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# An approach to anxiety during watch-and-wait for Chronic Lymphocytic Leukemia: Monitor and move on

by Nanette Cox-Kennett

## ABSTRACT

*Chronic Lymphocytic Leukemia (CLL) is the most frequently diagnosed hematologic malignancy with the majority of patients at diagnosis in the “watch and wait” stage of treatment – language that gives the perception of an axe waiting to fall, belying the fact that up to 30% of patients will never need treatment in their lifetime. While receiving active surveillance, patients report anxiety, distress, and depression, yet there is little research capturing the experience of this patient population, nor describing interventions to improve their experience (Damen, 2022). In an effort to “do something,” patients may turn to often expensive and unproven alternative therapies. At each clinic visit, there is an opportunity to provide relevant and understandable information, resources to address anxiety, and response to unmet needs to increase the patient’s experience of shared decision making. Reframing the experience to a more proactive perspective such as ‘Monitor and Move On’ versus ‘Watch and Wait’ may empower patients with CLL along their trajectory.*

## AUTHOR NOTE



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## INTRODUCTION

Chronic lymphocytic leukemia (CLL) is an indolent cancer of the B lymphocyte before it is transformed into an antibody producing plasma cell. It is the most commonly diagnosed leukemia of older adults in Canada with approximately 1,780 new cases annually according to 2018 statistics (Statistics Canada et al., 2023). Most patients are diagnosed after routine screening bloodwork or incidentally during other investigations, and are largely asymptomatic with few physical findings. Staging for CLL (Rai or Binet) includes a stage 0/1, with

no findings excluding a lymphocytosis or small areas of lymphadenopathy, and ends with cytopenias at stage 3 or 4 (Rai et al., 1975; Binet et al., 1981). It is at Stage 3 or 4 that treatment is considered. There is no proven survival advantage to early intervention (Owen, 2018). The majority of newly diagnosed patients will be classified as “watch-and-wait” until they meet internationally standardized treatment criteria (see Table 1), which has remained largely unchanged for decades.

A diagnosis of CLL will cause an individual to be anxious. To then be told

Table 1

Expected and treatable findings in CLL

What is normal or expected in CLL?	What do we treat?
The white cell count will increase	There is no magic number for treatment. If the white cell count doubles in less than six months (unrelated to infections), this may require treatment or closer monitoring.
Hemoglobin or platelets may vary due to auto-immune dysfunction or cells being trapped within the spleen.	Consistent hemoglobin or platelets less than 100 (i.e., Not variable) and unrelated to other causes (e.g., vitamin deficiency) Or Auto-immune crisis – where hemoglobin or platelets rapidly decline due to cell destruction that does not respond to steroids.
Lymph nodes increase in size	Massive lymph nodes (10 cm)
Spleen may increase in size	Spleen 6 cm below the ribs
Fever or night sweats	Daily and lasting for a prolonged period (more than two weeks at least) with no active infection
Feeling tired	Unable to perform work or usual activities unrelated to other illness and associated with high CLL burden of disease.
	Weight loss of 10% or more within six months for no other cause.

Adapted from Hallek et al., 2018

there is no treatment to be offered adds to this anxiety. To reassure an anxious, newly diagnosed patient, care providers must approach the first visit with an established plan to address frequently asked questions and utilize positive language to frame the future.

## BACKGROUND

In a survey of more than 100 patients, following the initial consult, patients have reported feelings of relief, as well as anxiety, and only 54% reported having all their questions answered (Association Community Cancer Centers, 2022). Confusion alongside ongoing anxiety and worry about the future were experienced following that appointment. This anxiety does not necessarily resolve with time. In a survey of 1,482 patients, Shanafelt and colleagues (2007) found more than half (55.9%) of patients continued to think about their CLL on a daily basis more than two years following diagnosis, and at three years there was no significant change in emotional well-being. A recent publication by Damen et al. (2022) explored the unmet supportive care needs specifically within this hematology population on watch-and-wait. More than a third of respondents had high levels of distress, anxiety, and depression. Poor coping and lower quality of life was significantly associated with higher unmet needs in younger aged individuals. Specific concerns included accessing information, results of testing, psychological supports, and personal-centred care.

To address these concerns, as well as others frequently voiced during initial consultation, structured CLL-specific education has been shown to increase patient knowledge, activation and engagement in shared decision making (Rocque et al., 2018). As oncology nurses are an integral part of the oncology care team and often the first professional to assess cancer patients' concerns during an initial consultation, a comprehensive and proactive assessment and planned intervention are recommended. Information which can be used by oncology nurses in discussion with patients who are newly diagnosed with CLL is presented below, organized according to commonly asked questions from patients.

### Why are you not treating now when it's early?

The public tends to be more familiar with solid tumours, as these types of cancer are more commonly diagnosed and come with the knowledge that advancing stage or metastatic disease is more likely incurable. With hematologic malignancies, there is no solid mass to invade other tissues and most leukemias are not traditionally staged for degree of severity. CLL patients require education that higher staging does not impact the degree of future response to treatment. Reassurance can be provided that early intervention has not shown to improve overall survival and is not recommended outside of clinical trials (Owen et al., 2018). In fact, early treatment has been shown to lead to CLL clone evolution, promoting resistance to therapy during the chemo-immunotherapy era (Gerber et al., 2017).

### What are you watching for?

Outlining the treatment criteria in everyday language is required. Concrete information in a handy reference tool (perhaps a screen shot on their phone) will empower patients to self-evaluate (see Table 1). While the test results regarding white cell count and clonal lymphocytosis are often what prompted diagnosis, a slow gradual increase in disease over time is expected with no absolute number that prompts a change in management. Additionally, lymphadenopathy may or may not be present and can wax and wane over time. Flares may occur with physical stressors. The location of lymph nodes requires review with the individual and the expectation that new and enlarging lymph nodes is to be expected. Significantly increasing lymphadenopathy over a short period of time, when the patient is not experiencing a physical stressor (illness), should be flagged to the oncology provider.

### When do you think I'll need treatment?

There are several CLL prognostic tools that utilize patient characteristics alongside multiple biomarkers including cytogenetic abnormalities and gene mutations. Not all of these tools are readily available at all treatment centres. These tools have been shown to predict time to first treatment or treatment-free

intervals, however they have not yet been perfected (Molica et al., 2016; Kleinstern et al., 2020). This knowledge is often desired by patients at the time of diagnosis, even though medical management remains unchanged. For that reason, such prognostications are not recommended at the time of first consult, but only when treatment is warranted (Owen et al., 2018).

An alternate argument could be made that high prognostic scores could guide those who might benefit from more stringent monitoring. However, it can be falsely reassuring for patients who have untested genetic mutations, which are not included in validated prognostic scoring systems (Kleinstern et al., 2020). There are also added costs to the healthcare system for more frequent monitoring. These specialized and costly tests would require repeating at the time treatment is warranted, as genetic mutations can evolve over time (Guieze & Wu, 2015).

Patients with very low-risk disease according to the CLL international prognostic index (CLL-IPI) have been shown to have a 1 in 3 chance of needing therapy at 10 years (Parikh et al., 2021). In a cohort of 705 newly diagnosed patients, Rassenti et al. (2008) found a median time to first treatment ranging from 2.5 years to 10 years with some patients reaching more than 20 years following diagnosis. Providing concrete, but generalized information about the pooled data for newly diagnosed patients with CLL regarding time to first treatment can assist with anxiety.

### What can I do to help myself?

Up to 66% of patients with CLL surveyed in 2014 were taking complimentary and/or alternative medicines (D'Arena et al., 2014). Reviewing information about these types of therapies at the time of initial consultation can build patient confidence in the provider team's awareness of alternative therapy and promote information sharing at future appointments. There are many supplements promoted for CLL management and the list grows annually. It can be confusing and difficult to differentiate between the many products on the market, as these products are largely unregulated. Currently,

Table 2

Summary clinical trials for CLL complimentary alternative supplements

	Supplement	Dosing	Trial	Participants	Results	Toxicity
Shanafelt et al., 2013	Anti-oxidant epigallocatechin gallate (EGCG) or Green Tea extract	EGCG 2000 mg BID x 6/12	Phase 2	n = 42 stage 1/2 CLL	ORR 2.4% 1/3 pts had 20% decrease in lymphocyte counts	GI toxicity, Liver toxicity *Health Canada safety alert regarding liver injury (Government of Canada, 2017)
Golombic et al., 2015	Curcumin	2000 mg daily x 6/12	Phase 2	n = 21 Stage 0/1 CLL	4/21 with 20% reduction in WBC 1/21 with WBC progression	GI toxicity
Sfeir et al., 2017	Vitamin D	50,000 iu weekly for up to 6 months then monthly up to 3 years	Phase 1 Phase 2 not yet reported (NCT01787409)	N = 13 CLL pts N = 145 with lymphoma	No CLL/lymphoma outcomes reported, *intervention trial not yet reported	1 pt transient (1 week) Mild hypercalcemia in the setting of acute kidney injury with antibiotics
Baron et al., 2018	Quercetin	500 mg BID x 3/12	Phase 1	N=3 failed prior therapy or no other therapy option	2/3 had stable lymphocyte count	No toxicity reported
Rojas-Gil et al., 2021	High oleocantha and high oleacein Olive oil from Corfu Greece	40ml/day x 3/12	Phase 2	N=22 Stage 0/1/2	Median WBC from 16.9 to 11.7 at end of treatment, no statistical difference in lymphocyte count observed.	No change to lipids noted

ORR = overall response rate

a summary of the evidence for effectiveness of green tea, curcumin, vitamin D, and extra virgin olive oil supplementation is warranted alongside concerns for drug interactions, if known (see Table 2). This list of four excludes complimentary therapies for which there is only invitro evidence and case reports, and focuses on those for which there is phase 1/2 clinical trial data. For those patients wishing to do their own research, defining good clinical data (trial data) and identifying reputable Canadian websites is helpful (e.g., lymphoma.ca or clcanada.ca).

#### How frequently will I be checked?

Monitoring CLL requires bloodwork and physical examination. At early-stage disease, this could either be deferred to a family healthcare provider or remain within specialist care. Frequency of bloodwork monitoring is not specified within current Canadian guidelines (Owen et al., 2018), but monitoring

trends in bloodwork at a minimum of six-month intervals is generally recommended. More frequent intervals may be based on shared decision making between patient and clinician.

For some patients, it is hypothesized that more frequent blood monitoring may assist in managing anxiety (Damen et al., 2022). Care providers utilizing an electronic medical record can encourage patient access to the electronic chart to facilitate successful review of test results. However, the patient requires foundational knowledge about the progression of lymphocytosis over time as an expected course. Awareness of the guidelines for treatment will also aid in their interpretation of results and reduce calls to specialty providers.

#### What happens when I need treatment?

Options for treatment will be dictated by patient specific factors including cytogenetics, molecular mutations,

medication interactions, and fitness for treatment (Owen et al., 2018). Patients may qualify for one or more treatment options depending on provincial funding models. Should there be more than one option, patients can expect a presentation of their individual prognostic findings alongside the outcome evidence and an opportunity for shared decision making. Comorbidities, adverse effects, medication interactions, and treatment scheduling (continuous versus fixed duration of treatment) may influence decision making on the part of the clinician.

#### How well does treatment work?

CLL has traditionally been considered incurable, but infinitely treatable. This perspective has improved over time with survival moving closer and closer to age-matched healthy controls (da Cunha-Bang et al., 2016). Treatment has changed radically with

the introduction of relatively well-tolerated oral novel agents including BCL2 inhibitors and BTKi inhibitors. Median progression-free survival has not been reached for many novel agents at four years of follow-up (Eichhorst et al., 2023; Sharman et al., 2022). For the first time, survival for patients over the age of 65 years and treated with first generation BTKi therapy has been shown to be equivalent at eight years to healthy matched controls (Ghia et al., 2023). Though increasingly less favoured, there is a subset of patients for whom older chemotherapy/monoclonal antibody therapy may be preferable, as there are reported plateaus in the progression-free survival curve which could indicate a functional cure (Fischer et al., 2016). Patients can be reassured that there are multiple options with excellent tolerability and outcomes.

#### Do I need to be worried about this?

The terminology ‘watch and wait’ is commonly used for this interval of no pharmaceutical management. However, both verbs imply passivity. In this practitioner’s practice, the ‘Ws’ of watch and wait have been inverted to ‘Ms’ and the terminology ‘Monitor and Move On’ is used instead. The words are pro-active and can be encouraging to the newly diagnosed individual.

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To monitor implies an active process of engagement with the bloodwork results, patient’s symptoms and physical findings. Patients are encouraged to participate in the process by following along in the electronic chart and documenting through available apps provided by national organizations (e.g., CLL Watch and Wait Tracker available through Lymphoma Canada at [lymphoma.ca](http://lymphoma.ca)). Monitoring trends over time will inform about the trajectory of CLL progression or perhaps even stability. It is important to stress the auto-immune and reactionary variability that can occur with bloodwork. The spleen may sequester platelets and lymphocytes will flare during times of physical stressors, as they are reactionary. For this reason, the trends are important and repeat serial testing can be reassuring. A platelet or hemoglobin value in a slowly declining trend over time is more concerning and predictive than a fluctuating value.

The second M for ‘Moving On’ implies ‘getting on with life in the meantime.’ Rather than waiting for treatment to begin, the aim here is to focus on the life to be lived. Any cancer diagnosis can be highly anxiety producing and the practitioner must not be dismissive nor minimize emotional

distress (Shanafelt et al., 2007). By the close of the initial CLL consultation, after reviewing the potential for a long treatment-free interval and possibly never requiring treatment in their lifetime, patients may choose to focus on living well. A referral to psychological support available through the cancer centre, the community, or national organizations is encouraged.

#### Future

Persons with CLL may experience a long treatment-free interval with potentially years of Monitoring and Moving On. For those whom medical management is indicated, CLL treatments may be administered over a course of time or continuous therapy. Another time of ‘watching and waiting’ is experienced for return of disease or progression while on treatment. Living with a chronic illness both on and off treatment will be the norm for a person diagnosed with CLL. The proficient oncology provider performs regular physical and emotional assessments to ensure supports and referrals are provided in a timely way. Future research in the management of anxiety utilizing both education that promotes patient activation, and the use of proactive language such as ‘Monitor and Move On’ during this timeframe is recommended.

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