
- Progression free survival was improved in patients with CLL when acalabrutinib was used alone or in combination with obin
- Del(17p)/TP53 mutation and unmutated IGHV: improved PFS with acalabrutinib alone and in combination with obinutuzumab
- Follow-up at 46.9 months
  - 74.9% and 69.3% in acalabrutinib + obin and acalabrutinib only continued treatment, respectively
  - 39% of patients crossed over to acalabrutinib arm

RCT: randomized controlled trial | ECOG: eastern cooperative oncology group
PFS: progression free survival | Obin: Obinutuzumab | ADE: adverse drug event

Lancet 2020; 395: 1278-1291

Zanubrutinib (Brukinsa®)

Study Design	Patient Population	Interventions	Outcomes
SEQUOIA RCT, multicenter (n=577)	▪ Treatment naïve CLL ▪ ≥ 65 years or <65 years with comorbidities ▪ ECOG ≤2	**No del(17p)** ▪ Group A: zanubrutinib ▪ Group B: bendamustine + rituximab **Del(17p)** ▪ Group C: zanubrutinib	▪ PFS at 24 mo (A vs B): 85.5% vs. 69.5% (p<0.0001) ▪ 2-year PFS: 85.5% vs. 69.5% ▪ Most common ADE: neutropenia, diarrhea, infection

Conclusions:
- Progression free survival was improved in patients with CLL treated with zanubrutinib
- No differences in PFS in patients with del(17p)/TP53 mutation
- Improved PFS in patients treated with zanubrutinib and unmutated IGHV

RCT: randomized controlled trial | ECOG: eastern cooperative oncology group
PFS: progression free survival | ADE: adverse drug event

Lancet Oncol 2022; 23: 1031-1043

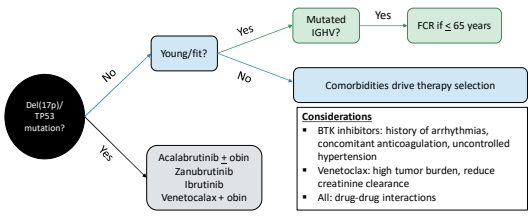
Venetoclax (Venclexta®)

Study Design	Patient Population	Interventions	Outcomes
CLL14 RCT, multicenter (n=432)	▪ Treatment naïve CLL ▪ CrCl 30 - 70 mL/min	**Fixed duration: 12 cycles** ▪ Obin + venetoclax ▪ Obin + chlorambucil	▪ PFS at 24 mo: 88.2% v 64.1% (p<0.001) ▪ 5-year TTNT: 72.1% vs 42.8% (p<0.001) ▪ MRD-: 42% vs 7% ▪ Most common ADE: neutropenia, diarrhea, infection

Conclusions:
- Progression free survival was improved in all patients with CLL treated with obinutuzumab + venetoclax
- More patients in the treatment arm were off therapy at 5 years than those receiving obintuzumab + chlorambucil
- MRD status was negative at the end of treatment in more patients treated in with obinutuzumab + Venetoclax
  - Follow-up at 4 years: 18.1% vs. 1.9%

Lancet 2020; 21: 1188-1200| N Engl J Med 2016; 374:311-322

Treatment Algorithm: First Line Therapy



Considerations
- BTK inhibitors: history of arrhythmias, concomitant anticoagulation, uncontrolled hypertension
- Venetoclax: high tumor burden, reduce creatinine clearance
- All: drug-drug interactions

IGHV: immunoglobulin heavy chain variable region
FCR: fludarabine + cyclophosphamide + rituximab | Obin: obinutuzumab

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Frontline Therapy Selection

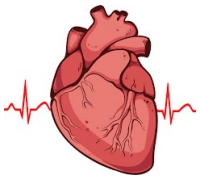
BTK Inhibitors	Venetoclax + Obinutuzumab
▪ Del(17p)/TP53 mutations ▪ No IV therapy component	▪ Therapy is finite (1-year)
▪ Off-target adverse events: atrial fibrillation, hypertension, bleeding ▪ Indefinite therapy	▪ Tumor lysis syndrome monitoring ▪ Neutropenia ▪ High-risk patients?

IV: intravenous

JCO Oncol Pract 2022; 18:109-113

Managing Cardiac Adverse Events

Atrial Fibrillation	• Rate vs rhythm Control • Stroke prevention
Hypertension	• Monitor blood pressure at each visit • Manage per guideline recommendations • Drug-drug interactions
Bleeding	• Avoid warfarin • Hold BTK inhibitor 3-7 days prior to surgery • Discontinue antiplatelet therapy



Haematologica 2017; 102:1629-1639

Treatment Schedule

Cycle 1	Cycle 2	Cycles 3-6	Cycles 7-12
Cycle 1, Day 22: 5-week ramp up phase **Venetoclax** ▪ Week 1: 20 mg ▪ Week 2: 50 mg ▪ Week 3: 100 mg ▪ Week 4: 200 mg ▪ Week 5: 400 mg		400 mg daily through cycle 12	

Obinutuzumab (Cycles 1-6 only)
- Cycle 1: 100 mg day 1, 900 mg day 2, 1000 mg days 8 and 15
- Cycles 2-6: 1000 mg day 1

Venetoclax (Venclexta). Prescribing Information. AbbVie Inc, December 2021
N Engl J Med 2016; 374:311-322

TLS Prophylaxis and Tumor Burden

	Tumor Burden		Prophylaxis		Blood Chemistry Monitoring
TLS Risk	Lymph Nodes (LN)	ALC	Hydration	Anti-hyperuricemic	Setting/Frequency
Low	All LN < 5 cm	<25x10^9	Oral: 1.5 – 2L	Allopurinol	Outpatient: ▪ Before initial and all ramp-up doses ▪ Post-dose: 6 and 24 hours after 20 mg and 50 mg doses
Medium	Any LN: 5-10 cm	≥25x10^9	Oral: 1.5 – 2L	Allopurinol	Outpatient (as above) Consider hospitalization for the following criteria: ▪ CrCl <80 mL/min at initial dose of 20 mg and 50 mg ▪ Poor oral intake, poor PS, uncontrolled diabetes, acute gout flare, heart failure
High	Any LN ≥ 10 cm Any LN ≥ 5 cm + ALC ≥25x10^9		Oral: 1.5 – 2L AND IV 150-200 mL/hr	Allopurinol (Consider rasburicase)	Inpatient (20 mg and 50 mg doses): ▪ Before each dose ▪ Post-dose: 6, 12, and 24-hr after initial doses Outpatient (subsequent doses) ▪ Before all ramp-up doses ▪ Post-dose: 24 hours after 100, 200, and 400 mg

ALC: absolute lymphocyte count | CrCl: creatinine clearance | PS: performance status

N Engl J Med 2016; 374:311-322

Limitations with BTK Monotherapy

Low rates of complete remission

- 27.6 months: 8%
- 42 months: 9%
- 60 months: 14%

Disease progression

- Treatment-naïve: 15.5%
- Progression on ibrutinib at 4 years: 19.1%

Resistance

- 85% of patients experience mutations in the BTK receptor

Blood Cancer J 2021; 11:79

Assessment Question

Which of the following statements is true?

A. Ibrutinib, acalabrutinib, and zanubrutinib have all shown benefit in patients with del(17p) mutations

B. More patients had progression free survival benefit in the ibrutinib + rituximab group compared to those receiving ibrutinib monotherapy in the Alliance Trial

C. Patients with unmutated IGHV had shorter time to disease progression when receiving ibrutinib + rituximab compared to those receiving standard chemotherapy, as shown in ECOG-ACRIN

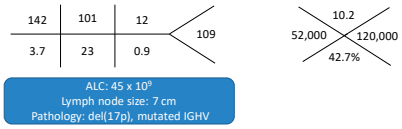
D. Acalabrutinib is a second generation BTK inhibitor and has the highest risk of cardiovascular events

Patient Case

MS is a 67 year old male with newly diagnosed CLL. He has a past medical history of hypertension, atrial fibrillation, and peptic ulcer disease. His current medications include lisinopril 20 mg daily, apixaban 5 mg twice daily, pantoprazole 20 mg daily, and vitamin D 1000 IU daily. He presents to your clinic to discuss treatment options.

The oncologist performed a physical exam and confirmed the patient has splenomegaly. Based on today's exam, what Rai classification stage does MS meet?

A. I
B. II
C. III
D. IV



ALC: 45 x 10^9
Lymph node size: 7 cm
Pathology: del(17p), mutated IGHV

Patient Case

MS is a 67 year old male with newly diagnosed CLL. He has a past medical history of hypertension, atrial fibrillation, and peptic ulcer disease. His current medications include lisinopril 20 mg daily, apixaban 5 mg twice daily, pantoprazole 20 mg daily, and vitamin D 1000 IU daily. He tells you that he is very physically active (walks ~3 miles per day). He presents to your clinic to discuss treatment options.

What treatment option(s) is MS eligible for?

A. Bendamustine + rituximab
B. BTK inhibitor
C. Obinutuzumab + venetoclax
D. Either B or C

Patient Case

MS is a 67 year old male with newly diagnosed CLL. He has a past medical history of hypertension, atrial fibrillation, and peptic ulcer disease. His current medications include lisinopril 20 mg daily, apixaban 5 mg twice daily, pantoprazole 20 mg daily, and vitamin D 1000 IU daily. He tells you that he is very physically active (walks ~3 miles per day). He presents to your clinic to discuss treatment options.

You are discussing obinutuzumab and venetoclax with MS. Which of the following counseling points is correct?

A. Venetoclax will be continued indefinitely after completing obinutuzumab
B. Obinutuzumab is administered on day 1 of each cycle for 6 cycles
C. A drug-drug interaction exists with venetoclax and pantoprazole requiring a switch to either an antacid or H2RA agent
D. MS will require inpatient admission for tumor lysis monitoring

Patient Case

MS is a 67 year old male with newly diagnosed CLL. He has a past medical history of hypertension, atrial fibrillation, and peptic ulcer disease. His current medications include lisinopril 20 mg daily, apixaban 5 mg twice daily, pantoprazole 20 mg daily, and vitamin D 1000 IU daily. He tells you that he is very physically active (walks ~3 miles per day). He presents to your clinic to discuss treatment options.

MS decides he would rather pursue treatment with a BTK inhibitor. Which BTK inhibitor would you recommend?

A. Acalabrutinib because it has been shown to have the lowest risk of cardiac events
B. Zanubrutinib because it requires the least number of tablets per day
C. Ibrutinib because it is the only agent approved in those with del(17p)

Cost Considerations

Costs in CLL Therapy

Economic Burden	Average Monthly Cost	Cost Effectiveness
• 2011: $740 million • 2025: $5 billion	• 2015: $17,422 • Excludes acalabrutinib, zanubrutinib, and venetoclax	• Ibrutinib cost estimated to need 72% reduction to be cost-effective

Pharmacoeconomics 2020; 38: 941-951

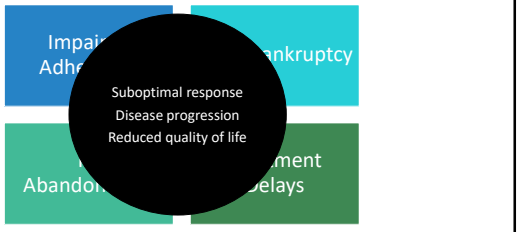
Adherence and Financial Burden

- ~65% of patients taking oral agents for CLL are adherent
- High costs
  - Poor adherence
  - Early discontinuation
- Adherence rates >80%
  - Lower health utilization rates
  - Lower medical costs
  - Higher prescription costs

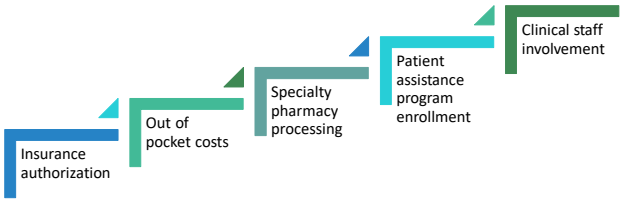
Risks of Financial Toxicity

- Impaired Adherence
- Debt/Bankruptcy
- Rx Abandonment
- Treatment Delays

Risks of Financial Toxicity



Barriers to Oral Oncology Treatments



J Oncol Pract 2017; 13:e29-e36

Impact of Combination Therapies

- Initial costs will be higher
- Strategies to offset cost over time
  - Shorter duration of therapy: currently 1 year
  - Longer duration off treatment: MRD testing
  - Improvements in progression free survival → patients living longer
- Combination therapies cannot be indefinite if cost reduction is goal

Future Directions

Gaps in Current Treatment Strategies

- Continuous vs. Fixed Duration
- Combination Therapies
- Treatment Resistance
- Role of MRD Testing
- Medication Adherence
- Financial Toxicity

Ongoing Trials: Fixed Duration

Trial	Treatment Regimen		
CLL17	Ibrutinib monotherapy	Obinutuzumab cycles 1-6 Venetoclax cycles 1-12	Ibrutinib cycles 1-15 Venetoclax cycles 4-15
MAJIC	Acalabrutinib cycles 1-12 Venetoclax cycles 3-12	Obinutuzumab cycles 1-6 Venetoclax cycles 2-12	N/A

clinicaltrials.gov

Ongoing Trials: Combination Therapy

Trial	Treatment Regimen: Newly Diagnosed CLL		
ACE-CL-311	Acalabrutinib + venetoclax	Acalabrutinib + Venetoclax + obintuzumab	FCR or BR
NCT03824483 (Phase 2)	Zanubrutinib + obinutuzumab + venetoclax		
NCT03737981 (Phase 3)	Ibrutinib + obintuzumab	Ibrutinib + obinutuzumab + venetoclax	
FLAIR (Phase 3)	Ibrutinib	Ibrutinib + venetoclax	

clinicaltrials.gov

Conclusions

- The development of targeted therapies for the treatment of CLL has shown an improvement in progression free survival for all risk groups
- Use of single-agent BTK inhibitors as indefinite monotherapy is associated with certain risks
  - Resistance
  - Adverse effects
  - Financial toxicity
- Fixed-duration therapies could minimize adverse events, improve quality of life, and reduce economic burden

Questions?

Treatment Strategies for Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

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