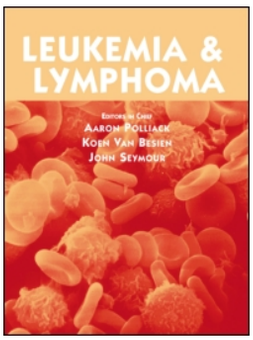

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REVIEW

Changing landscape of frontline therapy in chronic lymphocytic leukemia

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ABSTRACT

The therapeutic landscape for chronic lymphocytic leukemia has significantly evolved in recent years as our understanding of the biology of this disease has advanced. Chemoimmunotherapy has been the standard frontline treatment for patients of all age groups with chronic lymphocytic leukemia over the last decade. B-cell receptor signaling pathway plays a central role in the pathogenesis of chronic lymphocytic leukemia. The advent of novel small-molecule therapy for the treatment of chronic lymphocytic leukemia targeting the B-cell receptor signaling pathway has dramatically changed the therapeutic landscape with recent studies establishing ibrutinib, a Bruton's tyrosine kinase inhibitor, as the frontline treatment of choice regardless of patient's age, performance status or risk-category. Although these current advances along with the approval of other newer agents for the treatment of chronic lymphocytic leukemia is a significant step forward, newer challenges have emerged on how to best utilize these new treatment options.

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia seen in the Western population with approximately 20,720 new cases estimated to be diagnosed in 2019 [1]. CLL is characterized by progressive monoclonal expansion of mature-appearing neoplastic B lymphocytes with a distinct immune phenotype characterized by expression of B cell markers, such as CD19 and CD20, together with CD5 and CD23, which are not usually expressed on nonmalignant B cells, and the resultant accumulation of these functionally incompetent cells in the peripheral blood, bone marrow and lymphoid tissues [2].

The therapeutic landscape for CLL has significantly evolved in recent years. Chlorambucil, the historical standard frontline treatment, was replaced with combination chemotherapy in the 1990s and, recently, with more effective chemoimmunotherapy (CIT) regimens, which combine standard chemotherapy with anti-CD20 monoclonal antibodies (rituximab, obinutuzumab, and ofatumumab). In parallel, our understanding of the biology and pathogenesis of this disease has advanced significantly, leading to the development of novel agents. Targeted therapy directed against Bruton's tyrosine kinase (BTK) with the oral small-molecule inhibitor ibrutinib and B-cell lymphoma 2 (BCL-2) with venetoclax have revolutionized the frontline treatment algorithm for CLL [3]. Here we review the current therapeutic landscape for frontline treatment of CLL. PubMed database and Google Scholar were utilized for literature search using keywords: 'CLL', 'Targeted therapy' and 'Frontline Treatment.'

Chemoimmunotherapy era

In the 1980s and 1990s, the activity of different chemotherapy agents, such as alkylating agents like chlorambucil and cyclophosphamide, and purine analogs like fludarabine, was noted in patients with CLL [4–7]. Chlorambucil, the first agent to demonstrate activity in CLL, mainly relieved symptoms in many patients without any significant impact on survival [8]. Subsequent randomized trials showed that single-agent fludarabine was superior to chlorambucil [9] with improved median OS with fludarabine [10] and that the combination of fludarabine plus cyclophosphamide was superior to single-agent fludarabine [6,7] or chlorambucil [6] with improvement in overall response rate (ORR) and progression-free survival (PFS) as compared to single-agent therapy.

With the introduction of rituximab in the late 1990s, large phase II and III trials were conducted to determine the efficacy of CIT as compared with chemotherapy

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alone [11,12]. In a single-institution phase II trial of 300 patients, unprecedented results were seen with the fludarabine, cyclophosphamide plus rituximab (FCR) regimen leading to an ORR of 95% with a complete response (CR) rate of 72% [13]. The high efficacy of this regimen was confirmed in the pivotal international phase III German CLL Study Group (GCLLSG) CLL8 trial, in which 817 treatment-naïve (TN), physically fit patients were randomly assigned to receive 6 courses of either FCR or fludarabine and cyclophosphamide (FC); both objective response rate (90% vs. 80%) and CR rate (44% vs. 22%) were superior with FCR; the FCR regimen led to longer PFS (56.8 months vs. 32.8 months) and improved overall survival (OS) (not reached vs. 86 months), which was statistically significant in patients younger than 65 years of age [12].

The survival benefits of FCR vs. FC were further confirmed in updated study results showing a 5-year OS of 80.9% vs. 69.2%, respectively [13]. On multivariate analysis, the presence of TP53 mutations, del17p and unmutated immunoglobulin heavy-chain variable region gene (IGHV) had a negative prognostic impact on PFS and OS. Patients with mutated IGHV had a significantly longer median PFS with FCR as compared with FC (PFS, median not reached vs. 41.9 months) [13].

Long-term follow-up data from the original FCR phase II trial of 300 patients from M.D. Anderson Cancer Center also showed IGHV mutation as a strong predictor of long-term PFS. In this original cohort of 300 patients, 53.9% with mutated IGHV were still in remission at 12.8 years and no relapses were seen amongst 42 patients (14%) beyond 10.4 years follow-up, suggesting a plateau for IGHV mutated patients after 10 years, with the possibility of these patients being cured of CLL [14]. Thus, for patients with mutated IGHV, FCR remains an attractive option given long-term disease remission [15].

However, the tolerability of fludarabine-based CIT is limited. Toxicities are frequently seen including infections, myelosuppression and prolonged neutropenia [12,13]. Also, up to 5% of patients may develop therapy-related myelodysplastic syndrome/acute myeloid leukemia with FCR [16]. An alternate CIT, Bendamustine plus rituximab (BR) has also shown promising results as first-line treatment in patients with CLL. In a phase II trial (CLL2M study) of BR, ORR of 88% in TN patients was seen, with a median PFS of 33.9 months and OS of 90.5% at 27 months [17]. Twenty-six percent of patients were older than 70 years of age and these results held for this subgroup as well.

In the GCLLSG CLL10 trial, comparing BR with FCR, 561 TN, physically fit patients without del17p were randomly assigned to FCR or BR [18]. The PFS was significantly longer with FCR (57.6 months vs. 42.3 months) [19]. There was no difference in OS. Patients in the FCR group were less likely to complete the planned six cycles of treatment and they had more myelosuppression with severe neutropenia and infectious complications (39% vs. 25%). In patients older than 65 years of age (35% of enrolled patients), the PFS for the two regimens was similar, and BR was better tolerated. FCR was less well tolerated with greater incidences of neutropenia, infections and secondary neoplasms, especially in the older patient population ($\geq$65 years) [18]. Thus, CLL10 trial established the superiority of FCR as the treatment of choice for younger, fit patients with CLL. For patients older than age 65 who are physically fit and appropriate for CIT, either FCR or BR could be considered, with most practitioners preferring BR given the toxicity profile.

As many patients with CLL are elderly or have comorbidities, they are not suitable candidate for CIT and instead had typically been treated with low-intensity therapy with either single-agent alkylator such as chlorambucil [9], an anti- CD20 monoclonal antibody (such as rituximab) [20], or combinations thereof [21] with the goal to control or relieve symptoms related to CLL and ameliorate anemia and/or thrombocytopenia.

In older patients or in those not considered suitable candidates for fludarabine-based CIT, the addition of anti-CD20 antibodies such as rituximab, obinutuzumab or ofatumumab, in combination with chlorambucil, has shown better responses as compared to single-agent therapy with chlorambucil [21,22].

To improve outcomes in this frail population, the pivotal phase III CLL11 study combined obinutuzumab with chlorambucil and compared it with single-agent chlorambucil and chlorambucil plus rituximab. The final analysis of this study confirmed the superiority of obinutuzumab plus chlorambucil over rituximab plus chlorambucil as well as single-agent chlorambucil. At a median of 59.4 months, median PFS was 29.9 months in the obinutuzumab plus chlorambucil arm and 15.7 months in the rituximab plus chlorambucil arm, with the median time to next treatment also favoring the obinutuzumab plus chlorambucil arm (56.4 months vs. 34.9 months) [21]. The combination of obinutuzumab with chlorambucil significantly improved OS as compared to the rituximab plus chlorambucil combination (not reached vs. 73.1 months).

Similarly, another anti-CD-20 monoclonal antibody Ofatumumab was studied in frontline setting in patients not eligible for fludarabine-based therapy due to advanced age or comorbidities. In this multicenter phase III study (COMPLEMENT 1) 447 TN patients were

randomized to receive chlorambucil plus ofatumumab vs. chlorambucil monotherapy [22]. After a median follow-up of 29 months, the median PFS was significantly longer for ofatumumab plus chlorambucil as compared with chlorambucil monotherapy (22 months vs. 13 months). The combination also led to significantly improved ORR (82% vs. 69%) and superior CR rate (12% vs. 1%) as compared to chlorambucil monotherapy [22].

BTK pathway

Our understanding of the biology of CLL has advanced significantly over the past 10 years. B-cell receptor (BCR) signaling pathway plays a central role in the pathogenesis of CLL and targeting of this pathway through inhibition of BTK has delayed and prevented the onset of disease in experimental models [23,24]. Structurally, the BCR- complex consists of a membrane immunoglobulin (IgM) non-covalently bound to a heterodimer composed of CD79a/CD79b. In normal B cells, ligand binding of the BCR results in a signaling cascade that leads to proliferation, apoptosis, or anergy, depending on the stage of development and antigen ligated [25]. In CLL cells, however, the BCR is dysregulated and constitutively activated resulting in the propagation of proliferative and pro-survival signals [26,27]. Hence, key components of the BCR signaling pathway such as BTK and phosphoinositide 3-kinase (PI3K) have attracted significant attention as potential therapeutic targets in CLL and other B-cell malignancies.

The BCR- pathway downstream target BTK is a member of the tyrosine-protein kinase (Tec) family of kinases and plays a critical role in BCR signal amplification. Mutation of the gene encoding BTK is responsible for X-linked agammaglobulinemia (XLA) [28,29], a genetic disorder in humans characterized by developmental arrest at the pre-B stage and profound humoral immune deficiency leading to increased susceptibility to infections at an early age [30]. Activation of BTK results in cell survival and proliferation through the mitogen-activated protein (MAP) kinase pathway, PI3K/Akt pathway, and nuclear factor kappa B (NF-κB).

In addition to its involvement in BCR signaling, BTK also interferes with the interaction of CLL cells with the microenvironment; playing a role in regulating the signaling and function of other cell-surface receptors, notably adhesion molecules (integrins) [31] and chemokine receptors [such as CXC chemokine receptor 4 (CXCR4) and CXCR5] [32], thus affecting B cell migration and tissue homing. Since BTK plays a key role in CLL signaling, this is an attractive therapeutic target.

Ibrutinib is the first in class, orally administered, irreversible BTK inhibitor that forms a covalent bond with a conserved cysteine residue (Cys481) in the active site of BTK [33]. BTK inhibition with ibrutinib causes apoptosis *in vitro*, and significantly inhibits B cell proliferation and signaling both *in vitro* and *in vivo* [30]. In the initial dose-escalation phase I study in various B cell malignancies, 15 patients with CLL were enrolled, objective response was observed in 9/15 patients and the treatment was well tolerated [34].

In an open-label phase Ib/2 trial of 31 TN elderly patients with high-risk features, ORR was 71% with a 13% CR rate [35]. The RESONATE-2/PCYC-1115 study established ibrutinib in the frontline setting for elderly (≥65 years) CLL patients without del17p [36]. This was a multicenter phase III study that randomized 269 patients to single-agent ibrutinib vs. chlorambucil. At a median follow-up of 29 months, significantly better ORR was seen with ibrutinib as compared to chlorambucil (92% vs. 36%) and at 24 months ibrutinib resulted in significantly longer PFS (89% vs. 34%) [37]. Recently presented updated results at 60 months of follow-up showed an OS advantage for ibrutinib; OS rates were 83% with ibrutinib as compared with 68% with chlorambucil; 57% of patients crossed over on progression to the ibrutinib arm [38]. Responses with ibrutinib deepened over time, with an increase over time from 11% at the primary analysis at the median follow-up of 18 months to 30% at 60 months of follow-up.

Long-term follow-up data from other ibrutinib studies (PCYC-1102 and -1103 studies) have also demonstrated continued efficacy and improved tolerability of single-agent ibrutinib at 5 years; the ORR in TN was 87% with CR rates improving over time [39]. Also, improved tolerability was observed with longer use, as treatment-limiting adverse events (AEs) decreased from years 1 to 5. We are continuing to gain real-world experience with ibrutinib. A multicenter, retrospective cohort study examined CLL patients treated with frontline ibrutinib at 20 centers across the country, including community and academic centers [40]. Patients were categorized based on key inclusion criteria for the RESONATE-2 trial; age <65 vs. ≥65 and present vs. absent del17p. Of 391 included patients, 57% would have been excluded from this pivotal study. Forty-one percent of these patients were <65 of age and 30% had del17p. Patients <65 years of age were more likely to start at the recommended dose of ibrutinib (420 mg daily); patients who started at reduced doses were noted to have inferior PFS. At 13.8 months median follow-up, 24% of patients discontinued ibrutinib; toxicity being the most common

reason for discontinuation, although progression and/or transformation accounted for a larger proportion of discontinuations in patients <65 years of age and those with del17p. While response rates were similar for patients <65 years of age and those with del17p, patients with del17p had inferior PFS and OS.

Even though ibrutinib produces durable responses in the majority of patients, some patients relapse with either Richter's transformation or progressive CLL [41,42]. These relapses on ibrutinib are usually due to acquired mutations in BTK affecting the binding site of ibrutinib rendering ibrutinib a transient reversible inhibitor with decreased BTK binding affinity. Mutations can also occur in PLCG2, the protein immediately downstream of BTK, which allows for persistent activation of the BCR signaling pathway despite inhibition of BTK [43]. Acquired mutations in BTK or PLCG2 were seen in 87% of patients who progress on ibrutinib. These mutations can be detected a median of 9.3 months before clinical relapse [44]. Ongoing studies are looking at preemptively targeting these clones with additional therapies to see if overt clinical relapse can be prevented (NCT03513562) [45].

Targeting BTK and bcl-2: new standards

As noted, fludarabine- and bendamustine-based treatments are associated with significant hematologic toxicity, and the risk of toxic effects increases with age. Cytopenias can be prolonged, lasting more than 3 months in 19% of patients treated with fludarabine-based CIT in particular.

Recent exciting results from the ongoing phase III ECOG-ACRIN E1912, Alliance A041202 and iLLUMINATE trials have confirmed the superiority of ibrutinib-based regimens over CIT in the frontline setting and have led to the emergence of a new standard of care [46–48].

The benefit of ibrutinib relative to standard CIT in fit patients was assessed head to head in the phase III National Clinical Trials Network (NCTN) studies ECOG-ACRIN E1912 and Alliance A041202 in younger and older patients, respectively.

In the Alliance A041202 trial, TN CLL patients 65 years of age or older were randomly assigned to 3 different treatment arms: BR, ibrutinib or ibrutinib plus rituximab (IR) [46]. The baseline characteristics of the patients in all 3 arms were typical of a population with untreated CLL; median age was 71 years, 67% were men. Fifty-four percent of patients had high-risk disease according to the modified Rai stage, 53% had *ZAP70*-unmethylated disease on central testing (with *ZAP70*-unmethylated disease status used as a surrogate for IGHV-unmutated disease status) and 27% had del17p or del11q on local FISH analysis. By central FISH analysis 6% had del17p, 19% had del11q, 22% had trisomy 12 and 36% had del13q. Twenty-nine percent of the patients had complex karyotype, defined as at least three unrelated cytogenetic abnormalities as assessed by central review [49] and 10% had a mutation in *TP53* with a variant allele frequency of more than 10%. On the central sequencing of IGHV gene of 360 patients, 61% had IGHV-unmutated disease. There was a higher percentage of patients with a complex karyotype in the IR group than in the other two treatment groups. The two ibrutinib arms had a superior PFS as well as ORR as compared to the BR arm, with an estimated 2-year PFS of 87%, 88%, and 74% for ibrutinib, IR, and BR, respectively. No difference was observed between ibrutinib and IR, similar to the results of a previous randomized phase II trial of ibrutinib vs. IR performed by the MD Anderson group [50]. No difference in OS was observed with a median follow-up of 38 months (94% and 95% vs. 90%). The ORR was lower with BR (81%) than with the ibrutinib-containing regimens (93% with ibrutinib and 94% with IR). However, the CR rate was higher with BR than with the ibrutinib-containing regimens (26% vs. 7% and 12%). Also, the percentage of patients with undetectable minimal residual disease (MRD) was significantly higher with BR than with the ibrutinib-containing regimens (8% vs. 1% and 4%). The significantly lower rates of undetectable MRD with the ibrutinib-containing regimens than with BR reaffirm that treatment with single-agent ibrutinib needs to be indefinitely. Grade $\geq$ 3 hematologic adverse events were higher with BR (61%) than with ibrutinib or IR (41% and 39%, respectively), whereas grade $\geq$ 3 non-hematologic adverse events were lower with BR (63%) than with the ibrutinib-containing regimens (74% with each regimen). The incidence of secondary cancers was similar, occurring in 13% of the patients in the BR group, 13% in the ibrutinib group, and 16% in the IR group. Richter's transformation occurred in 1 patient in the BR group and in 2 patients in the IR group.

The E1912 trial randomized 510 patients under the age of 70 who did not have del17p to FCR vs. IR [47]. At a follow-up of about three years, the study demonstrated both superior PFS as well as OS for IR. The superiority of IR over FCR was independent of age, sex, performance status, disease stage or the presence/absence of del11q. Consistent with previous reports, a PFS benefit for IR over FCR was not observed in the subgroup of patients with mutated IGHV, suggesting that FCR could still be a reasonable

option for this subgroup, however, with the current follow-up, very few patients with IGHV mutated disease have relapsed in either group.

Incidence of grade 3 and 4 treatment-related adverse events was also lower in IR (56%) than with FCR (72%). As expected, FCR was more frequently associated with grade 3 and 4 neutropenia (44% vs. 23%) and infectious complications (17.7% vs. 7.1%). Thus, based on this study, while FCR could still be considered a reasonable option for young, fit, IGHV mutated patients lacking del17p or TP53 mutation, Ibrutinib should be the preferred frontline treatment for patients with unmutated IGHV.

The iLLUMINATE trial is comparing ibrutinib plus obinutuzumab to the standard chlorambucil plus obinutuzumab regimen in elderly or unfit patients with TN CLL. The ibrutinib-containing regimen achieved significantly higher 30-month PFS rates (79% vs. 31% for the standard) and reduced the risk of progression or death by 77% in the whole population and by 85% in the subgroup of high-risk patients (del17p, del11q, TP53 mutation or unmutated IGHV) [48]. Median PFS was not reached in the ibrutinib plus obinutuzumab arm and was 19 months in the chlorambucil plus obinutuzumab arm. More patients in the ibrutinib plus obinutuzumab group achieved CRs (19% vs. 8%) and MRD-negativity (35% vs. 25%). Taken together, the A041202 and iLLUMINATE trials establish ibrutinib-based regimens as the preferred frontline treatment for older/unfit patients.

The role of anti-CD20 antibodies as combination partners in this setting is for now debatable. Similar to the E1912 trial, the iLLUMINATE trial lacked an ibrutinib-only treatment arm, which makes it difficult to directly estimate the contribution of obinutuzumab to treatment responses, whereas a cross-trial comparison with the RESONATE-2 study suggests that OR and PFS rates are similar for ibrutinib and ibrutinib plus obinutuzumab [51].

Venetoclax-based chemotherapy-free combination was recently approved for the frontline treatment of CLL. Overexpression of the anti-apoptotic BCL-2 protein is one of the molecular hallmarks of CLL [52]. Venetoclax is an orally administered small molecule that targets BCL2, disrupting antiapoptotic signaling through BCL2, thereby inducing programed cell death of CLL cells [53]. Venetoclax has shown remarkable efficacy in patients with CLL [54,55]. Unprecedented MRD-negativity rates with durable responses have been observed with combination of venetoclax and obinutuzumab in patients with TN CLL [56]. Approval of this combination was based on the recently reported phase III CLL14 study that randomized 432 TN CLL patients with the Cumulative Illness Rating Scale (CIRS) score >6 or calculated creatinine clearance < 70 mL/min to receive fixed duration treatment with 12 cycles of either venetoclax plus obinutuzumab or chlorambucil plus obinutuzumab, with obinutuzumab given for first 6 cycles only in both arms [57]. The estimated PFS at 24 months was 88.2% vs. 64.1%. The PFS benefit with venetoclax plus obinutuzumab was observed even in high-risk subgroups with *TP53* deletion/mutation or both, and in patients with unmutated IGHV. The chemotherapy-free regimen led to superior CR/CRi (CR with incomplete hematologic recovery) as compared to the CIT arm (50% vs. 23%). These responses were deep, with very impressive MRD-negative rates seen in the venetoclax arm, both in the bone marrow (57% vs. 17%) as well as peripheral blood (76% vs. 35%). Although the 12-month, fixed-duration, chemotherapy-free combination reduced the risk of disease worsening or death by 65% as compared to chlorambucil plus obinutuzumab, longer follow-up will determine if the higher MRD-negative rates translate into a better survival outcome for these patients.

This regimen provides a time-limited option for patients, which has the benefit of better compliance as well as lesser toxicity besides being cost-effective. Also, the chance of developing resistant clones is reduced by fixed duration treatments. However, the comparator arm in this study was CIT which does not represent the current standard of care. Recently updated five-year follow-up of RESONATE-2 showed sustained PFS and OS benefit, including in high-risk patients, without any additional safety concerns [38]. Given long-term efficacy and safety data available for ibrutinib, a well-informed discussion is warranted between patients and the physicians, taking into consideration comorbidities like cardiac and renal function, concomitant anticoagulation use, uncontrolled hypertension as well as patient preference.

Future directions

Overall, ibrutinib is significantly superior to standard CITs and is now the preferred frontline treatment for most patients with CLL. However, responses to single-agent ibrutinib are rarely complete, hence necessitating continuous long-term treatment. Although effective in controlling the disease, long-term therapy with ibrutinib has its disadvantages including patient compliance, toxicities [42], high costs and the risk of developing acquired drug resistance [41,58,59], especially in high-

risk patients with del17p and/or TP53 mutation. The recently approved venetoclax plus obinutuzumab time-limited combination may address some of these limitations, however, longer follow-up is needed to determine the durability of these responses as well as potential survival benefit. With these two options available, a direct comparison in a randomized study would be ideal to determine the merits of these two treatment paradigms, vis-à-vis continuous indefinite treatment with ibrutinib or fixed duration combination with venetoclax plus obinutuzumab.

On-going and future studies are addressing these issues by identifying novel combination regimens which can lead to deeper responses, thus making discontinuation of therapy feasible. Promising early results of such combination therapy approaches which induce deep remissions and a high rate of MRD negativity have been published. One of the strategies of improving responses involves the incorporation of targeted therapies with CIT. Preliminary results of an ongoing phase II clinical trial with the combination of ibrutinib, FC, and obinutuzumab (iFCG) for young, fit patients with mutated *IGHV* and without del17p were reported [60]. Patients received only three cycles of FC chemotherapy and continued ibrutinib and obinutuzumab for up to a total of 12 cycles. Bone marrow MRD negativity rate of 87% was reported after three cycles and increased to 93% at 6 months. The CR/CRi rate was 44% after three cycles and increased to 78% after 6 cycles. All patients with negative MRD discontinued ibrutinib at 1 year; at a median follow-up of 5.5 months after discontinuation these patients continued to be MRD negative. Similar encouraging results have been reported with the combination of ibrutinib with six cycles of FCR (iFCR) followed by maintenance ibrutinib for two years in young, fit patients with CLL [61]. This trial included patients with both mutated and unmutated *IGHV* as well as patients with del17p. At 2 months after the last cycle of ibrutinib plus FCR bone marrow MRD-negative CR was achieved in 33% of patients. The best response of MRD-negative bone marrow was achieved in 84% of patients. With a median follow-up of 16·5 months, responses were durable and only one patient had disease progression.

Bone marrow MRD negativity has been shown to be a very strong predictor of long-term outcome. MRD-directed phase II CLL2-BIO and CLL2-BIG trials follow the so-called 'sequential triple-T' concept [62] where initial debulking treatment with bendamustine is followed by induction and MRD-tailored maintenance with ibrutinib plus ofatumumab or ibrutinib plus obinutuzumab [63]. Subsequently, in case of a CR and MRD negativity, maintenance treatment is terminated. Early results are encouraging; however, long-term data and randomized studies will be needed to determine whether these combinations are superior to ibrutinib alone.

Venetoclax has shown promise in combination with ibrutinib in the frontline setting. These two drugs have different mechanisms of action and non-overlapping toxicity profiles. They complement each other's activity on different disease compartments (ibrutinib is particularly effective at clearing nodal disease, whereas venetoclax is more effective at clearing blood/marrow disease). There is evidence of synergy in preclinical models [64]. In a phase II study of high-risk, older patients, after 12 cycles of this combination, 88% CR/CRi rate was observed with an impressive 61% MRD-negativity seen in the bone marrow [65]. After 18 cycles, responses deepened further, with CR/CRi rate increasing to 96% and MRD-negativity in bone marrow increasing to 69%. The combination treatment in this study will stop after a finite duration of 24 cycles. It will be interesting to see on the longer follow-up of this trial if these initial responses are durable and translate into longer treatment free intervals.

An ongoing phase II study is evaluating the triple chemotherapy-free combination of obinutuzumab, ibrutinib and venetoclax [66]. In this study, therapy is administered sequentially over the initial 3 cycle; obinutuzumab is started with the first cycle, ibrutinib is introduced at second cycle and venetoclax starts at cycle 3; this is done in order to limit the influence of ibrutinib on NK-cell mediated antibody-directed cellular cytotoxicity (ADCC) which is important for obinutuzumab activity, and to cytoreduce prior to initiating venetoclax, thereby limiting the risks for tumor lysis. Initial results in 25 TN CLL patients show an ORR of 84% with 8 CRs, including 1 with incomplete marrow recovery. At the end of treatment, 67% of these patients were MRD negative in the peripheral blood as well as bone marrow with MRD negative CR rate of 28%.

Given the superiority of ibrutinib and venetoclax plus obinutuzumab to CIT, ongoing and future studies that do not involve chemotherapy are of high clinical interest and will better define the role of these combinations to address the role of the depth of response as well as the possibility of finite duration of treatment. The recently opened cooperative group studies will try to address some of these questions in the setting of chemotherapy-free combinations. EA9161 is a randomized phase III study of the addition of venetoclax to ibrutinib and obinutuzumab vs. ibrutinib and

obinutuzumab in younger TN patients with CLL (NCT03701282) and A041702 is a similar study in older patients with TN CLL (NCT03737981) [67,68]. A041702 is also assessing the feasibility of treatment discontinuation based on the MRD status. Beginning cycle 15, patients who do not achieve a bone marrow MRD negative CR receive continuous ibrutinib in the absence of disease progression or unacceptable toxicity. Patients who achieve a bone marrow MRD negative CR discontinue treatment; this MRD negativity based treatment discontinuation will hopefully help to address the issue of a fixed –duration therapy.

As effective as ibrutinib is for long-term disease control in patients with CLL, some safety concerns remain including an increased incidence of atrial fibrillation, hypertension and bleeding, as well as ventricular arrhythmias and sudden death [69]. Of note, a greater number of unexplained or unwitnessed death were seen in the ibrutinib containing arms in the Alliance study [46]. In an attempt to address this, alternative BTK inhibitors with a better safety profile are being investigated. Acalabrutinib, a potent second-generation covalent BTK inhibitor, is highly selective as compared to ibrutinib, with minimal off-target activity and may offer the advantage of a different and milder side effect profile than ibrutinib. Monotherapy with acalabrutinib produced high response rates with an acceptable safety profile in a phase I/II ACE-CL-001 trial in patients with TN CLL [70]. In 99 patients, after a median follow-up of 42 months, ORR was 97%; 5% CRs and 92% partial responses. After three years, 98% of patients were still responding and 97% were progression-free. Acalabrutinib also holds promise in chemotherapy-free combinations. In a phase Ib/II trial, treatment with acalabrutinib plus obinutuzumab yielded high response rates that have been durable irrespective of high-risk disease status. In 19 TN patients, the ORR was 95% with the combination; CR was achieved in 31.6% patients. At 12 cycles, 26% of TN patients were MRD-negative in the bone marrow [71]. Accrual has completed on the triple combination chemotherapy-free arm of acalabrutinib with venetoclax plus obinutuzumab in TN CLL patients on this study (NCT02296918) [72].

Acalabrutinib is also under investigation in multiple phase III CLL trials. ELEVATE-TN (ACE-CL-007) is a randomized, multicenter, open-label phase III trial evaluating the safety and efficacy of acalabrutinib alone or in combination with obinutuzumab vs. chlorambucil in combination with obinutuzumab in TN patients with CLL [73]. In the trial, 535 patients were randomized (1:1:1) into three arms. Patients in the first arm received chlorambucil in combination with obinutuzumab. Patients in the second arm received acalabrutinib (100 mg twice daily until disease progression) in combination with obinutuzumab. Patients in the third arm received acalabrutinib monotherapy (100 mg twice daily until disease progression). This study has met its primary endpoint of improving PFS over obinutuzumab plus chlorambucil and will be presented at a major conference later this year. ACE-CL-311 is an ongoing phase III study evaluating acalabrutinib in combination with venetoclax with/without obinutuzumab vs. CIT in patients with TN CLL without 17p deletion or TP53 mutation [74].

Table 1. Treatment algorithm for TN CLL.

Patient characteristics	Treatment
Young /fit- IGHV mutated	Ibutinib/IR FCR(if no del17p) Alternative: VO/IO
Young /fit- IGHV unmutated	Ibrutinib/IR Alternative: VO
Elderly/fit	Ibrutinib or VO
Elderly/comorbidities or unfit	Ibrutinib or VO Alternative: CO(if no del17p)

IR: ibrutinib rituximab; FCR: fludarabine cyclophosphamide rituximab; VO: venetoclax obinutuzumab; IO: ibrutinib obinutuzumab; CO: chlorambucil obinutuzumab.

Summary

With the results of 3 large frontline studies confirming the superiority of ibrutinib, it appears that ibrutinib-based therapy should be increasingly adopted in the frontline setting, likely as a single agent in older patients. In a small number of younger, fit patients with mutated *IGHV* and non-adverse cytogenetics, FCR and FCR-like CIT could remain as an alternative based on the overall findings from the E1912 trial and long-term data from FCR300, while patients with unfavorable genomic features should receive ibrutinib, with or without a CD20 monoclonal antibody. However, the long-term risk of developing therapy-related myelodysplastic syndrome/acute myeloid leukemia needs to be taken into consideration when recommending FCR, especially in a younger patient. The recently approved venetoclax plus obinutuzumab combination offers a time-limited option for patients which has the benefit of better compliance as well as lesser toxicity besides being cost-effective. It would be ideal to compare these very effective frontline treatments in a randomized study to determine the merits of a time-limited regimen vs. continuous indefinite treatment of a chronic disease (Tables 1 and 2).

Although the current advances in CLL and approval of new novel agents represent a significant step

Table 2. Phase III clinical trials of frontline regimens for TN CLL.

Study (reference)	Regimens	Response	PFS	OS
RESONATE-2 [36]	Ibrutinib vs. chlorambucil	ORR: 86% vs. 35% (2.42; 1.91–3.07; $p < .001$) CR/CRi: 4% vs. 2%	Median PFS not reached vs. 18.9 months HR 0.16; 95% CI 0.09–0.28; $p < .001$ PFS rate at 18 months 90% vs. 52%	Median OS not reached in either group OS rate at 24 months 98% vs. 85% HR 0.16; 95% CI 0.05–0.56; $p = .001$
ALLIANCE A041202 [46]	Ibrutinib vs. IR vs. BR	ORR: 93% vs. 94% vs. 81% CR: 7% vs. 12% vs. 26%	Median PFS not reported PFS rate at 24 months 87% vs. 88% vs. 74% HR 0.39; 0.26–0.58; $p < .001$ (BR vs. I) HR 0.38; 0.25–0.59; $p < .001$ (BR vs. IR) HR 1.00; 0.62–1.62; $p = .49$ (IR vs. I)	Median OS not reported OS rate at 24 months 90% vs. 94% vs. 95% $p \geq .65$ for all pairwise comparisons
ECOG E1912 [47]	IR vs. FCR	Not reported	Median PFS HR 0.35; 0.22–0.5; $p < .001$ PFS rate not reported	Median OS HR 0.17; .05–0.54; $p < .003$ OS rate not reported
iLLUMINATE [48]	IO vs. CO	ORR: 88% vs. 73% (1.21; 1.06–1.37; $p = .0035$) CR/CRi: 22% vs. 8% (2.51; 1.21–5.21; $p = .0096$)	Median PFS not reached vs. 19.0 months (15.1–22.1) HR 0.23; 0.15–0.37; $p < .0001$ PFS rate at 30 months 79% vs. 31%	Median OS not reached in either group HR 0.92; 0.48–1.77 OS rate at 30 months 86% vs. 85%
CLL14 [57]	VO vs. CO	ORR: 84.7% vs. 71.3% ($p < .001$) CR: 49.5% vs. 23.1% ($p < .001$)	Median PFS not reported PFS rate at 24 months 88.2% vs. 64.1%	Median OS not reached in either group OS rate at 24 months 91.8% vs. 93.3% HR 1.24; 0.64–2.40; $p = .52$

IR: ibrutinib rituximab; BR: bendamustine rituximab; FCR: fludarabine cyclophosphamide rituximab; IO: ibrutinib obinutuzumab; CO: chlorambucil obinutuzumab; VO: venetoclax obinutuzumab; ORR: overall response rate; CR: complete remission; PFS: progression free survival; OS: overall survival.

forward in the treatment of CLL, newer challenges have emerged on how to best utilize these new treatment options. Ongoing studies are focusing on understanding how to best sequence these therapies or combine these agents in chemotherapy-free regimens, and how to manage patients who fail all these therapies either sequentially or in combination.

Disclosure statement

The authors have no conflicts of interest.

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