All in the family: back-to-back kinase inhibitors for the treatment of chronic lymphocytic leukemia

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All in the family: back-to-back kinase inhibitors for the treatment of chronic lymphocytic leukemia

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In this issue of *Haematologica*, Rogers et al. address a key sequencing question in the management of chronic lymphocytic leukemia (CLL) by reporting the results of the largest prospective clinical trial evaluating acalabrutinib for the treatment of CLL following intolerance to ibrutinib. While the Bruton’s Tyrosine Kinase inhibitor (BTKi) ibrutinib has led to a paradigm shift in the treatment of CLL away from chemoimmunotherapy, high rates of ibrutinib discontinuation remain a major problem.

Real world evidence (RWE) and long-term follow-up from clinical trials of ibrutinib have established that drug intolerance due to toxicity, rather than progressive CLL, is the most common reason for ibrutinib discontinuation. Real world data from 616 CLL patients treated with ibrutinib in clinical practice reported that 41% of patients discontinued ibrutinib (median follow-up 17 months), and more than half of all discontinuations were due to toxicity. RWE from the UK documents high rates of ibrutinib discontinuation due to reasons other than disease progression (17.5%). Furthermore, similar patterns have emerged with longer follow-up data from clinical trials, with more patients discontinuing ibrutinib due to toxicity rather than CLL progression. At five years of follow-up from the RESONATE-2 trial of ibrutinib for initial treatment of CLL, 41% of patients had discontinued ibrutinib therapy, with 21% discontinuation rate due to adverse events including atrial fibrillation. Furthermore, in a pooled analysis of CLL patients treated with ibrutinib on three randomized phase III studies, 11% of patients permanently discontinued ibrutinib due to adverse events and 13% of patients required dose reductions due to adverse events, highlighting the significant impact of adverse events on treatment with ibrutinib. These studies have clearly established that intolerance to ibrutinib is a common scenario encountered in clinical practice that may limit the clinical benefit of this drug that has been largely studied as a continuous therapy.

Given the clinical efficacy of BTKi in CLL, for patients who discontinue a BTKi due to intolerance, an important question is whether treatment with an alternative kinase inhibitor is an acceptable treatment option. This is particularly relevant given the development of more selective BTKis with fewer off-target effects. Newer BTKis include approved therapies such as acalabrutinib as well as emerging covalent and non-covalent BTKis in clinical development (zanubrutinib, LOXO-305, ARQ-351).

Previously, Awan et al. addressed this key question by conducting a small cohort study of acalabrutinib treatment for patients who discontinued ibrutinib due to intolerance (defined by the investigator’s discretion). In this study of 33 patients, the efficacy of acalabrutinib following ibrutinib was high (overall response rate 76%) with only 9% of patients discontinuing acalabrutinib due to an adverse event. However, this study examined only a small number of patients and lacked an objective definition of ibrutinib intolerance.

The study by Rogers et al. is the first study prospectively designed to answer this important sequencing question. Intolerance was defined as discontinuation of ibrutinib due to either persistent/recurrent grade 2 adverse events despite dose modification or interruption or persistent grade 3/4 adverse events. Sixty patients with relapsed and/or refractory CLL were treated with acalabrutinib (median prior therapies 2) with a prior median duration of ibrutinib therapy of 5.7 months. The approach was overall well tolerated, with the most common adverse events being diarrhea (53%), headache (42%) and contusion (40%). Only 40% of patients had occurrence of ibrutinib-related intolerance adverse events, and 67% of events were lower grade with acalabrutinib, with only one adverse event (increased liver function testing) occurring at a higher grade when receiving acalabrutinib compared to ibrutinib. Notably, more patients
discontinued acalabrutinib for CLL progression (23%) than adverse events (17%). Acalabrutinib following discontinuation of ibrutinib for intolerance was efficacious, with an overall response rate of 73% and a 24-month estimated progression free survival (PFS) of 72% (median follow-up 35 months). It should be noted that the majority (94%) of patients with available pre-treatment sequencing data did not have BTK or PLCG2 mutations prior to acalabrutinib initiation1.

In addition to the work presented by Rogers et al., two additional recent studies have also shown that treatment of CLL with an alternative kinase inhibitor following ibrutinib intolerance is safe and efficacious.7,8 A phase II study examined the phosphoinositide 3-kinase inhibitor (PI3Ki) umbralisib in 51 relapsed/refractory CLL patients who were intolerant to prior BTKi (n=44) or PI3Ki (n=7) and showed a median PFS of 23.5 months, with the majority (58%) of patients remaining on umbralisib for a longer duration than their prior kinase inhibitor therapy.7 Additionally, LOXO-305, a novel highly selective, non-covalent BTKi showed a favorable safety profile in 170 patients with CLL/SLL, with 86% of patients receiving a prior BTKi of which 33% discontinued the prior BTKi due to reasons other than progressive CLL.8 Furthermore, LOXO-305 had promising efficacy in this heavily pre-treated population with an overall response rate of 62% in 121 efficacy evaluable CLL/SLL patients that had previously been treated with a BTKi.8

Taken together, these studies challenge the traditional sequencing paradigm of switching drug classes in the setting of CLL therapy discontinuation for intolerance. We propose a sequencing algorithm incorporating this new data from Rogers et al. in Figure 1. While venetoclax is an acceptable option in the setting of BTKi intolerance,9 CLL remains an incurable, chronic disease and there is a strong scientific rationale to maximize clinical benefit from each drug class prior to exposing patients to the selective pressures of another therapeutic class. In the case of the common problem of intolerance to ibrutinib it is best to keep the solution "all in the (BTKi) family."
References


Figure 1. Treatment of CLL after intolerance to ibrutinib. A proposed sequencing algorithm for treatment of CLL following discontinuation of ibrutinib due to intolerance is depicted above. Abbreviations: iwCLL: International Workshop on CLL, BTKi: Bruton’s tyrosine kinase inhibitor, PI3K: phosphoinositide 3-kinase inhibitor
TREATMENT OF CLL AFTER INTOLERANCE TO IBRUTINIB

Reason for ibrutinib discontinuation

↓

Intolerance

↓

Is immediate treatment warranted?

↓

Yes

Consider treatment with alternative covalent BTKi acalabrutinib

OR

Treatment with venetoclax

OR

Treatment with PI3K inhibitor

↓

No

↓

Observe until iwCLL progression

Abbreviations: iwCLL: International Workshop on CLL, BTKi: Bruton’s tyrosine kinase inhibitor, PI3K: phosphoinositide 3-kinase inhibitor