

COUNTERPOINT Is BTKi or BCL2i preferable as first novel therapy in patients with CLL? The case for BCL2i

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We are fortunate to have a number of highly effective and generally well-tolerated treatment options for patients with chronic lymphocytic leukemia (CLL).^{1,2} These novel targeted agents have contributed greatly to the improvement in overall survival (OS) observed in population-based registries.³ Critically, in the frontline context where early treatment has no proven long-term benefits, but also in the relapse context, the initiation of treatment should be guided by the presence of active disease, as well defined by the iwCLL guidelines.⁴

Although there has been an appropriate profound shift toward the preferential use of targeted agents over chemoimmunotherapy, it remains important to identify the modest subset of patients for whom frontline FCR (fludarabine, cyclophosphamide, rituximab) chemoimmunotherapy is deliverable with acceptable safety and has a substantial likelihood of achieving cure; these patients have IGHV mutation but no *TP53* aberrations, are aged <65 years with a low comorbidity score (CIRS <6), and have adequate renal function (creatinine clearance [CrCl] >50-70 mL/min).⁵⁻⁷ In my practice, and supported by the recently updated 2021 European Society of Medical Oncology (ESMO) guidelines,⁵ the first consideration to be discussed with the patient is whether cure is potentially achievable with frontline FCR given their specific biologic risk profile, and, if so, after detailed discussions, including the potential risk of secondary myelodysplasia or treatment-related acute myeloid leukemia (t-MDS/AML)⁸ whether they wish to pursue that option.

There is still a small cohort of patients with very late relapses many years after well-tolerated frontline chemoimmunotherapy, where retesting shows that *TP53* aberrations are absent, for whom repeat chemoimmunotherapy is a potential consideration.⁵ This is a very small subset of patients, and the outcome for most patients with repeat exposure to chemoimmunotherapy is relatively poor.⁹ Repeat exposure to DNA-damaging genotoxic therapies will also increase the risk of development of t-MDS/AML in the long term.⁸ Thus, I do not support such an approach and strongly recommend treatment with one of the targeted-agent approaches in all patients with disease relapsing after chemoimmunotherapy.

In the current context of COVID-19, regardless of planned treatment, but especially if an anti-CD20 antibody is incorporated, ensuring that the patient is fully vaccinated is critical.^{10,11} However, I take time to convey the suboptimal efficacy of vaccination responses in patients with CLL and reinforce the ongoing need for behavioral risk-minimization strategies, including encouraging all family members and close contacts to also be vaccinated.¹⁰

Despite the above considerations, most patients will be unsuitable for chemoimmunotherapy.⁵ Thus, the major choice to be confronted is the preferred initial targeted agent approach; in most jurisdictions this is continuous single-agent BTK inhibitor (BTKi), predominantly ibrutinib (RESONATE and RESONATE-2),¹²⁻¹⁵ or a time-limited combination of venetoclax and anti-CD20 antibody (24 months of treatment with rituximab [MURANO study] or 12 months of treatment using obinutuzumab [CLL14 study; Ven-Obi]).¹⁶⁻²⁰ Unfortunately, there are no head-to-head comparisons for these approaches in the frontline or relapsed-disease context. In the frontline setting, there are 3 indirect cross-trial comparisons but they reported conflicting results: one did not find any difference in progression-free survival (PFS) between ibrutinib-rituximab and Ven-Obi,²¹ one found that ibrutinib was inferior to Ven-Obi,²² and the third, which also included acalabrutinib-based treatment, found that acalabrutinib-obinutuzumab was superior to Ven-Obi or ibrutinib-obinutuzumab.²³ However, methodologic flaws and the imbalance of baseline factors across trials make these indirect comparisons of questionable value.²⁴ In the setting of relapsed disease, one "real-world" comparison suggested a longer PFS with venetoclax compared with ibrutinib as first targeted agent,²⁵ whereas a network meta-analysis reported no difference in PFS or OS for venetoclax compared with an ibrutinib-based approach.²⁶ Given this inconclusive evidence base regarding the

superior efficacy of either approach, our considerations should include additional factors, such as tolerability, long-term toxicity, societal cost, and options for effective subsequent treatments.

Because BTKi's were approved earlier, the duration of follow-up of clinical trial data are longer, and many clinicians will have greater and longer experiences with this approach. The major supporting data for their use in the frontline setting come from the RESONATE-2 trial in which patients aged ≥ 65 years without del(17p) were randomized to ibrutinib, 420 mg daily indefinitely, or the questionable "standard of care," single-agent chlorambucil.^{14,15} The median age was 73 years, and 31% of patients had a Cumulative Illness Rating Scale (CIRS) score >6 . Response rates were high, but conventional complete remissions were rare. Although ibrutinib was unequivocally superior to the weak standard arm, our focus now is on the long-term outcomes: efficacy and toxicity. Recent long-term follow-up data describe a 61% PFS rate at 6.5 years with no apparent impact of IGHV mutational status.¹⁵ Although with currently shorter follow-up, these favorable outcomes were supported by the ALLIANCE trial, which also included patients aged ≥ 65 years, but with del(17p) allowed (although present in just 6%); the 2-year PFS rate was 87% overall, and it was 74% in those with *TP53* aberrancy.²⁷ There are also additional data supporting the efficacy of ibrutinib, albeit in combination with rituximab, in a younger population aged <70 years; the 3-year PFS rate was 89%.²⁸

A gap in the disease spectrum of CLL is the lack of inclusion of patients with *TP53* aberrancy in meaningful numbers in these frontline studies. This has been addressed, in part, by a retrospective aggregated analysis of 89 patients with del(17p) or *TP53mut* from four trials (some combination with anti-CD20 antibody); the 4-year PFS rate was 79%,²⁹ and two small single-arm trials each reported 6-year PFS rates $\sim 60\%$.^{30,31} Although ibrutinib, as well as other targeted agents, are definitively superior to chemoimmunotherapy for treating *TP53*-aberrant disease, this genomic abnormality still carries an adverse prognostic impact, as do treatment after failure of multiple prior lines of therapy and a complex karyotype (≥ 3 aberrations).³²

Despite this favorable efficacy, a number of concerning issues are related to the widespread application of continuous BTKi therapy with ibrutinib. In the context of the carefully selected patient populations in prospective clinical trials, the ibrutinib cessation rate due to toxicity was reported to be 15% to 30% at 3 to 5 years.^{13-15,32} However in the "real-world" setting, cessation rates vary, with some reports replicating clinical trial data up to 6 months of follow-up,³³ and others finding much higher cessation rates, up to 42% at a median follow-up of 17 months.³⁴ Discontinuation rates are also higher in patients with greater comorbidity burden, contributing to inferior outcomes in such patients.³⁵ This is an important consideration when comparing outcomes with those reported with Ven-Obi in the CLL14 patient population; comorbidity burden was much higher than in the RESONATE-2 population.

Although an infrequent cause for drug cessation, atrial fibrillation (AF) is a concerning adverse effect that occurs in up to 15% of unselected ibrutinib-treated patients within the first 3 to 5 years,^{32,36} with higher rates in those with a history of AF or the presence of risk factors, such as male sex, age >75 years, valvular heart disease, or concomitant hypertension, all of which are common in patients with CLL.³⁶⁻³⁸ AF is inconvenient and creates management complexities, including difficult decision making regarding anticoagulation in

the context of the established antiplatelet effects of BTKi's and the inherent 5% to 10% risk of major bleeding.³⁹⁻⁴¹ However, ventricular arrhythmias are usually fatal, and the risk of documented ventricular arrhythmias, cardiac arrest, or sudden cardiac death may be increased more than fourfold with ibrutinib treatment.^{42,43} These cardiovascular adverse events continue to occur throughout the treatment period; thus, cumulative rates over the full expected treatment duration for patients treated in the frontline will be higher still where the median duration of drug exposure potentially exceeds 10 years. This cumulative cardiovascular morbidity burden is especially concerning for hypertension, with grade ≥ 3 toxicity reported in 32% of patients in the frontline setting and in 25% of those treated at relapse with 5-year follow-up.³² Development of these cardiovascular adverse events is associated with an increased mortality risk.⁴³

Beyond the morbidity burden, there is a huge personal and societal cost associated with the widespread utilization of the continuous therapy paradigm, with projections for US per-patient out-of-pocket costs to reach \$57 000, lifetime treatment costs to reach \$604 000, and overall annual societal costs for CLL management to reach \$5.13 billion by 2025.⁴⁴ The preferential use of Ven-Obi over ibrutinib would reduce the total societal cost of care by \$300 942 per patient over the first 3 years of treatment.⁴⁵

Although all of the above issues are real and manifest, there are also theoretical biological reasons to avoid a continuous treatment paradigm that does not achieve deep remissions, leaving a substantial persisting measurable disease burden. Serial analyses of the persisting disease and its underlying clonal genomic composition during ibrutinib treatment showed ongoing clonal instability and acquisition of additional mutations.^{46,47} This mutational rate was highest among cases that carried *TP53* aberrations.⁴⁶ This may have implications for the likelihood of acquisition of BTK-resistance mutations, such as C481S or PLCG2,⁴⁸ because the presence of an *TP53* aberration is an independent predictor for the acquisition of such mutations, along with elevated levels of β_2 -microglobulin and lactate dehydrogenase, and relapsed disease status.⁴⁹ In this so-called "4-factor" model, even in the frontline setting, patients with three of these risk factors have a predicted 50% likelihood of developing an ibrutinib-resistance mutation within the first 4 years of treatment.⁴⁹

Some of these cardiovascular toxicities may be ameliorated by the preferential use of better-tolerated, but at least as effective (as shown in the relapsed/refractory [R/R] setting in direct randomized comparisons), and more selective second-generation covalent BTKi's, such as acalabrutinib⁵⁰ or zanubrutinib.⁵¹ However, the broader issues arising from the continuous therapy paradigm persist.

The data supporting the frontline approval of Ven-Obi are from the CLL14 study, in which patients with a CIRS score >6 or CrCl <70 mL/min but ≥ 30 mL/min were randomized to Ven-Obi (time-limited total treatment duration of 12 months for all patients, regardless of the depth of response) or the same duration of chlorambucil-obinutuzumab.¹⁸ The eligibility criteria resulted in a population with a median age of 72 years (identical to the RESONATE-2 ibrutinib population) but with a very high comorbidity burden; the median CIRS score was 9, and 86% had a CIRS score >6 . Also, del(17p) was not an exclusion criterion, and 14% of patients in the study had *TP53* aberrancy. As with RESONATE-2, the investigational arm (here Ven-Obi) was superior to the standard of care for PFS, but the major focus was on the outcomes of patients treated with Ven-Obi. Follow-up was

shorter than for the RESONATE-2 cohort; median 52.4-month follow-up data were reported recently.^{20,52} Although overall response rates were similar to those seen with ibrutinib, complete remissions were confirmed in 49.5%, and many responses were very deep; undetectable minimal residual disease (MRD) at the conventional 10^{-4} level was attained in 76% in the peripheral blood (PB), including a 70% PB undetectable MRD rate for those with del(17p). Highly sensitive next-generation sequencing assays revealed that 40% of Ven-Obi-treated patients achieved MRD levels of $<10^{-6}$ at 3 months after completion of therapy in PB analysis.²⁰ The depth of remission (using the conventional 10^{-4} threshold) is strongly predictive of the durability of remission after time-limited venetoclax combination therapy.^{17,20}

The reported PFS rates at key time points for the entire Ven-Obi-treated frontline cohort are 88% at two years and 74% at four years.^{19,20} In contrast to the ibrutinib data, IGHV mutational status retains prognostic relevance with time-limited venetoclax treatment; those with unmutated disease have a greater risk for PFS events (hazard ratio [HR], 2.14) attributable to more rapid re-emergence of MRD and disease regrowth. Concordant with the ibrutinib analyses, outcomes for patients with disease carrying del(17p) were also inferior, with a median PFS of 49.0 months (HR, 3.19; 95% confidence interval, 1.66-6.14). However, disease resistance on therapy was rare, and a number of these PFS events were due to unrelated deaths,⁵³ as may be expected in an elderly and comorbid population. Preclinical studies have shown that venetoclax's mechanism of action is independent of TP53,⁵⁴ and continuous single-agent clinical data from a less comorbid, but heavily pretreated, R/R population showed durable disease control^{55,56} despite del(17p). Nevertheless, although not affecting the overall response rate (HR, 1.3) or complete remission rate (HR, 1.2), TP53 aberrancy retains an adverse prognostic impact on PFS in multivariate analyses of single-agent treatment in the R/R setting (HR, 2.2).⁵⁷ This might be mitigated when combination therapy is applied; TP53mut status had only a modest and nonstatistically significant adverse impact on PFS outcome when venetoclax-rituximab was given using a 2-year time-limited treatment schedule.¹⁷ When prognostic factors for OS were explored across the range of novel agent classes, including BTKi and BCL2i-inhibitors (BCL2i) (here in combination with rituximab from the MURANO study), the same factors impacted outcomes equally with both approaches.⁵⁸ Thus, with the exception of IGHV mutational status, it appears that conventional clinical and laboratory adverse prognostic factors are largely shared across BTKi and BCL2i treatments. A key challenge to the field is to analyze genomic and molecular data more deeply with the goal of identifying specific biologic subsets of patients who may be optimally treated with either approach; however, suitable predictive tools are lacking.⁵⁹

The practical, logistical, and morbidity burdens of initiating venetoclax-based treatment with the well-documented issues of the weekly dose ramp-up, tumor lysis syndrome (TLS) prophylaxis and monitoring, the need for IV infusions of antibody, and the potential need for multiple (albeit, usually brief) inpatient admissions are very substantial.^{60,61} These concerns are further amplified during the current COVID pandemic by the greater need for patient contact with the health care system, as well as the inherent immunosuppressive effects of the anti-CD20 antibody on serological responses to vaccinations, including COVID-19.^{10,11} However, beyond the short-term burdens of the ramp-up period, and the moderate infection risk (15-20% grade 3+) during the combination-therapy period, ongoing toxicity burden is modest.^{16,20,62} Initial suggestions of an increased risk for second

malignancies have been resolved with longer follow-up.²⁰ Further, there is strong evidence that patient quality of life actually improves under venetoclax treatment, despite these burdens.⁶³

As with the BTKi's, continuous exposure to venetoclax provides a selection pressure for the development of resistance mutations; the best characterized are acquired mutations in *BCL2* that impair venetoclax binding but maintain its antiapoptotic actions.⁶⁴⁻⁶⁶ Other resistance mechanisms, including upregulation of other antiapoptotic BCL2 family members and metabolic reprogramming, also contribute to acquired resistance.^{67,68} Avoidance of the development of such acquired resistance through utilization of combination therapies to attain deep remissions, which then allow time-limited treatment, is a key overarching goal.^{69,70} The clinical realization of this goal appears to be possible, because acquisition of these BCL2-resistance mutations among patients with disease progressing after time-limited therapies has not been reported, acknowledging the very small numbers of cases analyzed to date.^{20,70}

Retention of venetoclax sensitivity at disease recurrence after time-limited therapy has two major implications: retreatment with reattainment of disease control is feasible, and conventionally defined PFS may not be the appropriate means to measure the duration of benefit of venetoclax or the best comparator to assess efficacy relative to continuous BTKi's. The potential for effective retreatment was established in a phase 1b combination study,⁷⁰ as well as in the MURANO cohort, with some patients attaining second undetectable MRD responses.⁷¹ Given this retained efficacy with venetoclax retreatment, even in just a proportion of cases, a better measure of efficacy may be the "time to venetoclax failure," which incorporates the clinical benefit of these subsequent responses.⁷⁰

The question of effective treatment sequencing using these drug classes is a potential consideration. Prospective trials and "real-world" data sets have established the efficacy of venetoclax following failure of a BTKi.^{33,72,73} The ability to treat effectively using the opposite sequence has been established, with two recent reports describing high response rates and a median PFS of 32 and 34 months for BTKi after venetoclax failure.^{74,75} Thus, there are equally strong data supporting the use of these largely non-cross-resistant drug classes in either sequence.⁷⁶

In summary, we are fortunate to have both of these highly effective treatment options for patients with CLL: continuous BTKi and time-limited BCL2i. In the absence of direct phase 3 comparative data, neither approach has clear evidence of superior efficacy, as measured by PFS (time to first disease progression), with the exception of perhaps those with unmutated IGHV status or TP53 aberrancy in the frontline setting, where BTKi appears to achieve longer initial disease control. However, this may be mitigated by the capacity to retreat with venetoclax-based therapies, acknowledging that the regulatory and funding status of this approach will likely vary across jurisdictions. There will be individual patients with specific organ function impairment or comorbidities for whom one approach may be strongly preferred (eg, BTKi in those with severe renal failure and venetoclax in those with a high risk for cardiac arrhythmias). In the short term, particularly over the first three to six months of therapy, initiation of BTKi therapy is far more logistically straightforward and less burdensome for patients; these considerations may hold sway during the current COVID-pandemic, although BTKi therapy itself also impairs the serological response to COVID-19 vaccination.⁷⁷ However, when we return to normal circumstances, for most

patients in whom the expected duration of time on a BTKi would be beyond two to three years, the cumulative toxicity and cost burden of continuous BTKi's, especially the cardiovascular risk profile, persuade me that time-limited BCL2i is the generally preferred approach. Patients and prescribers can be confident that most patients will achieve deep remissions, with undetectable MRD status predicting prolonged disease control, and know that retreatment with venetoclax at progression or class switch to a BTKi will deliver prolonged disease control. The major unmet need is the development of effective therapies for patients with disease that is resistant to both novel drug classes and for whom outcomes are truly dismal.⁷⁸

Authorship

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