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BRUTON TYROSINE KINASE INHIBITORS FOR B-CELL MALIGNANCIES

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Introduction

Over the last 10 years, Bruton Tyrosine kinase inhibitors (BTKi) have been a significant breakthrough for the treatment of B-cell malignancies, especially in chronic lymphocytic leukemia (CLL). Since the initial publication of the activity of ibrutinib in 2013,[1] many publications have highlighted the improved outcomes for patients with B-cell malignancies owing to the use of ibrutinib and other BTKi. BTKi monotherapy has been standard of care for many years and more recently, combination therapies that include targeted therapy or chemotherapy are being studied.

Ibrutinib is a first generation BTKi. In initial studies, toxicity was cited as the cause of ibrutinib discontinuation in up to 28% of patients.[2] This led to the development of acalabrutinib and zanubrutinib which are both second generation BTKi and are expected to have a better safety profile. Ibrutinib, acalabrutinib, and zanubrutinib are covalent BTKi. They form an irreversible covalent bond with the cysteine residue (C481) at the active binding site of Bruton tyrosine kinase (BTK).[3] Ibrutinib, acalabrutinib, and zanubrutinib are available to treat B-cell malignancies in Canada. Non-covalent BTKi, such as pirtobrutinib,[4] are being developed but are not yet available in Canada.

The indefinite duration of treatment with these BTKi therapies raises an important concern in terms of the long-term toxicity, which has a significant impact on our choice of therapy when more than one BTKi or even another treatment option is available.

This article will focus on major differences between the 3 currently available BTKi (ibrutinib, acalabrutinib, and zanubrutinib) for use by Canadian clinicians to treat patients with B-cell malignancies.

Chronic lymphocytic leukemia

A 55-year-old male patient with no history of medical issues was diagnosed with CLL 8 years ago. He initially presented with significant lymphadenopathy, weight loss, and cytopenia. Deletion 17p del(17p) and del 11q were negative. He was treated with 6 cycles of fludarabine, cyclophosphamide and rituximab (FCR) and had a good response and complete count recovery. He was under clinical observation for 8 years and recently presented with recurring systemic symptoms and thrombocytopenia. Bone marrow aspirate confirmed 90% infiltration by CLL. Notably, the patient was positive for del(17p). BTKi is considered the best treatment option for him. However, which BTKi should you choose, and why?

CLL is the most common leukemia in adults in Canada, with over 2000 patients diagnosed per year and more than 600 deaths occur annually owing to this disease.[5] In CLL, BTK is overexpressed and constitutively phosphorylated,

making it a target of choice for therapeutic intervention. Over the past 10 years, several phase 3 clinical trials have been conducted in patients with CLL who are treatment-naïve (TN) (**Table 1**),[6-12] and relapse/refractory (R/R) (**Table 2**).[13-18] The majority of the trials have compared BTKi to either immunotherapy or chemo-immunotherapy; however, very few trials have compared different BTKi therapies against each other.

Two recent studies directly compared two different BTKi in a head-to-head comparison. ELEVATE RR compared acalabrutinib to ibrutinib in the R/R setting.[17] The trial included 533 patients with R/R CLL with confirmed del(17p) and del 11q. The overall response rate (ORR) was 81% for acalabrutinib and 77% for ibrutinib. After a median follow-up of 41 months, the median progression-free survival (PFS) was 38 months for both treatment arms, meeting the pre-specified non-inferiority endpoint. Overall survival (OS) data is not yet available. The safety analysis showed that fewer patients treated with acalabrutinib experienced diarrhea (35% vs. 46%), arthralgia (16% vs. 23 %), hypertension (9% vs. 23 %), contusion (12% vs. 18 %), atrial fibrillation (9% vs. 16%), and muscle spasms (6% vs. 13%), but had higher rates of headaches (35% vs. 20%) and cough (29% vs. 21%) compared with ibrutinib. Overall, this more favourable safety profile resulted in fewer patients discontinuing treatment in the acalabrutinib arm (15% vs. 21%). Dose reductions and dose interruptions were comparable in both treatment arms.

The ALPINE study, conducted in patients with R/R CLL, compared zanubrutinib to ibrutinib.[18] Both high risk and standard risk R/R patients were included in the study. The ORR was 84% for zanubrutinib compared with 74% for ibrutinib. With a median follow up of 30 months, the PFS at 24 months was 78% for zanubrutinib versus 66% for ibrutinib (p=0.002). Median OS data is not yet available. Zanubrutinib was associated with less cardiotoxicity (21% vs. 30%), and a lower incidence of atrial fibrillation/flutter (5% vs. 13%) compared with ibrutinib. Major bleeding occurred with similar frequency in the two arms (4%) as did hypertension (24% and 23%). Zanubrutinib was associated with a higher rate of neutropenia (29% versus 24 %) along with similar rates of ≥ grade 3 infections (27% vs. 28 %) compared with ibrutinib. Zanubrutinib has been associated with a lower rate of treatment discontinuation due to adverse events (15% vs. 22%) compared with ibrutinib. Treatment discontinuations due to cardiac disorders were 0.3% with zanubrutinib versus 4.3% with ibrutinib. Notably, of the six deaths due to cardiac events that had occurred, all were in patients who received ibrutinib.

Overall, these 2 trials support the use of acalabrutinib and zanubrutinib in patients with CLL based on better safety profiles. Of note, zanubrutinib demonstrated a superior efficacy in the R/R setting. Real-world evidence comparing the efficacy of BTKi therapies in patients with CLL is limited. Roeker et al. recently published their research using the Flatiron health database.[19] Of the 2,509 patients included in the analysis, 90% received ibrutinib, and 14% received acalabrutinib. Time to treatment discontinuation was the primary outcome. The discontinuation rate at 12 months was 22% for the acalabrutinib cohort vs. 31% for the ibrutinib cohort (p=0.005). In another analysis, the discontinuation of BTKi (acalabrutinib and ibrutinib) was mainly for adverse events (52%) followed by disease progression (21%), highlighting the importance of adverse event minimization in these patients.[20]

Other B-cell malignancies

A 61-year-old male patient was diagnosed with Waldenström macroglobulinemia (WM) 5 years ago. He also had type 2 diabetes mellitus and hypertension. He presented with recurring epistaxis and a serum IgM level of >100 g/L. He initially completed 3 rounds of plasmapheresis, then went on to receive bendamustine and rituximab for 6 cycles with a very good partial response. His serum IgM level had significantly increased 2 years later, for which he was treated with bortezomib, dexamethasone, and rituximab for 6 cycles, and had achieved a partial response to this therapy. He recently presented with a rapidly progressive serum IgM level of >100 g/L and recurrent epistaxis. He underwent urgent plasmapheresis and now you want to offer him a BTKi. Which BTKi should you choose, and why?

BTKi have shown activity in a range of other B-cell malignancies. Phase 3 trials have been conducted in patients with mantle cell lymphoma (MCL)[21,22] and WM.[23,24] A small number of phase 2 trials have also been conducted in MCL,[25-27] WM, [28] diffuse large B cell lymphoma,[29] marginal zone lymphoma (MZL),[30,31] primary central nervous system lymphoma,[32] and follicular lymphoma,[33-34]

Outside the CLL setting, the only randomized trial comparing BTKi head-to-head is the ASPEN trial,[24] in which patients with WM who were TN or R/R with or without the MYD88 mutation received either zanubrutinib or ibrutinib. This trial showed comparable efficacy for those treated with zanubrutinib or ibrutinib in terms of achieving a very good partial response or complete response (28% vs. 19%), PFS (85% vs. 84% at 18 months) and OS (97% vs. 93% at 18 months). Zanubrutinib was associated with less toxicity and with lower rates of diarrhea (21% vs. 32%), contusion (13% vs. 24%), muscle spasms (10% vs. 24%), peripheral edema (9% vs. 19%), atrial fibrillation/flutter (2% vs. 15%), hypertension (11% vs. 16%), and pneumonia (2% vs. 12%). Zanubrutinib was associated with higher rates of all grade neutropenia (29% vs. 13%) which is consistent with other zanubrutinib trials. However, the higher rates of neutropenia did not translate into higher infection rates. The trial also evaluated zanubrutinib in the MYD88 ^{WT} population and demonstrated comparable efficacy and safety to the MYD88 mutant population. This trial supports the use of

Trial	Treatment arms	N	PFS	OS
ECOG-ACRIN E1912[6]	IR vs. FCR	529	89% vs. 73% at 36 months (p<0.001)	99% vs. 92% at 36 months (p<0.001)
FLAIR[7]	IR vs. FCR	771	86% vs. 73% at 48 months (p<0.0001)	92% vs. 94% At 48 months (p=0.96)
RESONATE-2[8]	I vs. chlorambucil	269	90% vs. 52% at 18 months (p<0.001)	98% vs. 85% at 34 months (p=0.001)
iLLUMINATE[9]	IO vs. CO	229	79% vs. 31% at 30 months (p<0.0001)	86% vs. 85% at 30 months (p=0.81)
Alliance A041202[10]	I vs. IR vs. BR	547	87% vs. 87% vs. 74% at 24 months (P<0.001 for I vs. BR, p=0.49 for I vs. IR)	90% vs. 94% vs. 95% at 24 months (p=0.65)
ELEVATE TN[11]	AO vs. A vs. CO	535	87% vs. 78% vs. 25% at 48 months (p<0.0001 for AO vs. CO, p<0.0001 for A vs. CO)	93% vs. 88% vs. 88% at 48 months (p=0.057 for AO vs. CO, p=0.156 for A vs. CO)
SEQUOIA[12]	Zanubrutinib vs. BR	479	86% vs. 70% at 24 months (p<0.0001)	94% vs. 95% at 24 months (p=0.87)

Table 1.*Major phase 3 trials in treatment naïve chronic lymphocytic leukemia patients; courtesy of Christopher Lemieux, MD, FRCPC A, acalabrutinib; AO, acalabrutinib+obinutuzumab; BR, bendamustine+rituximab; CO, chlorambucil+obinutuzumab; FRC, fludarabine+cyclophosphamide+rituximab; I, ibrutinib, IO, ibrutinib+obinutuzumab; IR, ibrutinib+rituximab; N, number of patients; OS, overall survival; PFS, progression-free survival*

Trial	Treatment arms	N	PFS	OS
RESONATE[13,14]	Ibrutinib vs. Ofatumumab	391	Median of 44 months vs. 8 months (p<0.001)	Median of 68 months vs. 65 months (HR: 0.639; 95% CI: 0.418-0.975)
ASCEND[15,16]	Acalabrutinib vs. investigator choice (BR or idelalisib-rituximab)	398	62% vs. 19% at 42 months (p<0.001)	78% vs. 65% at 42 months (p=0.078)
ELEVATE RR[17]	Acalabrutinib vs. Ibrutinib	533	Median of 38 vs. 38 months HR 1.00 (0.79-1.27 for non-inferiority)	NR in both treatment arms (HR 0.82; 95% CI, 0.59 to 1.15)
ALPINE[18]	Zanubrutinib vs. Ibrutinib	652	78% vs. 66% at 24 months (p=0.002)	NR in both treatment arms (HR 0.76; 95% CI, 0.51 to 1.11)

Table 2. *Major phase 3 trials in relapsed/refractory chronic lymphocytic leukemia patients; courtesy of Christopher Lemieux, MD, FRCPC BR, bendamustine+rituximab; HR, hazard ratio; N, number of patients; NR, not reached; OS, overall survival; PFS, progression-free survival*

zanubrutinib in WM, based on the improved safety profile. Considering MCL and MZL, for which we have phase 2 data on second generation BTKi, we also favour those BTKi over ibrutinib if available.

Consistently, second generation BTKi offer significantly fewer adverse events when compared with ibrutinib. Some of these adverse events are manageable and not problematic, although some adverse events can significantly impact the patient's treatment course. Atrial fibrillation (AFib) is the most problematic side effect associated with the use of BTKi. The mechanism underlying ibrutinib-induced AFib is not completely understood. Proposed mechanisms are off-target inhibition of cardiac phosphoinositide 3-kinase or receptor tyrosine-protein kinase ERBB-2 (HER2). However, HER2 is not inhibited with acalabrutinib and zanubrutinib,[35] which could partially account for the lower incidence of AFib associated with these second generation BTKi. A majority of patients with AFib will require preventive anticoagulation, thus increasing the patient's risk of a major hemorrhage given the antiplatelet effect associated with BTKi. Regardless of the mechanism, AFib increases the risk of all-cause and cardiovascular mortality.[36] Therefore, it is of vital importance to limit the risk of AFib in patients' receiving treatment with BTKi.

Other BTKi are currently in development. For example, pirtobrutinib, a selective, noncovalent (reversible) BTKi that inhibits both wild-type and C481-mutant *BTK*, which are the most common mutations associated with resistance to covalent BTKi.[37] Pirtobrutinib has shown promising results in MCL and CLL, including most patients previously treated with a covalent BTKi, and is associated with a very low rate of AFib (1%) and hypertension (4%).[4,38]

Conclusion

BTKi represent a significant breakthrough for patients with B-cell malignancies. However, the indefinite duration of therapy with BTKi, and the potential for toxicity, notably AFib, are important considerations in the treatment decision-making process. Second-generation BTKi are at least comparable to the first-generation BTKi, ibrutinib, in terms of efficacy, in most indications except in R/R CLL where zanubrutinib was shown to have superiority over ibrutinib. Second-generation BTKi have a better safety profile, making them the preferred choice for many patients, especially given that there is data supporting their use in specific diseases such as CLL and other B-cell malignancies.

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