short review

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Too frail or not too frail? Prognosis and treatment options in older CLL patients

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Summary Chronic lymphocytic leukemia (CLL) is a disease that primarily affects older patients, with a median age at diagnosis of 72 years. Older patients, in this review defined as 80 years or older, comprise about 20% of patients with CLL yet remain underrepresented in clinical trials. Available results indicate that with advancing age, treatment efficacy decreases with regard to progression-free survival, mostly due to an impaired tolerability, i.e., higher frequency and severity of adverse events, leading to weaker treatment adherence. This underscores the fact that even with the advent of novel agents, older patients remain a distinct patient group for which results from younger patients cannot reliably be superimposed. Older patients not only exhibit higher rates of comorbidities, especially of cardiovascular nature, but also more often show features of a symptom complex, associated with impaired physiological reserve to stressors and termed "frailty." Frailty itself has an overlap with symptoms of hematological diseases but was shown to independently impact survival in hematological malignancies. Data on treatment in this at-risk patient group are scarce. Initial results from prospective clinical trials, such as the CLL-Frail trial by the German CLL Study Group or retrospective analyses of venetoclax + obinutuzumab treatment, show that targeted treatment is highly effective in this age group and might overcome fitness impairments. However, shared decision-making remains vital so as to always align these treatment prospects with individual patient-specific outlooks and goals.

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Introduction

Chronic lymphocytic leukemia (CLL), the most common leukemia in the Western world, predominantly affects older adults, with a median diagnosis age of 72 years [1]. Treatment for CLL underwent a paradigm shift over the past decade with the introduction of targeted agents. Chemoimmunotherapeutic approaches such as fludarabine + cyclophosphamide + rituximab (FCR), bendamustine + rituximab (BR), or chlorambucil + obinutuzumab (ClbO) have been almost completely replaced in current guidelines by novel, oral agents such as Bruton's tyrosine kinase (BTK) inhibitors and BCL2-directed therapies such as venetoclax in combination with a CD20 antibody or a BTKi [2, 3]. While earlier guidelines distinguished patients not only by disease-specific risk based on genetic and biological risk profiles, but also by the fitness and/or age of the patients [4], the tolerability of targeted therapies has surpassed these boundaries and recommendations focus instead on patient-specific comorbidities or vulnerabilities such as renal function impairment as a relative contraindication for venetoclax-based therapies and cardiac comorbidities as a possible reason to avoid BTKi-based therapies [3]. Notably, frail patients are considered candidates for best supportive care rather than disease-directed therapy in these guidelines; however, there is currently no consensus on determining frailty.

The basis for this broad eligibility stems from trials showing the superiority of targeted agents that were specifically aimed at "elderly" or "unfit" patients. Ibrutinib, for example, was first approved as a frontline therapy based partly on the results of the RESONATE-2 trial, in which a progression-free survival (PFS) ad-

Table 1 Selected first-line, randomized phase 3 trials aimed at older or unfit patients with CLL

Trial	Number of patients	Median age (range)	Treatment comparisons	Main inclusion criteria	Primary endpoint (PFS)
RESONATE-2 [30]	269	73 (65–89)	Ibrutinib vs. chlorambucil	Age ≥ 65	HR: 0.16; 95% CI: 0.09–0.28; $p < 0.001$
CLL14 [11]	432	72 (64–85)	Venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab	Coexisting conditions (CIRS > 6 or CrCl < 70 mL/min)	HR: 0.31; 95% CI: 0.22–0.44; $p < 0.0001$
ELEVATE-TN [7]	535	70 (41–89)	Acalabrutinib ± obinutuzumab vs. chlorambucil + obinutuzumab	Age ≥ 65 or CIRS > 6 or CrCl 30–69 mL/min	HR: 0.10; 95% CI: 0.06–0.17; $p < 0.0001$
SEQUOIA [8]	479	70 (38–86)	Zanubrutinib vs. bendamustine + rituximab	Age ≥ 65 or CIRS > 6 or CrCl 30–69 mL/min	HR: 0·42; 95% CI: 0.28–0.63; $p < 0·0001$
GLOW [12]	211	71 (49–86)	Ibrutinib + venetoclax vs. chlorambucil + obinutuzumab	Age ≥ 65 or CIRS > 6 or CrCl 30–69 mL/min	HR: 0.216; 95% CI: 0.131–0.357; $p < 0.001$
Alliance A041202 [6]	547	71 (65–89)	Ibrutinib ± rituximab vs. bendamustine + rituximab	Age ≥ 65	HR: 0.36; 95% CI: 0.26–0.50; $p < 0.001$
Alliance A041702 [14]	454	74	Ibrutinib + obinutuzumab vs. ibrutinib + venetoclax + obinutuzumab	Age ≥ 70	HR: 1.20; 95% CI: 0.73–1.97[a]

CI confidence interval, *HR* hazard ratio, *CrCl* creatinine clearance, *CIRS* Cumulative Illness Rating Scale score
[a]Results of an interim analysis, performed after reaching a pre-specified number of events and published due to crossing of the futility threshold

vantage over ClbO was shown, with a 7-year PFS rate of 59% for ibrutinib vs. 9% for chlorambucil and a significant improvement in overall survival with a hazard ratio (HR) of 0.453 (95% CI: 0.276 vs. 0.743; [5]). These results were confirmed in the Alliance A041202 trial comparing ibrutinib + rituximab vs. bendamustine + rituximab; the results are presented in Table 1; [6]. Second-generation BTKi such as acalabrutinib and zanubrutinib were also superior to chlorambucil-based therapies in unfit patients [7, 8]. Importantly, they were recently shown to be at least equally effective in a head-to-head comparison with ibrutinib in relapse settings but had an improved side-effect profile, with especially reduced rates of cardiovascular toxicities such as atrial fibrillation or hypertension [9, 10].

Likewise, the CLL14 trial, the basis of the approval of venetoclax + obinutuzumab (VenO) for patients with preexisting conditions, was able to show a PFS improvement with an HR of 0.4 (95% CI: 0.31–0.52; $p < 0.0001$) compared to ClbO in the recently published 6-year follow-up [11].

The combination of BCL2 and BTK-directed therapies was also shown to be effective in the GLOW trial, aimed at older (< 65) or unfit patients (Cumulative Illness Rating Scale [CIRS] > 6/creatinine clearance < 70 mL/min) with an HR of 0.21 (95% CI: 0.14–0.33; $p < 0.0001$) compared to ClbO [12].

Finally, the concept of combining all treatment modalities to allow for a time-limited but highly effective treatment as recently shown in the CLL13/GAIA trial [13] was also implored in the Alliance-A041702 trial comparing ibrutinib + venetoclax + obinutuzumab vs. ibrutinib + obinutuzumab in patients aged 70 or older. Due to an increase in COVID-19 deaths in the triple-combination arm, however, the triple combination was inferior to ibrutinib + obinutuzumab with an HR of 1.2 (95% CI: 0.73–1.97) in the PFS analyses [14].

Although primarily aimed at patients with advanced age or impaired fitness based on CIRS score or renal function, the aforementioned trials reported median ages of around 71, and did not (yet) report subgroup analyses of older patients (i.e., aged 80 years or older). Additionally, clinical trials often exclude patients with investigator-assessed performance scores < 70% for Karnofsky scales or > 1 for ECOG, further limiting their applicability on older patients, some of whom are, e.g., dependent on wheelchairs or walkers.

Old, older, very old—does it matter?

While the mode of action of targeted agents is independent of the patient's age, data indicate that with increased age and fitness of the patient, efficacy is reduced, presumably due to impaired efficacy and thus treatment adherence [15].

Patients over the age of 80 make up 20% of patients diagnosed with CLL but comprise only about 5% of patients in clinical trials [16], indicating that even trials aimed at older and unfit patients tend to exclude patients over the age of 80 even though they tend to have different disease trajectories than their younger counterparts.

With advanced age, patients have higher rates and severity of comorbidities, which in turn have an impact on treatment tolerability and even overall survival [17–19], irrespective of the chronological age of patients. Additionally, frailty—a symptom complex characterized by diminished physiological reserve and in-

creased vulnerability to stressors—has a higher prevalence with increasing age but can also manifest in younger patients.

Frailty is a geriatric syndrome affecting approximately 7–12% of older adults [20]. It manifests as a state of increased vulnerability across multiple health domains, leading to adverse outcomes such as falls, disability, and hospitalizations and is associated with impaired overall survival in hematological diseases [21]. Symptoms include generalized weakness, exhaustion, slow gait, poor balance, decreased physical activity, cognitive impairment, and weight loss. Importantly, frailty is not reliably captured through current physician-employed fitness estimates such as the Karnofsky or ECOG performance scores [22], where patients might appear "fit on paper."

Thus, chronological age alone is an inadequate measure of a patient's overall health status. Biological age, encompassing factors such as comorbidities, functional capacity, and physiological resilience, often diverges from chronological age. This discrepancy is particularly evident in older CLL patients, where a close interplay between hematologic disease and comorbidities as well as an impact on frailty can be seen.

Current guidelines recommend frailty or geriatric assessment prior to treatment initiation in older patients at risk. While comprehensive geriatric assessment and determination of frailty are logistically and operationally challenging, simplified models such as the Clinical Frailty Scale (CFS; [23]), the G8 assessment tool [24], or the FRAIL [25] scale allow for a swifter assessment and still provide insight into the patients' current health status, albeit large-scale analyses on their implementation in hematological disorders or specifically CLL are lacking.

Available data on older and frail patients

As prospective data are scarce, historical and real-world data provide valuable insights into the efficacy and tolerability of targeted therapies in older patients with CLL. An analysis by Michallet et al. [26] reported a response rate of 69% in older, predominantly relapsed patients treated with ibrutinib, while data from the GCLLSG demonstrated an overall response rate (ORR) of 73% in patients aged 80 or older receiving frontline targeted therapy [16]. Although targeted agents have significantly improved CLL treatment outcomes, their effectiveness in older or frail patients is often compromised by reduced tolerability and a higher rate of early treatment discontinuation. Michallet et al. observed that 32% of patients discontinued therapy prematurely, with only 5.6% of cases attributed to CLL progression. Similarly, a real-world analysis of venetoclax in 342 CLL patients older than 75 found that 42% of patients discontinued treatment early, further highlighting the challenges associated with maintaining long-term therapy in this population [27].

The impact of geriatric impairments as indicators of frailty was evaluated in a retrospective analysis of the phase 2 HOVON139 trial, which tested venetoclax + obinutuzumab vs. FCR in 67 unfit patients. Van der Straten et al. were able to show that patients with geriatric impairments had an increased rate of adverse events and treatment discontinuation [28]. Nonetheless, treatment with venetoclax + obinutuzumab led to an improvement in the fitness status of more than half of the included patients, underscoring the potential positive impact of targeted treatment on frailty.

The only prospective trial aimed at this patient population so far is the CLL-Frail trial by the German CLL Study Group (GCLLSG), which evaluated acalabrutinib monotherapy in patients with CLL and a maximum of one previous therapy [29]. A total of 53 patients were included, and a median age of 81 years was reported with about 50% of patients exhibiting frailty according to self-assessment. Notably, frail patients were younger and had better renal function, indicating that these measures are not sufficient to capture true patient fitness.

With an ORR of 93.5% in patients receiving therapy for at least 3 months, a 1-year overall survival rate of 91% in the intention-to-treat population and an improvement in the frailty status in 50% of patients, acalabrutinib was shown to be highly effective in this age and fitness group. The safety data were reassuring, with no severe bleeding events and two cases of atrial fibrillation. However, about 60% of patients experienced grade 3 or higher adverse events and a third of patients discontinued treatment prematurely, and thus a thorough risk–benefit assessment and shared decision-making remain crucial.

Conclusion

By acknowledging that biological age does not always align with chronological age, and by focusing on individualized treatment plans that consider frailty, healthcare providers can improve outcomes and quality of life for this vulnerable population. The promising results from trials aimed at this patient population highlight the potential for targeted therapies to not only extend survival but also enhance the overall well-being of older CLL patients. Onkopedia guidelines, an important resource offered by the German-speaking hematological societies DGHO, OEGHO, and SGMO/SGH, recommend different treatments based on genetic risk profiling of the disease but underline the importance of patient-specific considerations such as comorbidities or personal preference when choosing the right agent [3]. However, frail patients remain a distinct subgroup for which currently only best supportive care is recommended. As shown in this review, frailty is often impacted by the underlying hematological disease and might improve through

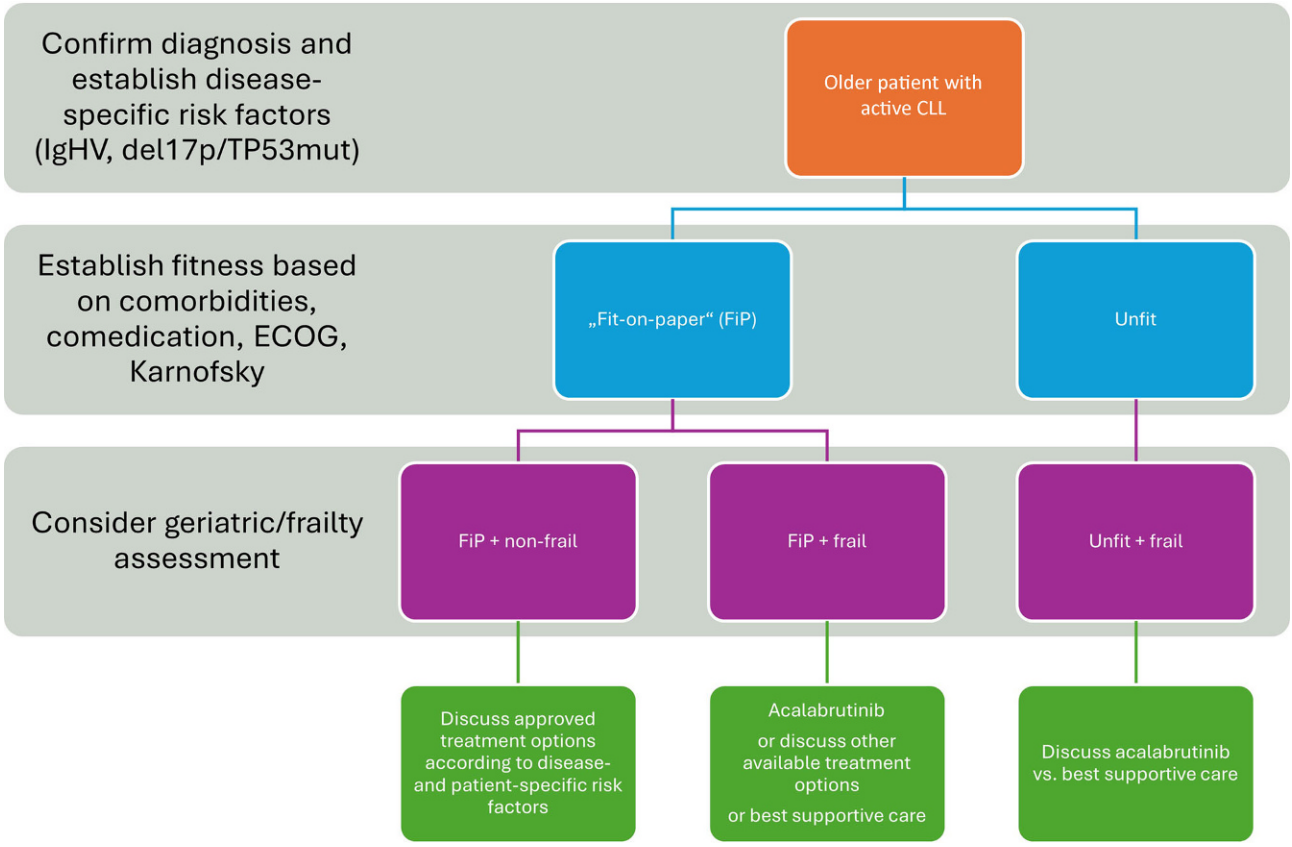

Fig. 1 Assessment and treatment approach for older patients with chronic lymphocytic leukemia (*CLL*). "Fit-on-paper" (*FiP*): includes the subgroup of older patients with CIRS scores ≤ 6, creatinine clearance > 60 mL/min, and ECOG < 3/Karnofsky > 60%. These should be assessed in combination by the treating physician rather than serving as cut-offs based on one specific value

treatment of CLL. A possible treatment algorithm incorporating these data to offer older patients a specific treatment is provided in Fig. 1.

Incorporating geriatric assessments into clinical practice is necessary for identifying frailty and can assist in guiding treatment decisions, to align with the patient-specific risk profile but also their own predefined goals of care. As the population ages, such personalized approaches will become increasingly important in managing CLL and other malignancies in older adults. Future studies should build on these findings to refine treatment approaches and ensure that frail and very old patients receive the best possible care.

Future directions

Given the aging population and the growing recognition of frailty as a critical factor in treatment decision-making, future research should focus on:

- Conducting further, ideally randomized, trials specifically designed for frail and very old CLL patients.
- Evaluating the impact of targeted therapies on functional independence, longitudinal fitness assessments, and quality of life in older and frail patients.
- Developing predictive models to guide treatment selection based on frailty status and comorbidities.

Take-home message

Older patients with CLL remain an at-risk patient cohort, due to higher rates of comorbidities, frailty, and an underrepresentation in clinical trials, leading to insufficient data to guide treatment decisions. The first prospective results indicate that targeted treatments exhibit remarkable efficacy and can improve patient-centered outcomes.

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