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Treatment Sequencing Learning Insights

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LEARNING OBJECTIVES

After this presentation, you will be able to:

1. Describe the two main types of targeted therapy for CLL
2. Understand how your health and preferences guide treatment choices
3. Know what happens if your first or later treatment stops working

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Two Cases

Susan through 3 Lines of Therapy

George through 1

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First Case: First-Line Treatment Options

CASE #1: SUSAN'S INTRODUCTION

- Susan is a 60-year-old who was diagnosed with CLL 3 years ago and has had no other health problems.
- Her biomarker testing at the time of diagnosis revealed:
  - IgVH unmutated
  - FISH testing showed a 17p deletion
  - No TP53 mutation
- Since that time, she has been on active surveillance (watch and wait) and is being followed by her local hematologist/oncologist every six months.

CASE #1: SUSAN (CONTINUED)

- While at a routine follow-up appointment, Susan shared that about 2 weeks ago, she started to develop drenching night sweats, worsening fatigue, and noted that the lymph nodes on both sides of her neck were bigger.
- When her doctor examined her, he felt enlarged lymph nodes in the neck, and he told her he could feel that her spleen was enlarged.
- Bloodwork is performed, which shows the following results:
  - Elevated Absolute Lymphocyte Count of 100 X 10^9 /L
    - (significantly higher compared to 40 X 10^9/L about 3 months ago)
  - Low Hemoglobin of 9 g/dL
  - Low Platelet count of 95 X 10^9 /L
  - Blood chemistries, LDH, and all other labs are within normal limits

CASE #1: SUSAN (CONTINUED)

- Since it is time to start treatment, her doctor orders repeat biomarker testing.
  - FISH testing is repeated and continues to show 17p deletion
  - There is still no TP53 mutation
- Her IgVH was not repeated, as it was tested upon diagnosis and found to be unmutated. IgVH does not change over time.
- Susan and her doctor discuss her treatment options now that it is time to start a first-line therapy.
- Her doctor explains that there are several different treatment options, but there are many things to consider when selecting which therapy will be the best one for Susan.
- She asks what those things are that should be taken into consideration.

CASE #1: SUSAN (CONTINUED)

- He explains the following should be taken into consideration:
  - Does she have a history of any other health problems?
    - Cardiovascular (heart)
    - Renal (kidney)
    - History of recurrent or serious infection
    - History of blood clots or bleeding disorders
  - What are the findings of her biomarker testing?
  - Is she taking any other medications?

CASE #1: SUSAN (CONTINUED)

- He also explains the following should be taken into consideration:
  - What are her treatment preferences and goals?
    - Take medication continuously versus for a limited amount of time
    - Oral medication vs. intravenous (IV)
  - Are there any financial considerations?
  - What is the proximity to the hospital or infusion clinic for close monitoring if necessary?

CASE #1: SUSAN (CONTINUED)

- She asks about chemotherapy, and if that is one of her treatment options.
- Susan's doctor explains:
  - While chemoimmunotherapy was the standard for treating CLL many years ago, newer therapies have proven to provide better outcomes.
  - There are now several other treatment options that will better control the cancer called targeted therapies and will not simultaneously damage healthy cells like chemotherapy is known to do.
  - Also, since she has a 17p deletion, research shows that chemoimmunotherapy will not effectively treat her CLL.

CASE #1: SUSAN (CONTINUED)

- Susan then asks about her first-line treatment options.
- Her doctor explains:
  - There are currently three approved first-line oral medications that are covalent BTK inhibitors:
    - Ibrutinib (first-generation and not generally recommended)
    - Acalabrutinib (second-generation)
    - Zanubrutinib (second-generation)
  - There is one approved oral BCL2 inhibitor available:
    - Venetoclax, which is usually combined with obinutuzumab (which is an anti-CD20 monoclonal antibody that is given IV (intravenously) in an outpatient infusion clinic setting) over a fixed duration.
    - The combination of venetoclax and acalabrutinib was recently approved as the first all oral time limited therapy.

CASE #1: SUSAN (CONTINUED)

- Since she has 17p deletion, her doctor says a covalent BTK inhibitor would be his first choice.
- He shares the most common side effects of BTK inhibitors are:
  - GI: Diarrhea, constipation, abdominal pain
  - Fatigue or tiredness
  - Muscle, joint, or bone pain
  - Easy bruising and bleeding
  - Infections, including pneumonia
  - Heart rhythm problems (atrial fibrillation) and hypertension
- She likes the simplicity of only one oral medication with one copay and the lack of need for close monitoring.

CASE #1: SUSAN (CONTINUED)

- After discussing her available treatment options, Susan and her doctor, through shared decision making, select zanubrutinib as the first line of therapy.

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Second-Line Treatment Options

CASE #1 SUSAN CONTINUED

- Four years after being on zanubrutinib, which she tolerated well, Susan sees her CLL specialist for her regular follow-up appointment at the age of 66.
- After having been in the normal range within 6 months of starting therapy, her routine bloodwork now shows the following:
  - Absolute Lymphocyte Count is trending upward with a value of 25 X 10^9 /L
  - Hemoglobin, platelets, and all other blood work are within normal limits
- She is having no symptoms, and the physical exam is unremarkable.
- She asks her doctor if it is time to consider switching to a different treatment regimen since her Absolute Lymphocyte Count is elevated.
- Her CLL specialist explains that:
  - A slightly elevated absolute lymphocyte count does not constitute a reason for switching treatment, but her labs will continue to be closely monitored for worsening trends over time, and she may need treatment soon.

CASE #1 SUSAN (CONTINUED)

- Three months later, Susan is seen again for her routine follow-up.
- His bloodwork now shows the following results:
  - Elevated Absolute Lymphocyte Count of 80 X 10^9 /L
  - Low Hemoglobin of 9.8 g/dL
  - Low Platelet count of 90 X 10^9 /L
- She reports feeling increasingly fatigued over the past couple of months and shares that she sometimes has difficulty performing normal day-to-day activities.
- Susan and her doctor both agree that her CLL has become refractory (resistant) to zanubrutinib, and it is time to switch to a new treatment.

CASE # 1 SUSAN (CONTINUED)

- She asks if she can try another covalent BTK inhibitors such as acalabrutinib.
- The doctor explains that when someone's CLL becomes refractory to one covalent BTK inhibitor, the other drugs in the same drug class will also likely not be effective.
- She then asks what are the other treatment options.
- Her doctor suggests that before the two of them discuss her next treatment options, he wants to first retest her biomarkers since it is time to start a new treatment.
- Her biomarker results before starting his zanubrutinib therapy six years ago were:
  - IgVH unmutated
  - FISH showed 17p deletion
  - No TP53 mutation

CASE # 1 SUSAN (CONTINUED)

- FISH and TP53 tests are repeated and now show:
  - FISH: still showed only 17p deletion
  - TP53: Mutated
- Her doctor also ran an additional test on her blood that indicates after taking zanubrutinib for four years she has developed a C481 mutation in the BTK protein that prevents binding and thus the benefits of all covalent BTK inhibitors.
- Her doctor suggests that her second-line treatment options to choose from are:
  - Pirtobrutinib, the only approved oral non-covalent BTK inhibitor that works in the presence of the C481 mutations.
  - The only approved oral BCL2 inhibitor, venetoclax, is usually taken in combination with rituximab or obinutuzumab as a fixed-duration therapy.

CASE # 1 SUSAN (CONTINUED)

- Susan asks his doctor which one he should choose.
- His doctor explains it is her personal preference. Factors to consider are:
  - Pirtobrutinib is a continuous therapy, meaning it is taken like zanubrutinib until it no longer works, or it is no longer tolerated.
  - Venetoclax is started at a lower dose and slowly increased over a period during which she would be closely monitored for tumor lysis syndrome (TLS) where the cancerous CLL cells are rapidly killed leading to potentially dangerous chemical imbalances in the blood.
  - Venetoclax is a time-limited therapy, meaning it is only taken for fixed duration to get the disease into remission, and then the drug is stopped.
  - Venetoclax is given with IV obinutuzumab, so she would need to receive the IV medication in a clinic setting and be monitored.

CASE # 1 SUSAN (CONTINUED)

- Through shared decision-making, Susan and her doctor choose to discontinue the zanubrutinib and begin venetoclax combined with obinutuzumab as her second-line of treatment. It is usually recommended that patients stay on their BTK inhibitor until they start their next therapy.
- This fixed duration therapy is usually taken for two years when used second line, then stopped.
- **NOTE:** The FDA has only approved venetoclax combined with rituximab in the relapsed/refractory setting, but most CLL experts prefer to use the more effective combination with obinutuzumab. Insurance will usually cover it.

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Third-Line Treatment Options & Beyond

CASE #1 SUSAN (CONTINUED)

- Susan got a deep response to venetoclax and obinutuzumab, which she tolerated well, but her CLL returns 2 years after the end of treatment with swollen lymph nodes, an enlarged spleen, increasing fatigue, and weight loss. She is now 71.
- Her prognostic markers are repeated and are unchanged.
- Her bloodwork shows:
  - Elevated Absolute Lymphocyte Count of 145 X 10^9
  - Low Hemoglobin of 8.9 g/dL
  - Low Platelet count of 76 X 10^9 /L

CASE #1 SUSAN (CONTINUED)

- Her doctor suggests that her third-line treatment options to choose from include:
    1. The oral noncovalent BTK inhibitor pirtobrutinib taken continuously which can work when the covalent BTK inhibitors no longer do.
    2. Retreatment with the oral BCL2 inhibitor venetoclax combined with the anti-CD20 monoclonal antibody obinutuzumab for a limited time.
    3. Enrollment in a clinical trial for the oral BTK degrader at the university hospital 40 miles away.
    4. Liso-cel (lisocabtagene maraleucel) , a CAR-T, an intense often inpatient cellular immune therapy that can lead to deep durable remissions.
    5. Allogeneic (from a related or unrelated donor) stem cell transplant, a high risk but potentially a curative option, usually consider a last resort.

CASE #1 SUSAN (CONTINUED)

- Susan and her doctor decide to retreat with venetoclax and obinutuzumab as she tolerated it well and enjoyed a total of 4 years of remission including the time on and off therapy.
  - Liso-cel and a transplant are more complicated and potentially toxic options, and they would not work as well with her high disease burden.
  - Pirtobrutinib is a good option, but she wants to go with a therapy she had success with and keep pirtobrutinib as a future option.
  - Clinical trials are always a good choice and the BTK degraders are promising, but she doesn’t want to travel and prefers what she knows.

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Second Case: First-Line Treatment Options

CASE #2 GEORGE INTRODUCTION

- George was diagnosed with SLL at 69 years old when a persistent swollen lymph node in his groin was biopsied.
- All his labs including his Absolute Lymphocyte Count were normal.
- George's nodes continued to grow in his neck, armpits and groin.
- He became increasingly tired and short of breath climbing stairs at home.
- Despite worsening labs and increasing symptoms, he has refused treatment.

CASE #2 GEORGE (CONTINUED)

- After three years, his fatigue is overwhelming and he finally agrees to treatment.
- His exam reveals mild pallor and multiple enlarged lymph nodes.
- His blood work show:
  - Elevated Absolute Lymphocyte Count of 30 X 10^9
  - Low Hemoglobin of 8 g/dL
  - Low Platelet count of 70 X 10^9 /L
  - Blood chemistry and tests for other causes of his anemia beside CLL are negative
- Biomarker testing revealed:
  - IgVH unmutated
  - FISH testing showed a 11q deletion
  - No TP53 mutation

CASE #2 GEORGE (CONTINUED)

- His doctor explains his options:
  - There are currently three oral medications that are covalent BTK inhibitors:
    - Ibrutinib (first-generation and not generally recommended)
    - Acalabrutinib (second-generation)
    - Zanubrutinib (second-generation)
  - There is one approved oral BCL2 inhibitor available:
    - Venetoclax, which is usually given in combination with obinutuzumab (an anti-CD20 monoclonal antibody that is given IV in an outpatient infusion clinic setting) over a fixed duration.
    - The combination of venetoclax and acalabrutinib was recently approved as the first all oral time limited therapy.

CASE #2 GEORGE (CONTINUED)

- George wants something that is easy and quick and will work on his higher risk disease.
- He does not like the idea of taking medicine long term and wants to avoid IVs.
- He and his doctor choose the all-oral time limited therapy (14 cycles, each 28 days long) of acalabrutinib and venetoclax.
- The risk of Tumor Lysis Syndrome (TLS) due to high disease burden should be reduced by the lead in with the first 2 cycles being acalabrutinib alone.

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Review and Summary of What We've Learned

TEST BEFORE TREAT

- Testing at time of diagnosis is not mandatory.
- Testing before each and every line of therapy is!
- Tests must include at a minimum:
  - IgVH mutation status (this is the only test that does not need to be repeated for each treatment because it does not change over time
  - FISH
  - TP53 mutation

TREATMENT CHOICES

- Today's CLL treatments are targeted therapies — drugs that attack specific proteins cancer cells need to survive.

  There are two main approaches:

  Option A: Time-Limited (Fixed-Duration) — Treatment for a set period (1–2 years), then stop.

  Option B: Continuous — A daily pill taken indefinitely.

  Neither has been proven better for overall survival. The choice depends on your individual situation.

There is no role today for chemoimmunotherapy in treating CLL.

OPTION A — TIME-LIMITED TREATMENT

Treatment for a set period (1–2 years), then stop

Regimens:

- Venetoclax (pill) + obinutuzumab (IV infusion) — blocks BCL-2 protein + targets CD20 on cancer cells
- Venetoclax + a BTK inhibitor (e.g., acalabrutinib) — two targeted pills for a defined period

What to know:

- Requires close monitoring for tumor lysis syndrome (TLS) in the first few weeks
- Low blood counts (neutropenia or low neutrophils) occur in about 50% of patients
- After completing treatment there is a monitoring phase with no medication

OPTION B: CONTINUOUS THERAPY

A daily pill taken every day, ongoing

Regimens:

- BTK inhibitors: acalabrutinib or zanubrutinib or pirtobrutinib (**NOTE:** pirtobrutinib is only approved for second line or later use). Ibrutinib is rarely used now due to having more side effects.

What to know:

- Easier to start — no TLS risk, no IV infusions
- Requires taking medication every day, long-term
- Possible side effects over time:
  - Increased bruising or bleeding
  - High blood pressure
  - Heart rhythm changes (atrial fibrillation)
  - Musculoskeletal pains
  - GI issues

SIDE BY SIDE COMPARISON

Time-Limited

- 1–2 years, then stop
- Venetoclax + obinutuzumab; Venetoclax + BTK inhibitor
- Blocks BCL-2 ± targets CD20
- Treatment-free interval
- TLS monitoring at start; low blood counts

Continuous

- Daily, ongoing
- Acalabrutinib; Zanubrutinib
- Blocks BTK
- Irregular Heart rhythm, bleeding, Increased blood pressure over time

KNOW YOUR HEART

BTK inhibitors can affect the heart.

If you have any of the following, your doctor may lean toward venetoclax-based therapy:

- History of atrial fibrillation (irregular heartbeat)
- Heart failure
- Need for blood thinners
- Uncontrolled hypertension

KNOW YOUR KIDNEYS

Venetoclax carries a risk of tumor lysis syndrome (TLS).

TLS risk is higher if you have:

- Kidney problems
- Bulky (large) lymph nodes or very high lymphocyte counts

If your kidneys are not working well, your doctor may:

- Choose a BTK inhibitor instead
- Use venetoclax with extra precautions and closer monitoring

With the slow ramp-up and appropriate precautions, TLS is rarely a serious problem today.

KNOW YOUR MEDICATIONS AND YOUR BIOMARKERS

Drug interactions:

- Blood thinners + BTK inhibitors → increased bleeding risk
- Some medications change how venetoclax is processed in your body
- PPIs decrease the absorption of acalabrutinib capsules but not tablets

Genetic risk profile:

- If your CLL has del(17p) or TP53 mutation → continuous BTK inhibitor therapy
- Venetoclax + obinutuzumab alone may not provide as durable a remission in this higher-risk group

KNOW YOUR LIFESTYLE PREFERENCE

Do you prefer a defined treatment period with a break afterward?

Time-limited therapy may be right for you

Are you comfortable taking a daily pill long-term if it means a simpler start?

Continuous therapy may be a good fit for you

How important is avoiding IV infusions or frequent clinic visits?

There is no single "best" treatment. Your values are central to the decision.

WHAT IF TREATMENT STOPS WORKING? AN OVERVIEW

CLL is a chronic disease. Many patients will need more than one treatment over their lifetime.

The good news: Multiple effective options exist at every stage.

Your next treatment depends on:

- What you received before
- How long it worked
- Your current health
- Your preferences

OPTIONS AFTER A TIME LIMITED VENETOCLAX BASED THERAPY

If your CLL comes back after completing time-limited treatment:

1. **Retreatment** with the same type of therapy (e.g., venetoclax-based) may be effective, especially if the remission lasted a long time

2. **Switching** to the other drug class (e.g., a BTK inhibitor) is also an option

AFTER A CONTINUOUS BTK INHIBITOR

If your CLL progresses while on a BTK inhibitor:

1. Switching to **venetoclax-based therapy** is a common next step
2. **Pirtobrutinib** is a newer "non-covalent" BTK inhibitor that works differently and can help when CLL has become resistant to standard BTK inhibitors. It is usually very well tolerated

If you cannot tolerate your BTK inhibitor due to side effects:

1. Switching to a different BTK inhibitor (e.g., from ibrutinib to acalabrutinib or zanubrutinib) often resolves the problem
2. Switching to a completely different drug class is another option

AFTER PROGRESSING ON BOTH: DOUBLE REFRACTORY

For patients whose CLL has progressed through both drug classes:

1. **Clinical trials** are strongly encouraged
2. **CAR T-cell therapy** (liso-cel or lisocabtagene maraleucel) is FDA-approved. Your own immune cells are modified to attack the cancer
3. **Pirtobrutinib** if not previously used
4. **Allogeneic (from a related or unrelated donor) stem cell transplant** may be considered for eligible patients. This is sometimes called a bone marrow transplant.

QUESTIONS TO ASK ABOUT YOUR TREATMENT SEQUENCING

Bring these to your next appointment:

- What genetic features does my CLL have, and how do they affect my options?
- Is time-limited or continuous treatment better for my situation?
- What side effects should I watch for, and when should I call?
- If my treatment stops working, what are my next options?
- Are there clinical trials I should consider?
- Should I see a cardiologist before starting treatment?

KEY TAKEAWAYS

- Two very effective first-line approaches: neither is proven better for survival
- Your heart health, kidney function, medications, genetics, and preferences ALL matter
- Treatment choice is a shared decision. Your values count.
- If treatment stops working, multiple next options exist
- Clinical trials are an important option at every stage
- You are an active partner in your care

THANK YOU FOR LEARNING ABOUT YOUR CLL TREATMENT OPTIONS

Your health. Your values. Your voice. Talk to your care team about what is right for you.

Because everyone is different and one size doesn't fit all…..

At CLL Society, we say:

If you know one CLL patient, you know one CLL patient

and

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