



CLL Society's Global Virtual Patient & Caregiver Educational Forum Commonly Asked Audience Questions

General CLL Questions and Definitions

How many people are currently diagnosed with CLL?

Surprisingly, the prevalence of CLL in the US is not really known but is probably somewhere around 160,000 and 200,000. About 22,000 new cases are diagnosed every year, and since we are living longer and fewer of us are dying, the total number of us is slowly growing.

About what percent of CLL patients never need treatment?

Somewhere between 15% to 30% of CLL patients never need treatment.

What is the average age of people when they are diagnosed with CLL?

72 years old.

Is there an ethnic proclivity for CLL?

CLL is more common in Eastern European Jewish men.

Is CLL a hereditary disease?

A small percent of CLL does run in families. About 5% of CLL patients will have a relative with some kind of leukemia. A person is at 8.5 times higher relative risk of getting CLL if they have a sibling or parent with CLL, but the absolute risk is still very low. Most people with CLL are the only one in their family who has this disease. MBL (monoclonal B cell lymphocytosis), a non-cancerous precursor to CLL, is also more common in the relatives of those CLL.

Would anyone recommend that our children get tested for risk of CLL?

No. Young children almost never get CLL, and adult children don't need to be tested unless they have an elevated lymphocyte count or symptoms.

What is MBL?

MBL stands for monoclonal B-cell lymphocytosis, a possible precursor to CLL. Find out more at: <https://cllsociety.org/2019/10/e-r-i-c-barcelona-2018-professor-john-seymour-on-mbl-or-monoclonal-b-cell-lymphocytosis-a-cll-chronic-lymphocytic-leukemia/>.



If you are diagnosed with MBL, does that mean your progression to CLL will take longer?

Most MBL patients don't develop CLL. About 1-2% of MBL patients progress to CLL yearly.

Is CLL staged like other cancers, such as Stage 1, 2, 3, and 4?

No, the Ann Arbor staging system is not used for CLL. Rai staging is most commonly used in the US. To read more about Rai staging, visit our website here:

<https://cillsociety.org/2016/03/rai-staging-cll-chronic-lymphocytic-leukemia/>

CLL patients are at a higher risk for secondary cancers. What are the most common secondary cancers?

About half of CLL patients will get skin cancer

How often should a CLL patient get a complete body screening by a dermatologist to catch any skin cancers as early as possible? Is there a particular type of skin cancer that occurs in conjunction with CLL?

Skin checks should be scheduled every six months or yearly. Discuss the interval with your doctor. From research published in *Blood*: The most frequent skin cancer was squamous cell carcinoma (59%), followed by basal cell (31%), melanoma (5%), and Merkel cell (1%).

What is the difference between chemotherapy and chemoimmunotherapy?

Chemotherapy involves drugs that kill all fast-growing cells, generally by damaging the DNA. Chemoimmunotherapy adds to chemotherapy an immune therapy that harnesses the body's immune system to attack the cancer.

What does "complex karyotype" mean, and how is this best treated?

"Complex karyotype" means 3 or more genetic mutations. Targeted therapies are probably the best treatment choice.

What is the difference between mutated immunoglobulin heavy chain variable region genes (IGHV) vs. unmutated IGHV?

IGHV mutation is a measure of the maturity the particular B cell clone that is the source of our CLL. Mutated cells are more mature and less aggressive and less resistant to chemo-immunotherapy. This is particularly important in predicting response to one of the most common chemoimmunotherapies, FCR (fludarabine, cyclophosphamide and rituximab) that may be curative for some patients with chronic lymphocytic leukemia.



CLL with mutated IGHV is thought to be a cancer of a more “mature,” “better educated” form of the B lymphocyte because it has been “mutated” to recognize a threat, and therefore is better behaved and slower growing than the less mature B cells with “unmutated” IGHV.

Please explain covalent versus noncovalent.

Covalent bonding is when two atoms share an electron pair. It is irreversible. Noncovalent bonds are weaker and reversible.

What constitutes a CLL expert physician?

While there is no strict definition of a CLL expert, the CLL Society generally considers an "expert" to be someone who spends the majority of their professional time working on CLL research and/or with CLL patients, rather than in the broader fields of hematology or oncology. Find out more here: <https://cllsociety.org/toolbox/cll-doctors/>.

Is green tea extract or EGCG beneficial and where can I obtain it?

EGCG is a component of green tea extract that is marketed as a dietary supplement in the U.S. Limited data show that one version of the compound killed CLL B-cells and appeared to diminish the level of disease in lab testing and a clinical trial.

The FDA does not evaluate over-the-counter EGCG supplements. Side effects can include liver failure, so patients considering taking EGCG should talk to their physician first and be monitored for liver disease. If you are currently taking a BTK inhibitor, you should not take EGCG because it can impede how this drug is absorbed in the body.

What can be done for extreme fatigue with CLL?

There are several non-pharmacologic and pharmacologic options for fatigue that we discuss in this article on the website: <https://cllsociety.org/2018/09/cll-related-fatigue/>

Are there research efforts to restore the immune system?

Yes, but it remains one of the biggest unmet needs in CLL. The CLL Society is trying to raise the funds and find the resources to move this research forward.

I've heard that people with CLL should not take vitamins as that might stimulate the immune system and possibly also stimulate the CLL. Is that true?

In most cases, there is no reason to take extra vitamins if you eat a balanced diet.

What supplements do you recommend, if any, to support immune function if a patient is already taking a medication such as ibrutinib? Is Vitamin D recommended?



Many people are low in vitamin D, so I recommend having your blood tested and taking enough vitamin D₃ so your level is well above the lower limit of normal. I don't recommend other supplements.

Do monoclonal antibodies also affect non-CLL cells?

Yes, monoclonal antibodies will latch on to and destroy any cell with the surface marker that is their target. For example, rituximab and other anti-CD20 monoclonal antibodies will also target normal B cells that have CD20 on their surface.

Is peripheral neuropathy a symptom of deterioration?

Peripheral neuropathy is uncommon in CLL and needs to be worked up.

My blood test results show my lymphocytes as a percentage. How does that relate to the 5000 number?

Always look for the absolute lymphocyte count (ALC) and ignore the percentages. Both are nearly always reported as part of a complete blood count. That said, if your white blood cell count (WBC) is 10,000 and you have 30% lymphocytes, then your absolute lymphocyte count is a very normal 3,000. Please see our normal lab values webpage here: <https://cllsociety.org/toolbox/normal-lab-values/>

Testing

What are the three most important tests?

The answer depends on why and when you are doing the testing. FISH analysis, IGHV mutation analysis, and TP53 mutation analysis are the most important predictive and prognostic tests needed before starting treatment. Please see our Test Before Treat™ one-pager here: <https://cllsociety.org/wp-content/uploads/2019/08/Test-Before-Treat-One-pager-V3.pdf>

Do you need to repeat prognostic testing? If so, at what point? When does test before treat apply?

IGHV doesn't change so doesn't need to be repeated. FISH and TP53 results can change and need to be repeated before each and every line of therapy.

Do FISH test results change?

Yes, FISH and TP53 results can change and need to be checked and rechecked before the first and any subsequent treatments. IGVH mutation status is considered stable over



time. Find out more here: <https://cllsociety.org/cll-101/what-doctors-say-about-test-before-treat/>

Is next generation sequencing available now and does that procedure have another name?

There are many sometimes confusing names for next generation sequencing, including NGS, gene testing, genetic testing and genetic blood cancer panels. The CLL Society is working with other cancer patient charities to promote harmonizing the terms used.

Can you comment on the risk/benefit of multiple CT scans, say six or so per year, to monitor lymph node size? Asking particularly as part of clinical trial criteria.

6 CTs a year are rarely clinically indicated. Radiation exposure increases cancer risk, but CTs can catch other cancers and medical problems early.

What does testing positive for PAX5 in CLL mean?

Paired box protein (PAX5) is a protein encoded by the PAX5 gene. PAX5 activates B-cell commitment genes and suppresses non-B lineage genes. PAX5 mutated CLL cases usually belong to the IGHV-mutated subgroup. PAX5 results can be helpful in distinguishing between various lymphoid malignancies such as classical Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL),

Treatment

Dr. Jacobs outlined reasons to begin treatment. What level of immune thrombocytopenic purpura (ITP) or low platelets warrants treatment?

ITP demands treatment of the ITP. If the ITP cannot to be controlled with specific ITP directed therapies, then sometimes treating the underlying CLL is tried.

Low platelets from CLL (not ITP) are a well-recognized indication to treat CLL. A platelet count of less than 100,000 is abnormally low and an indicator for treatment in most guidelines, but if it is stable and not in a free fall, then it is reasonable to discuss with your doctor the possibility of waiting and following the trend.

How low do hemoglobin levels drop before treatment is needed?

The National Comprehensive Cancer Network (NCCN) guidelines say treatment is needed if a patient's hemoglobin level is less than 10, but the decision to treat can depend on the rate of fall and other co-morbidities.



If in watch and wait status, what are keys numbers in blood tests that could point to increasing complications and whether to start treatments?

Falling hemoglobin and/or platelets are the most common reasons to start treatment.

When should a patient start looking into 2nd line therapy? Should I try to have everything lined up in advance?

You should always be looking at what your next step might be with your medical team, even if you are doing extremely well. You never know when you might relapse.

If I relapse or don't tolerate my current therapy, does this affect my choice for the next therapy down the line? In other words, does the order of therapies potentially matter?

The proper sequencing of therapies is an active area of research. It does matter if you stopped therapy due to intolerance or resistance. For example, if you are intolerant to ibrutinib and need to stop taking it, you may be able to take acalabrutinib. On the other hand, if you become resistant to ibrutinib due to a C481S mutation, you would also be resistant to acalabrutinib. In this case you might want to consider venetoclax as a single agent or combines with a monoclonal antibody.

If you have high-risk genetic markers such as 17p or TP53, does that indicate a need for early treatment?

Statistically, such markers predict early time to treatment for a group, but statistics don't apply to individuals, just groups, so there are many exceptions.

Is it safe to say that 2nd, 3rd, and 4th line therapies are patient specific, that there may never be an exact specific protocol to follow for relapsed patients?

That seems to be the case now. Maybe more research will give us perfect protocols, but I wouldn't hold my breath.

What is the treatment for auto-immune hemolytic anemia (AIHA)?

There are multiple treatments for AIHA, including steroids, rituximab, and IVIG to name a few.

What is the significance of umbilical cord bone marrow transplantation (BMT)?

Umbilical cord blood can be used when a traditional bone marrow match can't be found, though now there are other options.

Are there any new anticipated therapies?



Thankfully, many new therapies are in development. At the time of this writing, 283 studies related to CLL are recruiting or not yet recruiting patients according to ClinicalTrials.gov

What are some of the factors that help one decide between venetoclax, ibrutinib, and acalabrutinib? For example, do any genetic markers do better with one of these treatments?

That is a complicated question that is best answered in a thorough discussion with your doctors.

Any insight on whether acalabrutinib will be efficacious in patients who progressed on venetoclax and ibrutinib?

Odds are good that acalabrutinib will work post venetoclax, but not post ibrutinib alone or in combination, as both ibrutinib and acalabrutinib work the same way and bind at the same site on BTK.

What have been the reported "positives" and "negatives" of venetoclax from patients?

Positives: Venetoclax is a potent therapy with a good safety margin that can be taken for a limited duration usually when used with other drugs, producing very deep remissions.

Negatives: Venetoclax has potentially serious side effects, including tumor lysis syndrome and low blood counts, although those can usually be handled or prevented.

What is the duration of acalabrutinib treatment?

Acalabrutinib, like ibrutinib, is usually taken indefinitely until progression or intolerance.

If acalabrutinib has a better side-effect profile than ibrutinib, what are the reasons doctors would choose ibrutinib instead?

We have more data about ibrutinib because it has been used longer. Also, acalabrutinib should not be taken with certain other medications, such as Prilosec, because it needs some gastric acid in order to be absorbed. That drug interaction is not a problem with ibrutinib.

If patient stops responding to venetoclax and then acalabrutinib, what is the next treatment?

There are good treatment options, including clinical trials, to discuss with your doctors. For example, CAR-T, noncovalent BTK inhibitors that target C481S mutations, delta-



specific or pan-specific PI3K inhibitors, as well as SYK, MCL-1, and CDK9 inhibitors are some possibilities.

What can I do if I can't afford expensive oral treatment? Is this a part of the job of a patient navigator? What resources are out there?

The CLL Society website lists a variety of financial resources. Often the drug manufacturer can help. The Leukemia and Lymphoma Society (LLS) help line may be able to offer assistance. Please find resources here: <https://cllsociety.org/living-well-with-cll/financial-assistance/>

I have traditional Medicare. Is there something specific I should look for when researching for Part D coverage in 2021?

There are online tools that let you calculate your out of pocket expenses based on the meds you anticipate you will be taking. An insurance broker can run the numbers for you, too.

Can ibrutinib lead to a complete remission of CLL?

Yes, it can, but this is infrequent.

Measurable or minimal residual disease (MRD)

What is the difference between MRD positive and MRD negative?

MRD positive means that some level of minimal residual disease can be detected. MRD negative, or the newer preferred term, undetectable minimal residual disease (uMRD), means CLL is undetectable at the level of the test.

When measuring MRD, please discuss the correlation between samples obtained from bone marrow biopsies and peripheral blood draws.

The correlation between the MRD result obtained from a patient's bone marrow biopsy and the MRD result obtained from peripheral blood are close, but not 100% and vary depending on timing and the methods used.

Why is Dr. Mato a big fan of using blood versus bone marrow to test for MRD?

MRD testing using a blood sample is easier on the patient and less expensive, and it gives very similar information to that obtained from a bone marrow biopsy.

Is reaching uMRD possible for SLL patients?

Yes.



What are the percentages of patients that get a secondary cancer after being MRD negative or undetectable?

I am unaware of any research that addresses this. The ability to reach uMRD is a relatively new phenomenon.

After starting active treatment, when and how often should MRD be measured to determine the efficacy of the treatment?

MRD testing should only be considered when conventional testing suggests there is no disease. How often it's done after that is not established.

Do you think there will ever come a time when high risk patients, unmutated IGHV, TP53, 17p deletion, NOTCH 1, ZAP 70, will ever be considered uMRD?

If you mean, can CLL patients with high-risk prognostics reach uMRD, then the answer is a resounding yes!

CAR-T Therapy

What are the differences between CAR-T cells produced by different manufacturers?

There are many differences in the process and the end products.

Can you be older, such as over 70 years old, and receive CAR-T therapy? Is there an approximate age limit to this treatment?

Doctors are likely to be more concerned about your level of fitness than your chronologic age.

Is CAR-T cell therapy effective for patients who are 17p deleted or have unmutated IGHV?

Yes, it is.

What is the approximate cost of CAR-T therapy? Does insurance cover it for CLL?

CAR-T is a very expensive treatment. The cost for CLL is not yet determined as it is not approved, but the cost will likely be \$375,000 or more based on what it costs for other cancers. Private insurance offers excellent coverage for most approved indications and also for CAR-T in clinical trials. The CLL Society is proud to have been part of a working group that changed how Medicare and Medicaid pay for CAR-T so that coverage is



available for a huge segment of the population who may need it most. More information is available here: <https://cllsociety.org/2020/05/proposed-changes-to-reimbursement-to-help-pay-for-car-t-therapy-for-patients-covered-by-medicare-or-medicaid/>

Is CAR-T therapy a viable option when you have Richter's transformation?

CAR-T therapy is being looked at in clinical trials to treat Richter's transformation.

Richter's Transformation

How common is Richter's transformation (RT) in CLL patients? What are the common risk factors for getting Richter's?

RT is rare, but some believe it may be becoming more common as we live longer and are not dying of our CLL. The risk may be around 1-2% annually. It is estimated that between 10-15% of CLL patients may develop RT. Prior chemotherapy, unmutated IGHV, missing or mutant TP53, and NOTCH1 may increase the risk.

Does being uMRD reduce the risk of Richter's?

It makes sense that being uMRD would reduce the risk of Richter's. I think there are no data yet.

Can Richter's transformation recur even after a patient's diffuse large B-cell lymphoma (DLBCL) went into remission for some time? How likely is that?

Sadly, DLBCL can and does relapse.

How much higher is the risk of Richter's if a patient has NOTCH1?

Some retrospective studies have found that CLL patients with a NOTCH1 mutation are more likely than CLL patients without a NOTCH1 mutation to develop diffuse large B-cell lymphoma. However, prospective clinical trials are needed to investigate this.

Clinical Trials

Will clinical trials be conducted on treatment naive patients with the new treatments?

Yes, although usually the first trials of a new treatment are done on relapsed and refractory patients.



Can you address the role that the age of the patient plays in the different treatments that may be available and also how age affects one's eligibility for a clinical trial?

Older CLL patients are more likely to have comorbidities and so may not tolerate some therapies that have more severe adverse events. Decisions should be made on an individual basis.

Typically clinical trials have inclusion criteria and exclusion criteria that might tend to eliminate some older patients. Inclusion criteria may include age and indicators of fitness, for example, in order to be included, a patient must be 18 to 85 years of age, have an ECOG status of ≤ 2 and have adequate bone marrow function independent of growth factor. Exclusion criteria might include having undergone a bone marrow transplant < 90 days, having Richter's transformation, and having unstable angina.

Are there any clinical trials for ibrutinib or venetoclax for 2nd line therapy?

Yes. Please see our guide on how to use ClinicalTrials.gov here:
<https://cllsociety.org/2017/06/understand-get-clinicaltrials-gov/>

Is there a clinical trial for adding venetoclax if a BTK inhibitor is starting to show signs of losing effectiveness?

Venetoclax is often used alone or in combination with a monoclonal antibody when a BTK inhibitor fails. Several clinical trials are underway looking at venetoclax in combination with other agents for relapsed CLL patients.

Vaccines

What is the recommendation for the flu shot? Should we get the extra strength flu vaccine or two shots spaced out, one early in the season and one later?

There are no special recommendations for CLL patients, though the high dose quadrivalent vaccine makes sense. There are no data regarding the effectiveness of flu vaccines for CLL patients.

Does the Shingrix vaccine work for CLL patients?

We don't have good data, but based on data for other vaccines, my best guess is that it probably works, though less well than in those with a normal immune system. It is very effective for those with normal immunity, but we don't know how well it will work for us. Many CLL patients are getting the new vaccine as the risk/benefit seems positive. You



can find this answer and other commonly asked questions in our Ask the Doctor section of the *CLL Tribune* here: <https://cllsociety.org/2020/09/ask-the-doctor-q3-2020/>

Is it recommended for patients to stop a BTK inhibitor for several days prior to any vaccination to increase response?

Dr. Richard Furman addresses a similar question in the Ask the Doctor series. We do not know the impact of ibrutinib or other BTK inhibitors on one's response to a vaccine. Some data suggest that the immune system functions better once the CLL is under control. When we look at rate of infections in patients on ibrutinib, the rate decreases the longer one is on the ibrutinib and has their disease under better control. Please find similar questions published in our quarterly *CLL Tribune* here: <https://cllsociety.org/2020/06/ask-the-doctor-q2-2020/>

When can you get vaccines when getting IVIG?

This is an interesting question that Dr. Richard Furman answered as part of our Ask the Doctor series. We do often use IVIG as an immune suppressant, but that is usually with a dose that is far higher than what we use as monthly replacement. We do not expect this dose to be immune suppressant. Although we do not currently have data to support this, I would suggest waiting one week after IVIG and then receiving the vaccination.

COVID-19

Should being in a pandemic change your treatment choices for CLL? Any concerns about travelling out of state for clinical trials?

This is a personal decision to be made with your medical team. It makes sense if all else is equal to avoid air travel and recurrent trips to a hospital when the pandemic risk is high.

During the COVID-19 pandemic, what are recommendations for when to stick to telemedicine appointments and when to go into the office to see your physician?

That decision should be made case by case. If the disease is stable, most visits can be done virtually.

At this time, during the pandemic, what are your recommendations on having general healthcare appointments scheduled versus waiting? I'm considering colonoscopy, dental cleaning, dermatology appointment, etc.

There are risks with delaying care and risks with going to appointments with health care providers that you need to balance in discussions with your providers.



What are the recommendations as we move into colder months about groups of people in indoor spaces, the size of groups and the potential of becoming infected?

Recommendations are constantly changing, but we believe outdoors is safer than indoors and the smaller the group and the greater the social distancing, the lower the risk.

What is the death rate for people with CLL who are infected with COVID-19?

We really don't know. In a multi-center, international study 90% of CLL patients required hospital admission. At a median follow up of 16 days, the overall case mortality rate was 33%. However, these data are from early in the pandemic, and survival rates may be improving. Many cases may be mild or asymptomatic. We just don't know.

Should CLL patients have the COVID-19 vaccine when it's available? What are the stipulations we should be aware of when we have more information about the vaccine?

We need more information to best advise. I suspect CLL patients should be among the first to get the vaccine, but it's still too early to know.

What do we know about BTK inhibitors in COVID-19 in patients?

There are theoretical reasons to believe that BTK inhibitors could be helpful in CLL patients with COVID-19. Several ongoing trials are examining if BTK inhibitors are beneficial, but no data are available yet.