Chronic lymphocytic leukaemia (CLL) Patient Journey

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WHAT IS CLL?

CLL is a blood and bone marrow cancer that begins in the white blood cells called **B-lymphocytes**. It's the most common form of leukaemia in adults, typically affecting people over the age of 60.

Unlike acute leukaemias that progress rapidly, CLL develops very slowly. Many patients live for years without needing treatment and the majority will have a normal lifespan.

B lymphocytes (B cells) are the specialised intelligence and defence unit of your immune system. While other cells act like soldiers fighting hand-to-hand, B cells act like engineers who design and launch targeted smart missiles. These missiles are called antibodies.

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SYMPTOMS

Most with CLL have no symptoms at first. The condition is often discovered incidentally during routine blood work that reveals a high white blood cell count.

If symptoms do occur, they typically develop slowly as the disease progresses and many patients have no symptoms throughout their disease course.

COMMON SYMPTOMS

- **Swollen lymph nodes:** Usually painless lumps in the neck, armpits, or groin.
- **Fatigue and weakness:** Persistent tiredness that may not improve with rest.
- **Abdominal discomfort:** A feeling of fullness or pain below the ribs on the left side, often caused by an enlarged spleen.
- **Frequent infections:** Such as recurring colds, flu, or skin infections, due to a weakened immune system.
- **Easy bruising or bleeding:** Including nosebleeds or bleeding gums, caused by low platelet counts.
- **Shortness of breath:** Often a result of anaemia (low red blood cell count).
- **Fever:** Persistent high temperature without a clear infection.
- **Night sweats:** Severe, drenching sweats that may require changing clothes or bedding.
- **Unintentional weight loss:** Losing more than 10% of body weight over six months without trying.

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DIAGNOSIS AND INVESTIGATION

Diagnosing CLL is unique because it can often be confirmed through blood tests alone, without more invasive procedures like bone marrow biopsies.

INITIAL DIAGNOSTIC TESTS

Complete Blood Count (CBC) with Differential: This measures the number of red cells, white cells, and platelets. A hallmark is a high count of B-lymphocytes.

Peripheral Blood Smear: A pathologist examines a drop of blood under a microscope to look for abnormal cells. In CLL, these appear as smudge cells which are fragile leukaemia cells that burst during the slide preparation.

Flow Cytometry: This is the ***definitive test*** for confirming CLL. It identifies specific proteins (markers) on the surface of white blood cells to prove they are cancerous B-cells.

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PROGNOSTIC & GENETIC TESTS

Once diagnosed, these tests determine how quickly the disease might progress and which treatments will work best:

Fluorescence In Situ Hybridization (FISH): Checks for chromosomal abnormalities like deletions (17p or 13q) that influence the outlook.

IGHV Mutation Analysis: Determines if the immunoglobulin gene is mutated. A mutated IGHV generally indicates a slower-growing form of the disease while an unmutated type is more aggressive and doesn't respond to chemotherapy but responds to targeted treatments.

TP53 Mutation Testing: Identifies mutations that may make the cancer resistant to standard chemotherapy.

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TESTS FOR STAGING

Physical Exam: A doctor feels for enlarged lymph nodes, liver, or spleen.

Imaging (CT or ultrasound): Not always required, but checks for internal enlarged organs or nodes if symptoms are severe.

Bone Marrow Biopsy: While not strictly necessary for diagnosis, it may be done to see how much of the marrow is involved before starting treatment.

Once a diagnosis is made, you'll be assessed by a clinical haematologist or medical oncologist.

- **1/3 require treatment at diagnosis:** You already have symptoms or blood counts that meet the criteria for active disease.
- **1/3 will eventually require treatment:** You don't have symptoms, so you start in *Watch and Wait* but become symptomatic or show disease progression, such as rapidly rising white cell counts or falling haemoglobin later in life.
- **1/3 will never require treatment:** You have a very slow-growing form of disease and may live a normal lifespan, eventually passing away from causes unrelated to CLL.

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WATCH AND WAIT

Watch and wait is an active process, not a passive one. You'll typically have:

- **Regular check-ups:** These usually occur every three to six months initially, though they may become less frequent if the disease remains stable.
- **Blood tests:** Monitoring trends in your CBC, specifically looking at white blood cell counts, platelets, and haemoglobin.
- **Physical exams:** Doctors check for swelling in your lymph nodes (neck, armpits, groin) and spleen.

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TREATMENT

Treating CLL isn't based on the diagnosis alone, but on the presence of active disease.

Treatment is triggered by symptoms, such as:

- **B-symptoms:** Unintentional weight loss (>10% in six months), drenching night sweats, or persistent fevers.
- **Marrow failure:** Worsening anaemia (fatigue/shortness of breath) or low platelets (easy bruising/bleeding).
- **Physical changes:** Massive or painful enlargement of the spleen or lymph nodes.
- **Autoimmune issues:** Anaemia or low platelets caused by the immune system (AIHA/ITP) that don't respond to standard steroid treatment.
- **Extranodal involvement:** CLL cells affecting other organs like the skin, kidneys, or lungs.
- **Lymphocyte doubling time (LDT):** An absolute lymphocyte count that increases by more than 50% in two months or doubles in less than six months.

CHEMOTHERAPY VS TARGETED THERAPIES

Modern treatment has shifted away from traditional chemotherapy toward targeted therapies that specifically attack cancer cells with fewer side effects.

While chemotherapy attacks all rapidly dividing cells, targeted therapies target specific proteins or pathways that allow CLL cells to survive and have fewer side effects.

- **Chemotherapy:** Non-specifically kills fast-growing cells (cancer, hair, gut, blood).
- **Targeted treatments:** Targets specific mutations or proteins (BTK, BCL-2) to stop cancer growth while sparing more healthy cells.

ADMINISTRATION & DURATION

- **Chemotherapy:** Usually delivered via IV infusions in fixed cycles (six months).
- **Targeted treatments:** Taken as a daily pill (maintenance) or fixed-duration oral/IV combinations.

EFFICACY

- **Chemotherapy:** Less effective for high-risk patients (those with TP53, del(17p) mutations or unmutated IGHV CLL). Used mainly in young, fit patients with mutated CLL.
- **Targeted treatments:** Shown to be superior in nearly all clinical trials, offering longer remission and better survival even in high-risk groups.

SIDE EFFECTS

- **Chemotherapy:** Severe cytopenias, hair loss, nausea, vomiting, infections, risk of myelodysplasia.
- **Targeted therapies:** Irregular heartbeat, hypertension, bleeding.

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TARGETED THERAPIES

- Treatment is typically divided into ***fixed-duration therapy*** (taken for a set period, like one year) and ***continuous therapy*** (taken indefinitely). The choice is a major decision point. Neither is objectively better for every patient; instead, they offer different lifestyle and clinical benefits.

FIXED-DURATION THERAPY

Examples: venetoclax + obinutuzumab (1 year) or venetoclax + ibrutinib (15 months).

PROS

- **Treatment-free interval:** Allows you to finish therapy and live life without daily CLL medication.
- **Lower resistance risk:** Finite exposure reduces the chance of cancer cells developing mutations to the drug.
- **Deep remission:** Higher rates of Undetectable Measurable Residual Disease (uMRD).

CONS

- **Intensive start:** Requires a logistically complex five-week ramp-up and IV infusions (obinutuzumab).
- **Relapse risk:** Disease may eventually return once treatment stops, requiring future monitoring. High-risk limits: may be less effective for those with 17p deletion or TP53 mutations compared to continuous drugs.
- **Renal issues:** Not suitable for patients with significantly impaired kidney function due to tumour lysis syndrome (TLS) risk.

CONTINUOUS THERAPY

Examples: zanubrutinib, acalabrutinib or ibrutinib.

PROS

- **Simplicity:** Typically involves taking 1–2 pills daily without complex IV schedules or frequent hospital visits.
- **Proven for high-risk:** Often the preferred choice for patients with aggressive genetic markers like del(17p), TP 53, and unmutated IGHV. .
- **Immediate control:** Quickly brings high white blood cell counts down with fewer early-treatment risks like TLS.

CONS

- **Chronic side effects:** Long-term use can lead to hypertension, bleeding, or atrial fibrillation.
- **Drug resistance:** Continuous exposure can pressure cancer cells to mutate, making the drug stop working overtime.

Did you know?

Early treatment of asymptomatic CLL hasn't been shown to improve survival.

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SUPPORTIVE THERAPIES AND SCREENING

Patients with CLL have a significantly higher risk of developing secondary cancers, particularly skin, lung, and prostate, due to long-term immune system dysfunction. Standard cancer screening should be followed, but with critical modifications to account for this increased risk.

SUPPORTIVE THERAPIES

Because the cancerous B-cells don't function correctly, the immune system is weakened, making patients more susceptible to infections. To minimise infections, the following are recommended:

- Vaccines: flu, pneumonia, and shingles.
- For severe recurrent infections, immunoglobulin infusions are considered.
- Rarely prophylactic antibiotics and antivirals are considered.

References

- *Blood Cancer United (formerly Leukemia & Lymphoma Society) booklet on CLL*
- *Mayo Clinic guide on CLL for patients*
- *CLL Society guide for patients*
- *Cleveland Clinic CLL guide for patients*

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