

POINT Is a BTKi or BCL2i preferable for first “novel” therapy in CLL? The case for BTKis

Elizabeth A. Brem and Susan O'Brien

Chao Family Comprehensive Cancer Center, University of California, Irvine, Orange, CA

This article has a companion Counterpoint by Seymour.

Introduction

Currently, there are 2 main classes of oral small molecules for the treatment of chronic lymphocytic leukemia (CLL): Bruton tyrosine kinase inhibitors (BTKis) and the B-cell lymphoma 2 inhibitor (BCL2i) venetoclax. Both can be effective options, but for the majority of patients our first choice is a BTKi.

The BTKi ibrutinib was first approved in 2014 and has completely changed the treatment paradigm in CLL/small lymphocytic lymphoma (SLL). Now, 8 years after the initial clinical studies were started, it has an established track record of durable responses. Although there were some significant toxicities that emerged, namely atrial arrhythmia and bleeding, there is now long-term experience with toxicity management. Nearly all adverse events of interest decrease in frequency over time with the 1 exception being hypertension (all grades, 11% during 0-1 years of therapy, 20% at >2-3 years of therapy).¹ In addition, these toxicities appear to be less frequent with “next generation,” more specific BTKis. Thus, BTKis are an efficacious and tolerable choice for the majority of patients.

Why pick a BTKi as initial therapy for CLL?

Although venetoclax and the anti-CD20 antibody obinutuzumab (V+G) have been shown to be an effective regimen in frontline treatment of CLL, this regimen has never been compared with effective chemoimmunotherapy in the upfront setting. The CLL14 study randomized patients to V+G vs chlorambucil with obinutuzumab (C+G)²; the latter regimen produces progression-free survival (PFS) rates significantly shorter than more effective chemoimmunotherapy regimens. Only a BTKi has been shown to improve PFS compared with that seen with effective, commonly used chemoimmunotherapy regimens in the frontline setting.

Alliance trial A041202 was a randomized, phase 3 study in patients 65 years of age and older with previously untreated CLL. Patients were randomized 1:1:1 to bendamustine-rituximab (BR), ibrutinib, or ibrutinib-rituximab (IR). The primary end point was PFS. The 2-year PFS was nearly identical between the group receiving ibrutinib alone and those who received IR (87% and 88%) and was superior to that seen with BR (74%). There was no significant difference in overall survival (OS) among the 3 arms. In all subgroups analyzed, hazard ratios for disease progression or death favored the use of ibrutinib-based therapy.³

Similarly, E1912 randomized patients who were <70 years of age with previously untreated CLL to ibrutinib-based therapy or fludarabine, cyclophosphamide, and rituximab (FCR) in a 2:1 fashion. The 3-year PFS in the ibrutinib group was 89.4% compared with 72.9% in the FCR arm. Three-year OS, a secondary end point, favored the ibrutinib arm (98.8% vs 91.5%).⁴ Taken together, E1912 and A041202 support the idea that BTKis are preferable to chemoimmunotherapy as initial therapy for most patients with CLL.

Ibrutinib not only binds to BTK with high affinity (50% effective concentration [EC50], 5-10 nM), but also binds to a number of similar kinases, such as interleukin 2-inducible T-cell kinase (ITK), epidermal growth factor receptor (EGFR), Fms-like tyrosine kinase-3 (FLT3), TEC, and KIT.⁵ As a result, there has been an effort to develop more specific inhibitors of BTK with the hypothesis that these more specific inhibitors would have reduced toxicities. Acalabrutinib was designed to not only be more selective for BTK, but to also have more favorable plasma exposure and oral absorption. Acalabrutinib has a shorter half-life than ibrutinib (0.6-2.8 vs 4-6 hours for ibrutinib) and thus requires twice-daily dosing.⁵

The ELEVATE-TN study evaluated acalabrutinib in patients with previously untreated CLL. Eligible patients were older than 65 years or were younger than 65 years but with comorbidities or reduced renal function (defined as a Cumulative Illness Rating Scale [CIRS] score of >6 or creatinine clearance <70).

Patients were randomized 1:1:1 to acalabrutinib, acalabrutinib with obinutuzumab (A+G), or C+G. The primary end point was PFS to be compared between A+G and C+G. At a median follow-up of 28.3 months, the 2-year PFS was 93% for A+G, 87% for acalabrutinib alone, and 46% for C+G. Median OS had not been reached at the time of publication, but there was a suggestion of an OS benefit with acalabrutinib therapy. Estimated OS at 24 months was 95% in both acalabrutinib arms and 92% for C+G.⁶

Acalabrutinib has a unique toxicity of a transient headache. Atrial fibrillation was rare: 4% of any grade in the acalabrutinib arm and 3% for the A+G arm. Grade 3+ hypertension events were also uncommon (3% or fewer in all 3 arms). Bleeding was more likely in the acalabrutinib-containing arms but was still quite infrequent (2% grade 3+ events compared with 0% with C+G).⁶ ELEVATE-TN suggests that acalabrutinib is similarly effective to ibrutinib in the upfront treatment of CLL, and, thus far, it appears to be well tolerated.

CLL with TP53 mutation/17p deletion

Although we feel that the data cited herein support the use of a BTKi for most patients requiring initial therapy for CLL, we would like to emphasize that the case is even stronger for those whose disease has a 17p deletion or other alteration in TP53. Ibrutinib has been quickly incorporated into the treatment paradigm for such patients as these patients are known to have poor responses to chemoimmunotherapy: 3-year PFS is only 18% with FCR therapy.⁷

For patients whose disease has an aberration in TP53, there is very limited evidence for upfront use of venetoclax. In CLL14, only 8.5% of patients had a 17p deletion and 11.1% had any TP53 mutation in the V+G arm. Regardless of treatment arm, patients with TP53-mutated and/or 17p-deleted disease had inferior outcomes. PFS at 30 months for those without a TP53 aberration treated with V+G was ~85% whereas the PFS at 30 months was ~60% for those with a TP53 aberration treated with V+G.² In contrast, in A041202, there was a clear benefit to the use of ibrutinib over BR when a 17p deletion was present. The hazard ratio for risk of death or disease progression for ibrutinib compared with BR for those with 17p or 11q deletion was 0.44 (0.27-0.72).³

Recently, a pooled analysis of 89 patients with CLL/SLL and a 17p deletion or TP53 mutation who received frontline ibrutinib-based therapy was presented. With a median follow-up of 50 months, the median PFS was not reached. PFS at 48 months was 79%, and median duration of ibrutinib therapy was 46 months. Thus, ibrutinib clearly shows sustained efficacy in this population. These numbers compare favorably with those seen in patients with an absence of a TP53 mutation or 17p deletion treated with upfront ibrutinib. Although one must always be cautious with cross-trial comparisons, this analysis shows a sustained response that is better than what was seen with V+G in CLL14.⁸

It appears that other BTKis will be similarly effective in this subgroup. In ELEVATE TN, ~9% of patients in each arm had 17p-deleted disease and ~11% had disease with a TP53 mutation. Hazard ratios greatly favored acalabrutinib therapy in these patients: 0.23 (95% confidence interval [CI], 0.09-0.61) for those treated with acalabrutinib alone and 0.10 (95% CI, 0.03-0.34) for those who received A+G.⁶ In the ASCEND study of acalabrutinib vs investigator's choice, which enrolled patients who had received at least 1 prior therapy, PFS at 20 months was similar for patients

treated with acalabrutinib monotherapy regardless of TP53 mutation/17p deletion status. In patients with a TP53 alteration, the PFS at 20 months with acalabrutinib therapy was ~85%, compared with 0% in those treated with investigator's choice (predominately idelalisib with rituximab).⁹

IgVH-unmutated CLL

In both arms of the CLL14 study, the majority of patients had immunoglobulin variable region heavy chain (IgVH)-unmutated disease. PFS was improved with V+G for those with both IgVH-mutated and -unmutated disease, but there was a more pronounced PFS benefit for those with IgVH-mutated disease. For those treated with V+G, 30-month PFS was ~90% for those with IgVH-mutated disease and was ~85% for those with IgVH-unmutated disease.²

Large studies of upfront treatment with ibrutinib have shown similar PFS rates between patients with IgVH-mutated and -unmutated disease. In A041202, the 30-month PFS for those treated with ibrutinib was ~90% for both IgVH-mutated and -unmutated subsets.³ In E1912, 3-year PFS with ibrutinib-based treatment was ~88% for those with IgVH-mutated disease and nearly 91% for those with IgVH-unmutated disease.⁴ Obviously, there are caveats to these subgroup analyses, but the available data suggest the potential for improved PFS with BTKi treatment of those with IgVH-unmutated disease.

Sequencing considerations

Many patients with CLL need multiple therapies during their lifetimes, such as younger patients or those who are older but have high-risk features. BTKis are clearly effective therapies, but of course the risks of toxicities, such as arrhythmia, are present with their use. For patients likely to need multiple therapies, one could argue for choosing the therapy with a higher risk of toxicity first when the patient may be better poised to tolerate these adverse effects. Arrhythmia, hypertension, etc, are likely to be more frequent and harder to manage with age. Venetoclax-based therapy can then be reserved for progression. In contrast, an older patient with comorbidities and/or low-risk disease may be better suited for time-limited therapy with venetoclax.

Comorbidity considerations

Some clinicians may have pause to use ibrutinib in those with a history of arrhythmia, particularly if not well controlled. There may also be hesitation to recommend ibrutinib for those on anticoagulant (AC) or antiplatelet (AP) agents. Available data suggest that it is reasonable to use ibrutinib with either an AP agent or an AC, but "triple" therapy of ibrutinib, AP, and AC may carry an increased risk of major bleeding. In a secondary analysis of the RESONATE study, which enrolled patients with relapsed/refractory CLL, patients were identified who were assigned to ibrutinib and were on AC, AP, or a combination of AC and AP. Among the patients not on any AC or AP, 5% of patients on ibrutinib had any bleeding event and 1% experienced major bleeding. On AC alone, 5% of patients had any bleeding and 2% experienced major bleeding. On AP alone, 3% of patients had any bleeding and 1% experienced major bleeding. There was 1 major bleeding event for a patient on both AC and AP, but because the number of patients on both AC and AP was small ($n = 17$), this equals 6% major bleeding with combined AC and AP.¹⁰

A larger retrospective study examining rates of major hemorrhage in patients on ibrutinib-containing therapies included data from 15 clinical studies; this data set included patients with lymphomas and not just CLL/SLL. Nearly one-half of patients were on AC and/or AP (47%) at some point. Low-molecular-weight heparin was the most common AC used. In terms of AP, aspirin and nonsteroidal anti-inflammatory drug use were most common. Bleeding events were more common in patients with mantle cell lymphoma (MCL) compared with that seen in CLL and the group as a whole, perhaps due to the frequency of gastrointestinal tract involvement in MCL. Major bleeding occurred in 6% of patients on ibrutinib and AC at any point and 4% of those on ibrutinib and AP. In the total cohort, major hemorrhage occurred in 4.1% of patients on ibrutinib, and 1% of patients discontinued ibrutinib due to major hemorrhage. In this data set, 10% of patients were on both AP and AC, but the rates of bleeding in this “triple-therapy” subgroup was not specifically presented in the publication.¹¹

Thus far, risks of atrial arrhythmia and bleeding complications appear to be less with subsequent BTKis. Admittedly, head-to-head data are lacking to date, and thus some clinicians may reasonably choose to use venetoclax-based therapy in patients requiring AP and AC or with a history of atrial arrhythmias while waiting longer-term follow-up with acalabrutinib.

For those with a history of renal disease, there may be a higher likelihood of complications related to tumor lysis syndrome (TLS) if venetoclax-based therapy is chosen. Both ibrutinib and acalabrutinib have minimal renal excretion, so BTKis may be a better choice for those with a history of renal insufficiency.

Logistic considerations

BTKis are efficacious and US Food and Drug Administration (FDA) approved as oral single agents. Venetoclax is approved with obinutuzumab in the upfront setting and with rituximab in the relapsed setting. The ability to avoid anti-CD20 therapy by choosing a BTKi provides 2 benefits: (1) eliminating trips to the infusion center and (2) avoiding further suppression of humoral immunity that may be imparted by the antibody, which may be particularly of interest in the current COVID-19 era. Choosing a BTKi also avoids hospitalizations or frequent labs/visits to monitor for TLS that may otherwise be needed with the initiation of venetoclax. For patients who live in rural areas, live a far distance from the treating clinician's office, have limited transportation, have impaired mobility, etc, an oral BTKi may be a much more practical option.

COVID-19 considerations

The American Society of Hematology (ASH) has asked a number of experts for advice regarding initiating therapy during the pandemic. These experts agree that, for patients who require therapy, monoclonal antibodies and initiation of venetoclax should be avoided if possible.¹²

There is potential for other benefit to using a BTKi in the current COVID-19 era. A case series of 6 patients with Waldenström macroglobulinemia suggests that ibrutinib may protect against severe pulmonary inflammation in COVID-19 infection. This protective effect was hypothesized based on previous work in influenza mouse models. Five of the 6 patients described were taking ibrutinib 420 mg daily when they contracted COVID-19. None of these 5 patients reported dyspnea or required supplemental oxygen. The sixth patient was taking 140 mg of ibrutinib when COVID-19 was contracted.

This patient required hospitalization and eventually mechanical ventilation. After intubation, the ibrutinib dose was increased to 420 mg with subsequent improvement in respiratory status. The patient was able to be on room air 4 days after the increase in ibrutinib dose.¹³ There are, of course, many caveats to these data, such as the small number, lack of any control, and a different disease state. However, observations like this have led to larger studies of BTKis in patients with COVID-19. Two phase 2 studies of ibrutinib in patients with COVID-19 infection are ongoing: 1 for those who require supplemental oxygen (NCT04375397) and 1 for those with a history of malignancy or a precursor condition like monoclonal gammopathy of undetermined significance or myelodysplastic syndrome (NCT04439006). It should be noted that a phase 2 study of acalabrutinib vs best supportive care in patients hospitalized with COVID-19 infection (CALAVI study) did not meet the primary end point of reduction in respiratory failure and mortality. That being said, acalabrutinib has a more narrow kinome profile than ibrutinib,⁵ and there could be anti-inflammatory effects of ibrutinib that are independent of its effect on BTK.

Other considerations

Although venetoclax-based therapies are effective, there is some suggestion that tolerability could be an issue. MURANO was a phase 3, randomized study of patients who had received 1 to 3 prior therapies; at least 1 regimen must have contained chemotherapy. Patients were randomized to venetoclax with rituximab (V+R) for a 2-year duration of treatment or BR for 6 cycles. The overall response rate was 92.3% with V+R and 72.3% in the BR group. At just under 2 years of follow-up, median PFS had not been reached in the V+R group and was 17 months in the BR group. Although the response rate and PFS rates appear to be similar for V+R compared with ibrutinib or acalabrutinib in similar populations, it should be noted that there was significantly more dropout in the V+R arm compared with that seen with BR in MURANO. Forty-eight patients discontinued venetoclax during the study for a variety of reasons (disease progression, adverse effects) compared with only 27 patients assigned to BR.¹⁴

Summary

We now have over 6 years of follow-up from large, randomized phase 3 experiences with ibrutinib, demonstrating long-term efficacy in all subgroups. No new toxicity signals have emerged with long-term follow-up, and the most concerning toxicities are still relatively uncommon. In an integrated safety analysis of 3 key studies, 11% of patients had atrial fibrillation of any grade and there was only 1 grade 5 bleeding event.¹ The increased selectivity of the newer BTKis has thus far led to fewer atrial arrhythmias in studies of these agents to date. Bleeding may be a class effect of the BTKis, although it is also less common in studies with acalabrutinib.

Only a BTKi has shown an improved PFS compared with that seen with both BR and FCR in frontline, randomized phase 3 studies. E1912 also suggests that BTKis may have an OS benefit when compared with chemoimmunotherapy.⁴ There was a suggestion of improved OS with acalabrutinib-based therapy in ELEVATE-TN over C+G.⁶ Venetoclax (V+G) has never been compared in a randomized fashion to effective, commonly used chemoimmunotherapy and has a similar OS compared with that seen with C+G for frontline treatment of CLL.² Patients with TP53-mutated or 17p-deleted disease may particularly benefit from BTKi use. There is also a

suggestion that BTKi-based therapy may lead to an improved PFS for those with IgVH-unmutated disease.

BTKis are effective, tolerable oral agents that can be used without anti-CD20 therapy and TLS monitoring, making them the preferred choice for many patients requiring upfront therapy for CLL/SLL. Admittedly, many questions remain, including whether combination approaches (ie, BTKis with venetoclax) will improve outcomes compared with single-agent strategies, what is the optimal duration of therapy, and whether this duration should be guided by assessment of minimal residual disease. Ultimately, decisions should be made on a case-by-case basis for individual patients based on their disease, comorbidities, and unique circumstances (Table 1).

Authorship

Contribution: E.A.B. and S.O. performed the literature search and wrote the paper.

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ORCID profile: E.A.B., 0000-0002-3265-9841.

Correspondence: Elizabeth A. Brem, University of California, Irvine, 101 The City Dr South, Orange, CA 92868; e-mail: ebrem@hs.uci.edu.

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Table 1. Available “novel” agents for upfront treatment of CLL/SLL

Therapy	PFS at 2 y		PFS at 5 y		OS at 2 y	
	%	Ref.	%	Ref.	%	Ref.
Ibrutinib	87; 95	15; 3,4	70	15	98	16
Acalabrutinib	87	6	TBD		95	6
Acalabrutinib and obinutuzumab	93	6	TBD		95	6
Venetoclax and obinutuzumab	88	2	TBD		91.8	2

Ref., reference number; TBD, to be determined.

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