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GUIDELINES - EXPERT OPINION

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Fitness beyond age: Multidisciplinary expert opinion on redefining fitness for targeted therapies in chronic lymphocytic leukemia

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Abstract

Advancements in the understanding of chronic lymphocytic leukemia (CLL) have transformed patient care, leading to the development of novel targeted therapies. Traditionally, patient fitness for treatment was based on the tolerability of chemoimmunotherapy such as fludarabine–cyclophosphamide–rituximab. As the CLL patient population is predominantly older, age has historically been a major factor in how a physician selects a patient's treatment. However, as a patient's fitness goes beyond age, the definition of patient fitness should also evolve. Here, we provide suggestions for the current best practice on assessing fitness for treating CLL. Considerations for treatment include assessment of polypharmacy, history of infections, cardiovascular and renal comorbidities, functional status, cognitive and psychological status, nutritional status, and social support. The flow of assessments can start with a typical clinical evaluation followed by geriatric, cardiovascular, and renal reviews, if needed, and include collecting a patient's full history to evaluate their risk of complications with specific CLL treatments. The severity of a patient's cardiovascular profile can range from low to high risk; for those at high risk, collaboration with a cardiologist is recommended. Geriatric assessment is advised to determine baseline frailty and resilience to tolerate treatments, to avoid inappropriate treatment or undertreating patients based on chronological age, and to align the patient's fitness status with the most optimal treatment. Continuous monitoring and assessment, regardless of therapy, are recommended. Patient preferences are also integral to this decision-making process. Looking beyond a patient's age and basing treatment selection on their fitness is key in the new era of treatment in CLL.

INTRODUCTION

For many years, chemoimmunotherapy, such as fludarabine–cyclophosphamide–rituximab, bendamustine–rituximab, and chlorambucil–obinutuzumab, was the standard first-line treatment for patients with chronic lymphocytic leukemia (CLL).[1] However, progress in understanding the biology of CLL has led to the development of novel targeted therapies, which now account for the vast majority of treatments for CLL, when there is access.[2–5] These advances include the introduction of covalent Bruton's tyrosine kinase inhibitors

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(BTKis; ibrutinib, acalabrutinib, and zanubrutinib), BCL-2 inhibitors (venetoclax), anti-CD20 monoclonal antibodies (rituximab and obinutuzumab), and noncovalent BTKis such as pirtobrutinib.[6,7] More recently, fixed-duration treatment with venetoclax–obinutuzumab or BTKi–venetoclax has demonstrated improved outcomes versus chemoimmunotherapy.[6,8–11]

Each treatment option has a unique safety profile, with different adverse events being associated with each therapy at varying rates.[12–21] These adverse events seen with novel therapies differ from the hematologic events most commonly experienced with chemoimmunotherapy (e.g., myelosuppression, immunosuppression, infections, and high rates of other malignancies) and, in general, occur with lower frequency. Given that these newer treatments are better tolerated than chemoimmunotherapy, but with differing adverse event profiles to consider, it is important to select the treatment that will provide the best outcome for each patient, in terms of both efficacy and safety. In the chemoimmunotherapy era, age was the main factor in determining the fitness of patients with CLL, together with renal function and overall comorbidity burden (assessed with tools such as the Cumulative Illness Rating Scale [CIRS] and the Charlson Comorbidity Index) in the case of fludarabine-based treatments.[22] However, although fitness remains important, previous definitions are outdated, as the influence of age on prognosis is less pronounced given the overall higher tolerability of novel therapies.[22,23] A more individualized treatment selection, considering key comorbidities, social determinants of health, and frailty status, may be more appropriate.[22,24]

In this article, we provide our expert opinion on assessing the fitness of patients with CLL who are referred for targeted therapies, including advice for treating older patients for whom there are additional factors that must be considered before treatment. These suggestions are a result of discussions from a series of multidisciplinary expert meetings between oncologists from Europe, the United States, Brazil, and Australia, as well as cardio-oncologists, geriatricians, and a patient advocate. The meetings were held to align on practice-driven expert opinion, prioritizing the assessment of patient fitness for targeted treatment beyond age and the application of redefined fitness criteria for novel therapies. The experts were identified based on their varied locations and contributions to the field. The overall aim was to start a discussion on the concept of fitness and to share our perspectives and practical advice for revising the concept of fitness and how it is evaluated in clinical practice.

INDIVIDUAL ASSESSMENT FOR PERSONALIZED TREATMENT

Traditionally, assessment tools to evaluate fitness in CLL included the CIRS, Eastern Cooperative Oncology Group performance status, and geriatric assessment,[25–28] which have overlapping and complex elements (Figure 1). These tools have been recommended in guidelines,[25,29] but others may be used in patients with CLL. While these tools provide a general assessment of a patient's overall health status, risk assessments often assign equal weight to all factors and do not consider the characteristics of individual patients with CLL. In addition, each individual tool has its own limitations. For instance, the CIRS requires an assessment of 14 different organ systems,[30,31] which may be clinically impractical.[29,32] These limitations highlight an unmet need for redefining fitness for personalized treatment in CLL. Key factors that require assessment in the modern era are history of infections, cardiovascular and renal comorbidities, functional status, cognitive and psychological status, nutritional status, social support, and polypharmacy and potentially over-treatment (where the risks of the adverse effects may outweigh the benefits for a specific patient, often in the elderly) (Figure 1). These factors should be considered when therapeutic benefit is expected with any therapy applied. With the advances in therapies, the more traditional tools are less relevant in aiding treatment decisions; it is now more relevant to focus on individual comorbidities rather than using scoring systems that aggregate multiple existing conditions together. For example, a patient

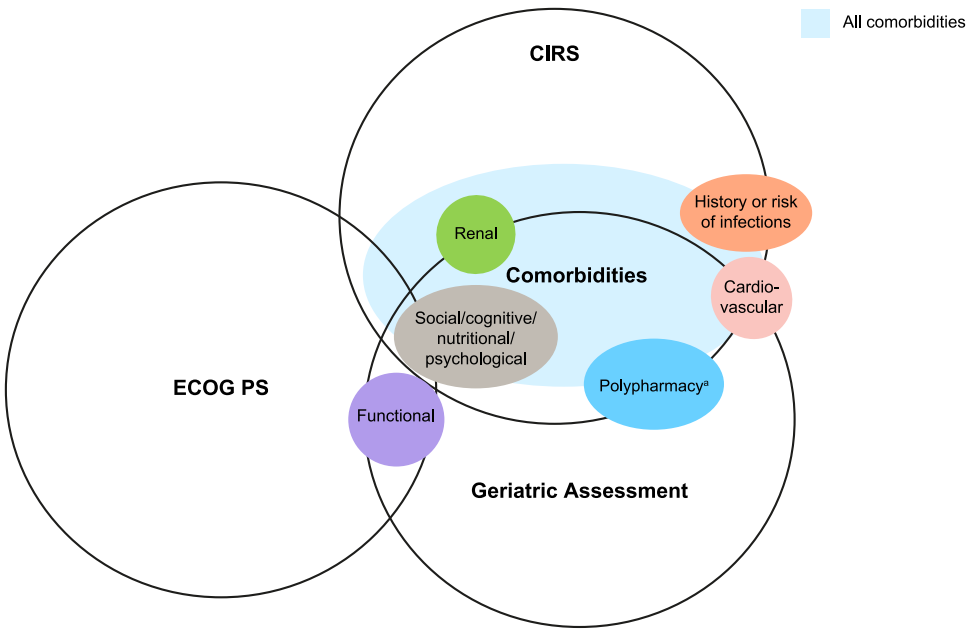

FIGURE 1 **Current tools for assessment of fitness in patients with chronic lymphocytic leukemia.** [a]Includes potentially inappropriate medication and drug–drug interactions, where the risks of adverse effects may outweigh the benefits for a specific patient. CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status.

with end-stage renal disease (e.g., glomerular filtration rate (GFR) <30 mL/min) with another mild condition but no cardiac disease and a patient with severe cardiac disease (e.g., coronary artery disease and high-grade arrhythmia) without any renal disease may have the same CIRS score, but their underlying comorbidities would result in very different treatment suggestions.

When redefining fitness, any modern definition must consider the efficacy and tolerability of targeted treatments. Traditionally, age and comorbidities have been used as enrollment criteria for trials involving standard regimens such as chemoimmunotherapy. These criteria are still incorporated into modern clinical trials and are used during treatment selection, but this may not be appropriate for the current era of novel therapies, as age may not be as critical as a decision lever as during the era of chemotherapy.

Fitness should be redefined as a multifaceted approach, with core assessments including assessment of specific comorbidities (i.e., infections, renal, and cardiovascular), polypharmacy, functional status, cognitive and psychological status, and social support. Each of these factors must be identified so that they can be addressed accordingly (Figure 2). Social determinants of health and nonconventional risk factors, including polypharmacy and poor functional, cognitive or nutritional status, can negatively impact overall or progression-free survival and increase the risk of severe infections.[33–36] However, to our knowledge, there are no prospective studies on how interventions on these factors affect treatment outcomes for patients with CLL receiving BTKi or BCL-2 inhibitors. Patients with longer life expectancy, for whom the development of resistance or toxicity associated with long-term medication exposure is most likely, may benefit most from fixed-duration treatment. An assessment of life expectancy is therefore also considered useful. Life expectancy, independent of CLL, is another measure and can be estimated using ePrognosis (https://eprognosis.ucsf.edu/), which estimates life expectancy in an individual without CLL and takes into account competing causes of mortality.[37] This website may provide additional information to help select therapeutic regimens and was recommended for consideration on a case-by-case basis.

Assessment of lower resilience is also important. Lower resilience has several facets, including the socioeconomic status of the patient, availability of resources, and the presence/absence of care partners,[38] and relates to the degree of individual lower resilience to tolerate specific treatments. It is therefore important to carry out an evaluation using geriatric assessment to determine which specific domain is more relevant, for informing treatment decision-making and designing a plan tailored to any identified patient vulnerabilities. Relevant domains include comorbidities, social status, nutritional status, and social support. In addition, care partners, logistics, and family support are important and included under the umbrella of the social domain of the geriatric assessment. Care partners play a crucial role in supporting patients with frequent hospital visits, particularly in the setting of intravenous therapies such as venetoclax–obinutuzumab.[34] Social support has emerged as a relevant consideration before treatment, given that most novel therapies are administered orally and are thus taken outside the hospital setting.

It is also important to involve patients and their care partners in their treatment decisions and to clearly explain potential treatment options and listen to their preferences. This is particularly important given that only around half of patients believe that they are sufficiently involved in choosing their treatment at the time of their initial diagnosis of CLL.[39] Also, around half of care partners and patients report that the diagnosis of CLL was not explained by their healthcare provider in a way that they could understand.[39]

A re-evaluation of polypharmacy is also advised on an individual basis. It is recommended to assess the patient's concomitant medications at the initial clinic assessment and take measures to reduce or remove medicines that may impact their CLL treatment.[40] This should be in accordance with the prescribing information for each CLL therapy. Regardless of which additional specific tools or measures are used, an individualized assessment of each patient by the hematologist was agreed to be an essential first step (Figure 3). The flow of assessments should start with the usual clinical assessment, and then focus on additional cardiovascular, renal, and geriatric assessments, if needed. Continuous monitoring and review are recommended as required.

GERIATRIC ASSESSMENT

Frailty, or lower resilience, is generally defined as an age-related clinical condition of increased susceptibility to stressors and reduced intrinsic capacity.[41] Patients who are fit have normal intrinsic

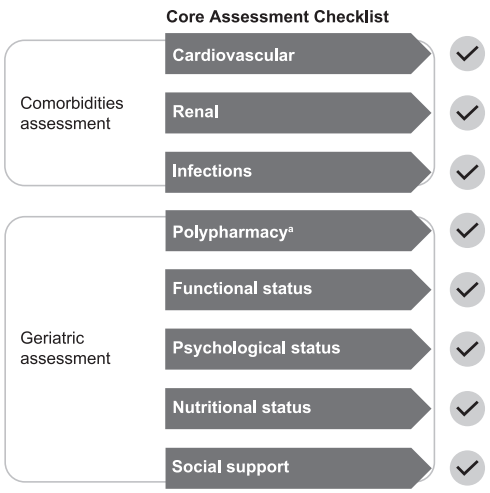

FIGURE 2 **Recommended checklist for core assessment of fitness.** [a]Includes potentially inappropriate medication and drug–drug interactions, where the risks of adverse effects may outweigh the benefits for a specific patient. CV, cardiovascular.

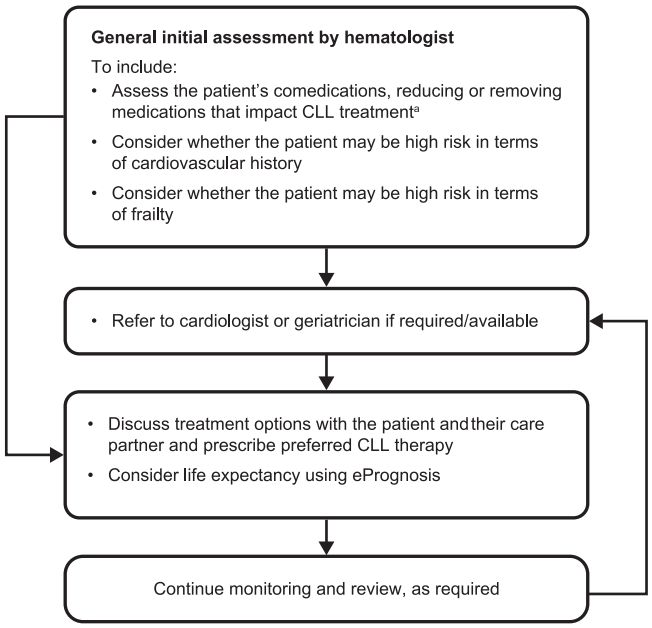

FIGURE 3 **Flowchart of suggested key steps in the assessment of fitness.** [a]The prescribing information for each chronic lymphocytic leukemia (CLL) therapy should be consulted before administration.

capacity.[41] In contrast, unfit patients have reduced intrinsic capacity. As a result, older adults with frailty are at increased risk of adverse health outcomes.[41] Frailty is defined phenotypically in the Fried frailty criteria as having three or more of the following: weight loss, exhaustion, weakness, slow gait, and decreased physical activity.[42] Alternatively, it can be defined in terms of deficit accumulation in the Rockwood frailty index, which includes various diseases, signs from clinical examinations, and functional impairments.[43] This index determines whether frailty is present or not and allows for its quantification. Here, we avoid the negative language associated with "vulnerability" and "frailty" and use "lower resilience" to describe these patients.

Patients with very low resilience are less able to tolerate stressful treatment regimens such as chemotherapy and chemoimmunotherapy. However, new targeted treatments are less physically demanding and more tolerable to those patients who used to be considered less resilient. The level of resilience should therefore be considered before the specific therapy the patient is exposed to. Ultimately, the goal of incorporating geriatric assessment into the expert opinions described here is to avoid undertreating patients due solely to age-related impairments and to correct any identified impairment.

If during initial consultation the physician prefers further assessment of these geriatric factors before deciding on the best course of therapy, then geriatric assessment is recommended when time and resources allow. Several geriatric screening tools exist to inform treatment choices[44] (Table 1), although clinicians may be unaware of their availability. These tools may be used as part of a comprehensive assessment, if resources permit. While these tools are generally well validated in patients with cancer and hematological malignancies, specific validation for novel therapies in CLL is pending.[22,38,44–49]

The Geriatric 8 (G8) and the Vulnerable Elders Survey-13 (VES-13) should be used as screening tools to identify patients who may be resilient; both are mentioned in the American Society of Clinical Oncology (ASCO) guidelines for practical assessment and management of vulnerabilities in older patients.[29,50] The G8 screening tool has eight questions, and the total score ranges from 0 to 17.[46] Patients who score ≤14 are at high risk for lower resilience and may benefit from a comprehensive geriatric assessment.[44,51] The VES-13 is a 13-item function-based scoring system that considers age, self-rated health, physical function limitations, and functional disabilities.[45] Patients with a score of ≥3 are classified as vulnerable for death or functional decline[45] and are more likely to benefit from a comprehensive geriatric assessment before cancer treatment. Both of these tools can be used in settings without available geriatricians to identify patients at high risk who require further geriatric assessment (Figure 4). A preference was given to the G8 screening tool, as it has been validated in older patients with cancer, including hematologic malignancies,[46] whereas the VES-13 was only validated in elderly community-dwelling individuals.[45] Alternatively, the Geriatric Assessment in Hematology assessment may also be used in centers without a geriatrician, as it can be performed easily by a nurse or hematologist without training in geriatrics.[44,47,48,53] However, it primarily focuses on identifying patients using a cutoff point to indicate high risk of toxicity to treatment and oversimplifies treatment tolerability. The Elderly Prognostic Index is not recommended, as it has only been validated in patients with diffuse large B-cell lymphoma.[49]

The ASCO guidelines also advise checking for nutritional status, cognition, social activity/support, functional status, psychological status, comorbidity, gait speed, and fall history.[29,50] It should be noted that it is not mandatory to check everything, but as the patient is assessed further, more information will be available to guide treatment. Information on non-oncologic interventions is also included in the ASCO guidelines, including nutrition counseling for patients with

TABLE 1 Overview of available geriatric assessment tools and expert opinions.[22,38,44–49]

Tool	Assessed domains	Methods (time to do the test)	Expert recommendation
Geriatric 8 (G8) screening tool[46]	Age, weight loss, body mass index, motor skills, psychological status, number of medications, and self-rated health status	Administered by HCP; self-administered version available (5 min)	Recommended screening tool. This score is very simple. In the absence of a geriatrician, it helps draw the clinician's attention to factors that can be addressed by other specialists
Vulnerable Elders Survey-13 (VES-13)[45]	Age, self-rated health status, functional limitations, and functional disabilities	Self-administered (5 min)	May be recommended as a screening tool (G8 preferred)
Geriatric Assessment in Hematology (GAH)[44,47,48]	Number of medications, gait speed, mood, ADL, self-rated health status, nutrition, psychological status, and comorbidities	Administered by HCP (10–12 min)	Recommended screening tool and as a short geriatric assessment if a geriatrician is not available

Abbreviations: ADL, activities of daily living; HCP, healthcare provider.

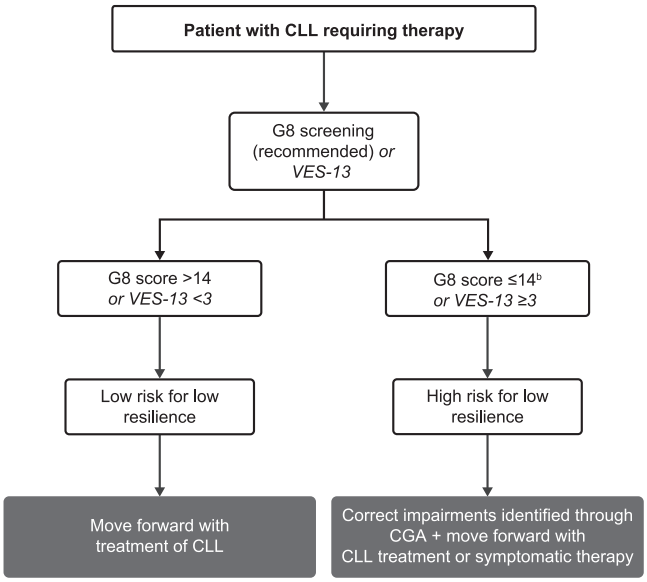

FIGURE 4 **Recommended geriatric assessments and treatment in settings with and without a geriatrician available.**[a] This is a recommendation only, and it aims to broaden access to therapy for older patients rather than restrict it. [a]American Society of Clinical Oncology (ASCO) guidelines and International Society of Geriatric Oncology (SIOG)[52] recommend use of the following appropriate domains: physical function/performance (falls in the last 6 months/physical function 4-m gait speed), functional status (Older American Resources and Services [OARS], Instrumental Activities of Daily Living [IADL]), nutrition/weight loss (single item from the Geriatric 8 [G8] and the Mini Nutritional Assessment), social support (Medical Outcomes Survey social support 8 item), psychological (PROMIS Anxiety 4-item, GDS-5), comorbidity (OARS comorbidity, hearing, vision), cognitive function (Mini-Cog), and use of the G8 screening tool with the Vulnerable Elders Survey-13 (VES-13) as an alternative. [b]ASCO and SIOG guidelines state that if a geriatrician is available and the G8 score is ≤14, the patient must be evaluated by a geriatrician before the final decision of treatment. CGA, comprehensive geriatric assessment; CLL, chronic lymphocytic leukemia.

weight loss >10% from baseline weight, physical/occupational therapy referrals for patients with a deficit in instrumental activities of daily living and history of falls in the last 6 months, and social support/assistance at home.[29] However, it is important to understand that the relevance of these guidelines will differ between patients.

Although monotherapy use seems more feasible in patients with lower resilience, there is no reason to exclude these patients from treatment with combinations of drugs as is typically done with fixed-duration treatments, such as ibrutinib–venetoclax or venetoclax–obinutuzumab. Fixed-duration treatments have demonstrated benefit in CLL and are attractive as they offer treatment-free time to the patient, thus limiting the overall exposure to drugs.[54] This was evident in three pivotal clinical trials, with fixed-duration ibrutinib–venetoclax in the GLOW study, which included older, less resilient patients aged ≥65 years with a CIRS score of >6 and creatinine clearance (CrCL) of <70 mL/min,[10,17] and in the CLL14 study of fixed-duration venetoclax–obinutuzumab, which included older patients aged 71–72 years with a CrCl of <70 mL/min and CIRS scores of >6.[55] Fixed-duration treatment might be considered also in older, less resilient patients who may be at risk from adverse events and poor adherence as, for example, 15-cycle (13.8-month) ibrutinib–venetoclax treatment may reduce the risk of cumulative toxicities associated with long-term use of continuous BTKis.[3]

It is important to consider that patient resilience can also depend on the status of the CLL and can improve during CLL treatment with targeted therapies because it reduces any lower resilience due to cancer (CLL). For example, when receiving ibrutinib–venetoclax, patients with CLL receive 3 months of ibrutinib run-in, which usually improves the patient's resilience.[17] Similarly, for patients with CLL treated with venetoclax–obinutuzumab, geriatric burden (e.g., mobility issues, cognitive decline, and mood issues) as a surrogate of frailty decreases over the course of treatment[56] and re-evaluation is recommended during treatment due to its dynamic nature.

CARDIOVASCULAR ASSESSMENT

Atrial fibrillation (AF) and hypertension are common in older adults[57,58] and also occur frequently in patients with CLL. Cardiovascular adverse events are a recognized class effect of BTKi therapies.[59–63] Cardiovascular risk should therefore be assessed before treatment, and careful control or prevention of comorbidities should be taken to improve patient selection and care.[64,65] All patients should be screened for undiagnosed cardiovascular conditions and existing ones optimized before therapy. As cardiovascular profiles vary in severity,[57,58,64] and no specific risk scores exist for CLL treatments, cardiology (or cardio-oncology) evaluation is advised for patients who are at high risk (see Figure 5) or those with new cardiovascular symptoms.[64]

Suggestions for cardiovascular workup were developed (Figures 5 and 6) based on current symptoms, history of cardiovascular disease, and related risk factors. Patients should monitor blood pressure (BP) at home and remain alert to symptoms such as syncope, palpitations, or exertional fatigue. For patients considered to be at low risk for cardiovascular disease, follow-up by a hematologist is sufficient. Cardiovascular assessments, including home BP measurement and opportunistic AF assessments, are recommended for these patients, and the patient should be made aware of any new symptoms to watch out for. Patients considered at high risk for cardiovascular disease should be referred to a cardiologist for additional support.

Patients can monitor their BP at home, ideally weekly during the first month of treatment and every 2–3 weeks thereafter. Cardiovascular risk evaluation is recommended if the systolic BP is ≥180 mmHg or diastolic BP ≥110 mmHg, and any cancer therapy associated with hypertension should be deferred or temporarily withheld until the BP is controlled to values <160 mmHg (systolic) and <100 mmHg (diastolic). It should be emphasized that these suggestions are for best practice, not mandatory, and are not included in the product labels. Importantly, if a specific assessment is not available and the patient is asymptomatic, this does not need to be a contraindication for prescribing any therapy, including a BTKi; local guidelines should also be followed.[66] Further details on the tests for baseline cardiovascular assessment and monitoring specifically during BTKi therapy are shown in Figure 6. Notably, the risks of cardiovascular events, what symptoms to look out for, and what the patient is expected to do should be clearly explained to the patient and their care partner.

RENAL ASSESSMENT

Renal function decreases with age, making renal impairment common in older patients who may also be diagnosed with CLL.[67] Renal impairment occurs in 24% of patients with newly diagnosed CLL and is associated with significantly shorter survival than patients without kidney disease.[67] The mechanism of renal impairment can be due to aging, but the CLL infiltrate can rarely compress the renal tubules and microvasculature, resulting in intrarenal obstruction and ischemia.[67,68] Other causes of renal impairment include glomerular diseases, electrolyte disorders, and extrarenal obstruction.[69] It is therefore important

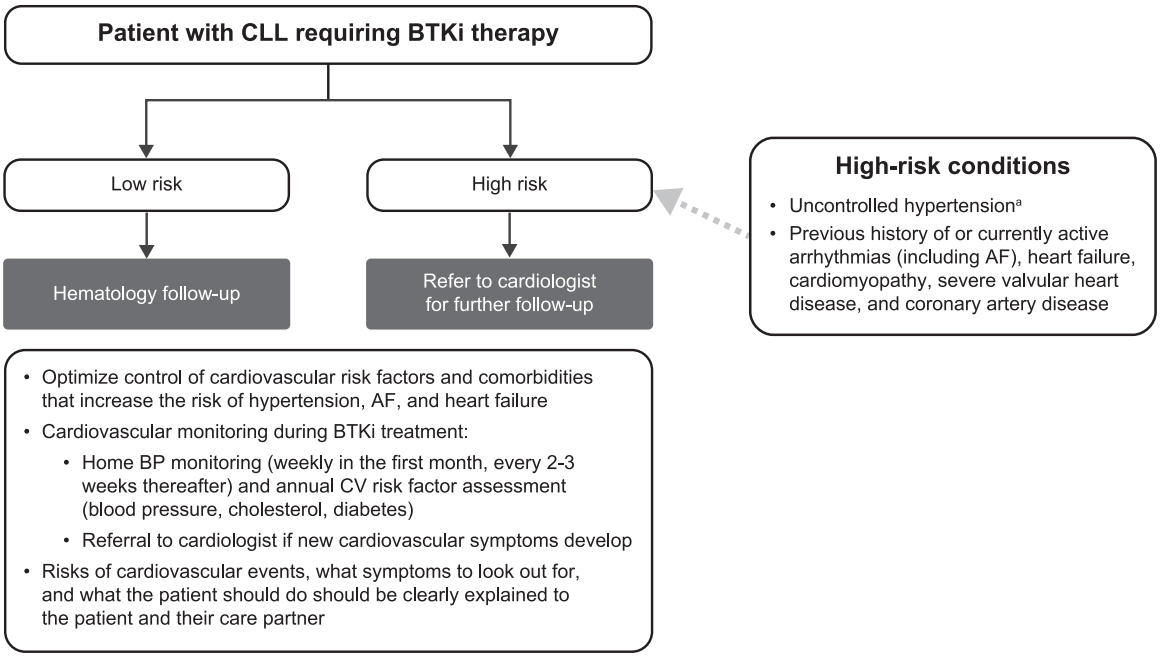

FIGURE 5 **Recommended workup and monitoring before and during Bruton's tyrosine kinase inhibitor (BTKi) therapy.** [a]Blood pressure should be controlled before initiating a BTKi (<160/100 mmHg) and during BTKi treatment; closer cardiovascular surveillance is required for patients with coronary artery disease. AF, atrial fibrillation; BP, blood pressure; CLL, chronic lymphocytic leukemia; CV, cardiovascular.

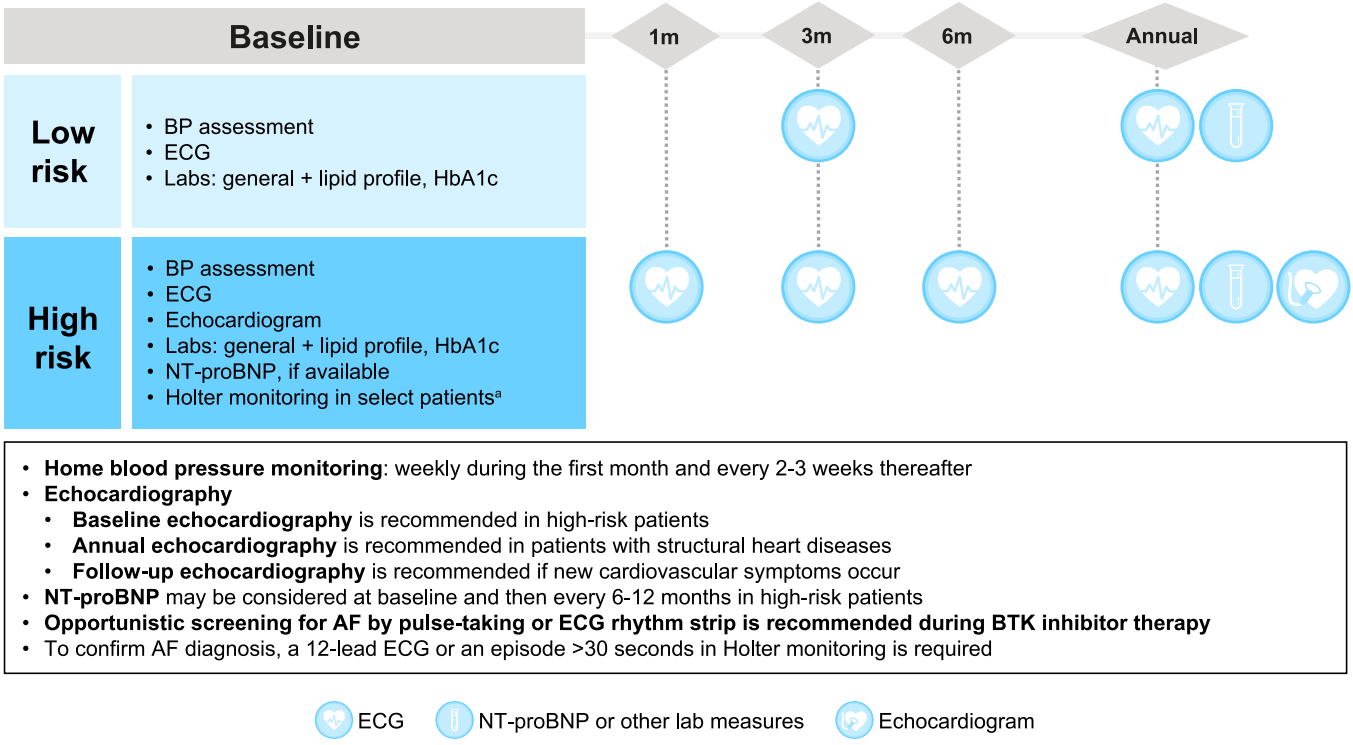

FIGURE 6 **Specific tests for cardiovascular assessment and monitoring during Bruton's tyrosine kinase inhibitor (BTKi) therapy.** [a]Patients with symptoms suggesting atrial fibrillation (AF) not documented by electrocardiogram (ECG). The suggestions provided are aligned with the European Society of Cardiology recommendations for patients receiving BTKi therapy.[40] BP, blood pressure; HbA1c, glycated hemoglobin; m, month; NT-proBNP, B-type natriuretic peptide.

to assess patients to determine any renal impairment before starting treatment with novel targeted therapies. Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the management of chronic kidney disease recommend referral to specialist kidney care services for patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1.73 m^2).[70] The prescribing information for each drug should also be consulted for any treatment recommendations based on renal impairment.

RISK OF INFECTION

Patients with CLL are particularly vulnerable to infections as a result of a dysregulated immune system and may have had an increased risk of infections for several years before diagnosis.[71,72] It is therefore important to assess the patient's infection history before starting treatment with novel targeted therapies, although there are limited guidelines on infection risk assessment that can be used easily in clinical practice.[73,74] From the information available, the patient's medical history, assessment of risk factors for developing secondary antibody deficiency, and assessment of serum IgG levels and antibody levels should be reviewed regularly in order to assess the risk of infections and treat them effectively.[74,75] German CLL guidelines also recommend careful monitoring of chronic or recurrent bronchitis together with intensive treatment.[76]

Hypogammaglobulinemia is an inherent immune defect in patients with CLL that may contribute to their infection risk.[77,78] Accordingly, current guidelines recommend routine IgG testing for patients with CLL.[77] However, guidelines vary on how and when immunoglobulin replacement therapy (IgRT) should be given to patients. Current guidelines either recommend evaluating IgG levels in patients with infections requiring hospitalization or intravenous antibiotics and treating with monthly immunoglobulin (IgRT) if IgG levels are <500 mg/dL or treating patients with severe or recurrent infections with IgRT if IgG is <400 mg/dL.[77] Recurrent infections are specific to the organ/system affected and are typically defined as infections that occur repeatedly over a defined period of time, for example, at least three events per year.[79]

All patients should be informed about their immune status and how they can live their lives despite being immunocompromised. Importantly, there is a general lack of awareness surrounding the immune-related challenges specific to patients with CLL and of information on how patients should manage being immunocompromised.[74] As living with the risk of infection can be debilitating to patients and affect their everyday lives, patients should be encouraged to receive all relevant vaccinations,[74] with the exception of live vaccines.[76] For patients undergoing treatment for CLL, vaccination responsiveness is reduced.[80] The overall immune response to vaccination varies depending on disease stage, type of CLL-directed treatment, vaccine type, and schedule. Recommended routine vaccinations include those for influenza, COVID-19, pneumococcal disease, herpes zoster, respiratory syncytial virus, tetanus, and hepatitis B.[80]

The risk of infections is high with chemotherapy. Infections continue to be a significant cause of morbidity and/or discontinuations with novel therapies and can lead to death if not adequately treated.[81] Infection is still, therefore, an important adverse event in CLL to monitor, reduce the risk of, and treat appropriately and promptly.

OTHER CONSIDERATIONS

Tumor lysis syndrome

Tumor lysis syndrome (TLS) occurs with cytotoxic chemotherapy, anti-CD20 monoclonal antibodies, and novel targeted agents such as venetoclax.[55,82,83] TLS is life-threatening if untreated and can lead to renal failure, arrhythmias, and death.[83] Patients with high tumor burden (any lymph node with a diameter of ≥5 cm or a high absolute lymphocyte count (ALC) of >25 × 10^9/L) are at higher risk of TLS when starting venetoclax treatment.[55] Impaired renal function (CrCl <80 mL/min) and concomitant medications such as CYP3A4 inhibitors further increase the risk of TLS in patients treated with venetoclax.[55,84] Prophylactic measures to prevent TLS include adequate oral and intravenous hydration to promote excretion of uric acid and phosphate and monitoring for laboratory signs of TLS (hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia) during the ramp-up phase.[55,82] Hospitalization to ensure sufficient intravenous hydration and TLS monitoring is recommended for patients with a high risk of TLS (any lymph node ≥10 cm or any lymph node ≥5 cm and ALC ≥25 × 10^9/L).[55] Given that laboratory-confirmed TLS associated with obinutuzumab was reported in some patients before venetoclax treatment in the CLL14 study of fixed-duration venetoclax–obinutuzumab,[85] monitoring for laboratory signs of TLS is recommended after the first infusion of obinutuzumab, particularly in patients with bulky disease.[55,82,85] Referral to a nephrologist is recommended for patients who are at high risk of TLS before starting treatment, particularly those with a CrCL of <80 mL/min.[69]

Infusion-related reactions

Anti-CD20 monoclonal antibodies, including obinutuzumab, are associated with a risk of infusion-related reactions, which occur within hours of infusion initiation due to cytokine release and inflammation.[86] Common symptoms include flushing, chills, rash, hypotension, tachycardia, and dyspnea, which might be of particular concern in individuals with lower resilience, including pre-existing cardiovascular comorbidities.[86,87] The patient should be monitored during the infusion, and healthcare providers should be prepared to act promptly according to institutional procedures and the drug's prescribing information.[87] Premedication is recommended but varies according to the drug used; premedication treatment includes corticosteroids (e.g., dexamethasone), antihistamines (e.g., diphenhydramine), and antipyretics (e.g., acetaminophen).[87] Depending on the severity of the infusion-related reaction and symptoms identified, treatment should be stopped or the infusion slowed down.

PATIENT PERSPECTIVE

Patients need to be aware of the benefits, risks, and potential impact on their ability to make decisions independently and on their quality of life that are associated with the treatment options available; currently, only 43% of patients report that they are given clear information on the side effects of treatment.[39] Patients should therefore be actively involved in treatment decisions, with clinicians offering treatment choices and making sure that the patients understand the implications of each treatment. The patient's support system is another important consideration and is a key factor for medication adherence and monitoring, particularly in patients with some degree of cognitive impairment. The patient's support system may also benefit patients who live further away from the hospital or who live rurally. Importantly, the lack of social support can be addressed and should not limit patient treatment.

JR, patient advocate: in 2011, at the age of 39, I was diagnosed with CLL. Fortunately, I had the opportunity to take part in a clinical trial in the United Kingdom for a novel BTKi in 2014. Initially, as a younger patient with CLL, mortality was my biggest fear, and my aim was getting my children through to the next phases of their lives,

looking only at the next 5 years. However, that phase has moved on, and I am still receiving a BTKi in frontline treatment. While mortality from the CLL itself, or from infection, other malignancy, or some other adverse event, is still a major concern, I now hope to have a normal life expectancy. There are a few key points that I want to highlight from my perspective as a patient and from my discussions with other patients. I believe that all patients with CLL want to understand their treatment options when they are discussed with them. They should therefore be included in conversations with their healthcare providers as part of what I term "Better decision-making at all treatment crossroads of the patient pathway." "Fitness" is a vague term, and given that patients with CLL feel so unwell before diagnosis, they may not be able to consider themselves in any way "fit." Fitness should therefore be explained to the patient as "suitability for treatment," "fitness for treatment," or "medical fitness" at the start of their patient pathway. Although fewer patients are dying from this disease today, adverse events will always be a concern. Accordingly, healthcare providers need to educate us on the symptoms of possible adverse events that we need to look out for during treatment and what to do if we are experiencing them. In particular, information on how to reduce the risk of infection is very important to us.[39] With higher tolerability of novel therapies versus chemoimmunotherapy, a patient's age should not be a barrier to them receiving the best possible treatment. Finally, healthcare providers should be aware that most patients are considering their next treatment well before they need it. Although most patients (~70%) generally prefer oral therapies,[39] most would prefer a shorter treatment duration with fixed-duration therapy.[88] Personally, I would consider fixed-duration treatment if it were available, but I would have to consider the impact of potentially increased adverse events and hospitalization, even for a limited time, as I would need to take into account the potential disruption to my life and ability to work versus the therapeutic benefit. Ultimately, in the era of new treatments that allow patients to live with a chronic cancer such as CLL with a near-normal life expectancy,[89] I believe that as treatment decision-making evolves, the patients should remain at the center of all treatment decisions.

SUMMARY

Redefining fitness to be relevant to current personalized, targeted therapies is a necessity for the treatment of CLL. A patient's fitness assessment before and during treatment is recommended to be based on a comprehensive assessment tailored to individual patient needs. It should consider core clinical, psychological, and social parameters as well as additional cardiovascular, renal, and geriatric assessments as needed. The goal is to design a tailored oncological and non-oncological (nutrition counseling, etc.) treatment for an individual patient, not only to a specific disease, with more individualized management so that the patient can continue treatment and achieve maximal benefit. Suggestions include the usual initial clinical core assessments by the hematologist, including an assessment of the patient's concomitant medications, reducing or removing medications according to whether they may impact CLL treatment, and an initial consideration of whether the patient may be at high risk in terms of lower resilience with a cardiovascular history. Based on these initial assessments, referral to a cardiologist may be required for patients who could be at high risk for cardiovascular comorbidities. Also, referral to a geriatrician may be required based on the initial screening for lower resilience. Treatment options can then be discussed with the patient and their care partner, and may include consideration of life expectancy, potential adverse events, duration of therapy, and patient preference. It is very important that the patient and their care partner should be at the center of the decision-making process and be provided with all the necessary information on treatment options.

Age is clearly a less important factor when determining fitness for BTKi therapy than other factors, such as cardiovascular fitness evaluated by cardiovascular assessment and geriatric assessment assessing polypharmacy, functional status, psychological status, and social support. Notably, most patients are suitable for treatment with novel therapies, including BTKis. It is important to note that the expert opinions described are for best practice; physicians should always follow local guidelines and, importantly, lack of access to any of the recommended assessments should not prevent treatment in any patient. Older patients are often excluded from clinical studies, so taking care to understand their comorbidities and preferences ensures optimal individualized treatment for these patients. This also highlights the need for more trials in this older patient population. As the treatment landscape evolves for CLL, it is important that the assessments and patient selection for each treatment also evolve to ensure optimal outcomes for all patients, regardless of their chronological age.

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Raúl Córdoba: Conceptualization; writing—review and editing; writing—original draft. **Stephan Stilgenbauer**: Conceptualization; writing—review and editing; writing—original draft. **Paolo Ghia**: Conceptualization; writing—original draft; writing—review and editing. **Alessandra Tedeschi**: Conceptualization; writing—original draft; writing—review and editing. **Lindsey Roeker**: Conceptualization; writing—original draft; writing—review and editing. **Myriam Rodriguez-Couso**: Conceptualization; writing—original draft; writing—review and editing. **Stephen P. Mulligan**: Conceptualization; writing—original draft; writing—review and editing. **Samir Kanaan Nabhan**: Conceptualization; writing—original draft; writing—review and editing. **Jan Rynne**: Conceptualization; writing—original draft; writing—review and editing. **Teresa López-Fernández**: Conceptualization; writing—original draft; writing—review and editing.

CLINICAL TRIAL REGISTRATION

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Raúl Córdoba: speaker bureau and consultancy for AbbVie, AstraZeneca, BeiGene, Gilead Sciences, Johnson & Johnson, Lilly, and Roche; advisory role for Genmab and Regeneron. Stephan Stilgenbauer: consultant, advisor, and/or speaker for AbbVie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Galapagos, Gilead Sciences, GSK, Hoffmann-La Roche, Johnson & Johnson, Lilly, Novartis, and Sunesis. Paolo Ghia: research funding and honoraria from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Johnson & Johnson, Lilly/Loxo Oncology, and MSD; honoraria from Galapagos and Roche. Alessandra Tedeschi: member of advisory board and speakers bureau for AbbVie, AstraZeneca, BeiGene, Johnson & Johnson, and Lilly. Lindsey Roeker: consultant for AbbVie, Ascentage, AstraZeneca, BeiGene, Johnson & Johnson, Loxo Oncology, Pharmacyclics, Pfizer, and TG Therapeutics; member of a data safety monitoring committee (DSMC) for Ascentage; CME speaker for DAVA, Curio, Medscape, and PeerView; holds minority ownership interest in Abbott Laboratories; travel support from Loxo Oncology; research funding (paid to the institution) from Adaptive

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