Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Editorial
Volume 27 Issue 1 - May 2024
DOI: 10.19080/CTOIJ.2024.25.556203

Cancer Ther Oncol Int J


# Challenges with Bruton's Tyrosine Kinase Inhibitors Treatment

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**Submission:** May 15, 2024; **Published:** May 27, 2024

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**Abstract**

Bruton's tyrosine kinase (BTK) is a critical kinase in the proximal B-cell receptor (BCR) signaling that regulates proliferation and survival of B cells. BTKis are an effective novel agent that evolved considerably over the past decade for treatment of chronic lymphocytic leukemia (CLL). BTKis are continued until disease progression or development of unacceptable adverse events. Indefinite inhibition and extended exposure to BTKis can result in the development of adverse effects (AEs) and discontinuation of the drug after several years. So, long-term toxicity of BTKis should be of particular concern to get extended clinical benefit. The most concerning AEs of BTKis are infections, hemorrhage, atrial fibrillation, and headache.

**Keywords:** Bruton's tyrosine kinase; B-cell receptor; Ibrutinib; Atrial fibrillation; Clinical benefit

**Abbreviations:** AE: Adverse Events; BCR: Proximal B-cell Receptor; BTK: Bruton's Tyrosine Kinase; BTKis: BTK Inhibitors; ITK: Interleukin-2-Inducible T-cell Kinase; TEC: Tyrosine Kinase Expressed in Hepatocellular Carcinoma; CLL: Chronic Lymphocytic Leukemia; SLL: Small Lymphocytic Lymphoma; WM: Waldenström's Macroglobulinemia; MZL: Marginal Zone Lymphoma; MCL: Mantle Cell Lymphoma; cGVHD: : Chronic Graft-Versus-Host Disease; CGRP: Calcitonin Gene-Related Peptide; NSAIDs: Nonsteroidal Anti Inflammatory drugs; ADLs: Activities of Daily Livings; PPIs: Proton Pump Inhibitors; AUC: Area Under the Concentration-time Curve

## Introduction

Bruton's tyrosine kinase (BTK) is a critical kinase in the proximal B-cell receptor (BCR) signaling that regulates proliferation and survival of B cell. BTK also participates in antigen independent Toll-like receptor signaling, chemokine receptor signaling, and regulation of B cell adhesion, migration, and tumor microenvironment forces [1]. Inhibition of BTK impairs BCR signaling, cell proliferation and migration [2].

Ibrutinib, acalabrutinib and zanubrutinib are three approved BTKis) that bound covalently and irreversibly to cysteine 481 in the ATP binding pocket of BTK [1]. Ibrutinib (Imbruvica) is the first in class BTKis [3]. Acalabrutinib (Calquence) and Zanubrutinib (BGB-3111) are potent second generation BTKis [4]. Ibrutinib was FDA approved for treatment of patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia (WM), marginal zone lymphoma (MZL), and relapsed/refractory mantle cell lymphoma (MCL) in 2013 and for treatment of chronic graft-versus-host disease (cGVHD) in 2017 [3]. Acalabrutinib was FDA approved in 2019 for treatment of adults with previously untreated CLL and granted accelerated approval for treatment of MCL who received at least one prior therapy. Zanubrutinib was FDA approved in 2023 for treatment of CLL or SLL [4].

### Similarities and Differences Between Ibrutinib, Acalabrutinib and Zanubrutinib

Based on the difference in their biochemical binding kinetics, ibrutinib is the most potent BTKis followed by zanubrutinib and acalabrutinib. Acalabrutinib had a shorter half-life than ibrutinib. In addition, acalabrutinib had the lowest off-target rate and the highest selectivity followed by zanubrutinib and ibrutinib. The shorter half-life and selective properties of acalabrutinib allowed it to achieve complete and continuous inhibition of BTK without increase in the toxic effects resulting from alternative kinases inhibition [1].

## Adverse Events (AEs) in Approved BTK Inhibitors (BTKis)

BTKis are continued until disease progression or development of unacceptable AEs [1]. Indefinite inhibition and extended exposure to BTKis can result in development of adverse effects and drug discontinuation after several years [2]. So, the long-term toxicity of BTKis should be of particular concern to get extended clinical benefit [1]. The most concerning AEs of ibrutinib, acalabrutinib and zanubrutinib treatment are bleeding, infections, atrial fibrillation, and headache. The frequency of these AEs was diverse between them [1]. Ibrutinib-related emergent AEs in the integrated analysis of RESONATE and RESONATE-2 are bleeding, infections, and atrial fibrillation. The prevalence of most AEs trended down over time. The prevalence of hypertension increased, but its incidence decreased after 1 year [1]. Acalabrutinib showed a similar incidence of infections and bleeding and a lower incidence of atrial fibrillation, but it easily causes headache [1]. Zanubrutinib showed a higher incidence of hematologic AEs, while atrial fibrillation, rash or bleeding was rare [1].

BTKis toxicity is mediated by on target inhibition of BTK and by variable off-target inhibition of other kinases possessing an analogous cysteine such as ITK (interleukin-2-inducible T-cell kinase), and TEC (tyrosine kinase expressed in hepatocellular carcinoma)- family kinases [2]. Irreversible binding to ITK and TEC -family kinases, potentially disrupt normal T-cell, macrophage, and platelet function. The AE profile of Ibrutinib may be influenced by its off-target effects. Platelet dysfunction and the increased risk of bleeding with ibrutinib is attributed to its effects on BTK and TEC; rash and severe diarrhea are possibly related to its effects on EGFR (epidermal growth factor receptor), while development of atrial fibrillation has been shown to be due to molecular target of the CSK (C-terminal Src kinase). Acalabrutinib and Zanubrutinib may have fewer adverse events than ibrutinib as a result of their higher target selectivity [4]. Acalabrutinib does not inhibit Src-family kinases [5] and showed almost no inhibitory activity on EGFR; TEC kinase or ITK. This higher target selectivity possibly contributes to the higher specificity and well tolerated performance of acalabrutinib. Zanubrutinib is similar to acalabrutinib with less activity on TEC and ITK [1].

## Adverse Events (AEs) of Approved BTKis of Concern

### Headache

It is the most common AE of acalabrutinib therapy. It occurs in 22% to 51% of patients receiving acalabrutinib. It usually occurs early in the course of treatment. It is mild; typically occurs within 30 minutes of acalabrutinib dose. Treatment-related headache is of limited duration. It should abate over a period of up to 4 weeks. The mechanism(s) of headache is unclear. It could include calcitonin gene-related peptide (CGRP) agonism. It does not need medical intervention in many cases. It can be managed effectively with acetaminophen or caffeine. Nonsteroidal anti-inflammatory drugs (NSAIDs) use should be avoided if possible. Treatment discontinuation occurs in only 1% of acalabrutinib-related headaches [5].

### Atrial fibrillation

The incidence rate of atrial fibrillation in clinical trials on ibrutinib treatment was 3% and 6% after a 9-months and 18 months follow-up respectively. The 2-year incidence rate-based on randomized and observational studies-was 10% to 16%. The incidence rate of atrial fibrillation in clinical trials on acalabrutinib treatment after a follow-up period ranging from 14 to 28 months was approximately 0%-5%. The time to onset of atrial fibrillation after treatment initiation ranged from 23 days to more than 1-3 years. The slope is slightly higher in the first 6 months, then becomes stable [5]. Monitoring of atrial fibrillation is indicated in patients receiving acalabrutinib therapy. Administration of direct oral anticoagulants is recommended without the necessity to withhold acalabrutinib. Acalabrutinib discontinuation should be considered if atrial fibrillation is not medically controlled [5].

### Hypertension

Grade ≥3 hypertension (≥160/100 mm Hg) was reported in 38% of patients treated with ibrutinib; 18% of them did not have previous hypertension at baseline. After a median follow-up of 18 months, hypertension of all grades was observed in 14% of patients (4% were grade 3). In acalabrutinib treated patients, grade ≥3 hypertension was reported in 2%-7% of patients after a median follow-up ranging from 14 to 28 months. In the ACE-CL-001 phase 2 study, 18% of patients on acalabrutinib experienced hypertension of all grades (10% were grade 1-2, and 7% were grade ≥3) after a 41-month follow-up period [5]. Proposed mechanisms of hypertension include PI3k/Akt inhibition, leading to downregulation of PI3Kp110 alpha and nitrous oxide production [2]. Hypertension should be managed with antihypertensive medication [5].

### Neutropenia

Neutropenia is commonly observed in patients treated with BTKis due to on-target toxicity effect. Grade ≥3 neutropenia was reported in 10%-16% of patients treated with acalabrutinib monotherapy, 10% of patients treated with ibrutinib, and 44% of patients treated with zanubrutinib. Dose interruptions are recommended for the first to third occurrences of grade 3 or 4 neutropenia. Dose discontinuation is recommended after a fourth occurrence [5].

### Infections

Grade ≥3 infections developed in 17.9% of ibrutinib-treated patients and in 14% of patients receiving acalabrutinib monotherapy. In CLL patients treated with zanubrutinib; infections


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of any grade occur in 64% of treatment naive CLL patients (13.8% were grade ≥3) and in 39% of R/R CLL patients (≥1 was grade ≥3 infection). Most were respiratory tract infections and were effectively managed without a dose reduction or treatment discontinuation. Prophylactic treatment should be considered in patients at a higher risk of developing opportunistic infections [5].

**Bleeding**

BTKis may increase the risk of bleeding by impairing collagen induced platelet activation. Inhibition of Src-kinases is suggested to be associated with bleeding. Acalabrutinib has less inhibitory potential on Src-family kinases compared with ibrutinib. Monitoring for signs of bleeding is important in patients receiving acalabrutinib therapy [5].

**Diarrhea**

It occurs early in BTKis treatment (before month 6) with a predominantly self-limited course. Ibrutinib-related diarrhea is probably EGFR mediated. Rates of diarrhea are similar in ibrutinib and acalabrutinib (despite differences in EGFR binding). Most BTKis-related diarrhea is managed with supportive care, antimotility agents, and nighttime dosing of drug (in the case of ibrutinib) to mitigate symptoms. Drug is temporary holds in grade ≥3 diarrhea [2].

**Fatigue**

Fatigue is a commonly reported early symptom in the course of BTK inhibition. It is reported in 36% of patients on ibrutinib (0% to 3% were grade 3) and in 28% to 34% of patients on acalabrutinib (0% to 2% were grade 3). It is usually self-limited. Dose interruption is not typically advocated particularly if fatigue occurs early after therapy initiation. Consider a drug holiday or dosage reduction if fatigue persists or occurs significantly later during the course of therapy, to assess whether it is drug related or not [2].

**Arthralgia and myalgia**

Arthralgia and myalgia are seen in 11% to 36% of patients on ibrutinib. The majority of arthralgias developed at 7 months after treatment initiation. It is a dynamic pattern of migratory arthralgias that can be debilitating. Risk factors included female sex and treatment-naive status. Observation is recommended for grade 1 to 2 arthralgia, with dosage reduction when symptoms affect activities of daily living (ADLs). Dose holds were recommended for grade ≥3 arthralgia (affecting self-care ADLs), with rechallenge at lower dosages if symptoms resolve. Severe arthralgia demonstrates a variable response to short-course steroids and anti-inflammatory agents (which must be cautiously used given the potentially higher risk of bleeding on BTKis). Arthralgia was associated with ibrutinib discontinuations in 42% of patients in real-world data [2].

## Selection of BTKis treatment

**i.** Different BTKis were chosen, according to their differential toxicity performance in clinical practice. Acalabrutinib is not recommended for patients with headaches. Ibrutinib is not recommended for patients with a high risk of cardiovascular or cerebrovascular diseases. Zanubrutinib may be a better choice in these cases (1).

**ii.** BTKis are not recommended for patients with any of the following: history of ventricular arrhythmia, family history of sudden cardiac death, severe uncontrolled hypertension, severe or uncontrolled congestive heart failure (LVEF less than 30%) [6].

**iii.** Consider any approved BTKis in patients with no cardiovascular risk factors [6].

**iv.** Consider second-generation BTKis (acalabrutinib or zanubrutinib) in patients with cardiovascular risk factors (e.g., well-controlled atrial fibrillation, hypertension) [6].

## BTK inhibitor resistance

The three BTKis ibrutinib, acalabrutinib and zanubrutinib target BTK at the C481 site; therefore, it may not be effective to switch to another BTKis when resistance occurs. Acquired resistance to BTKis may be overcome by using third-generation non-covalent BTKis that do not rely on interaction with Cys481. These agents remain investigational or combine BTKis with PI3K, SYK, or BCL-2 inhibitors to inhibit bypass signaling activation; or to treat with other novel therapies such as chimeric antigen receptor T-cell immunotherapies [1].

## Clinical Practical points

**i.** Co-administration of acalabrutinib with proton pump inhibitors (PPIs) should be avoided. Co-administration of acalabrutinib with omeprazole 40 mg for 5 days is associated with a 43% reduction in the area under the concentration-time curve (AUC) [5].

**ii.** Monitor blood pressure at least biweekly for the first 3-6 months of BTKis treatment [6]. The dosage of antihypertensive medication has to be adjusted once any BTKis therapy is discontinued [5].

**iii.** The combination of BTKis with anticoagulants should be used with extreme caution [1].

**iv.** It is recommended to continue BTKis particularly the covalent BTKis during the transition period until the next line of therapy particularly venetoclax treatment is started and its target dose is reached. A disease flare phenomenon, characterized by rapidly progressive symptoms and adenopathy and rarely histopathologic evidence of Richter transformation, may occur during interruption of BTKis treatment [1].


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## Conclusion

The long-term toxicity of BTKis should be of particular concern to get extended clinical benefit. There is some difference in the pharmacodynamics and pharmacokinetics among the three BTKis, ibrutinib, acalabrutinib and zanubrutinib. These diversities have to be translated into a clinical benefit. Head-to-head randomized clinical trials are still needed to determine which BTKis is the best-in-class drug.

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