ABOUT THE AUTHOR

Anthea Peters, MD

Dr. Anthea Peters is a hematologist based at the Cross Cancer Institute in Edmonton, Alberta and an Associate Professor in the Department of Oncology at the University of Alberta. She completed her MD at the University of Saskatchewan, internal medicine residency training at the University of Alberta and hematology training as well as a lymphoma fellowship at the University of Calgary. Her clinical and research interests are centered around lymphoma and chronic lymphocytic leukemia (CLL), with a special interest in post-transplant lymphoproliferative disorders. She is currently the clinical lead for lymphoma and CLL for Northern Alberta.

SAFETY AND TOLERABILITY OF BRUTON'S TYROSINE KINASE INHIBITORS IN THE TREATMENT OF WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia (WM) is an indolent B-cell non-Hodgkin lymphoma (NHL) characterized by malignant B cells that produce IgM monoclonal protein. Like other indolent B-cell NHLs, treatment is indicated when patients are symptomatic with lymphadenopathy, splenomegaly or have detrimental cytopenias, but uniquely hyperviscosity and other complications related to gammopathy may present a need for treatment[1]. Currently in Canada chemoimmunotherapy using bendamustine and rituximab (BR) is the favored therapeutic combination for treatment-naïve patients with WM due to a superior efficacy and toxicity profile compared to rituximab plus CHOP[2] and a fixed duration schedule[3]. The availability of Bruton's tyrosine kinase inhibitors (BTKi) have transformed the treatment landscape for patients with WM, particularly in the relapsed setting. Ibrutinib, a once-daily BTKi, was approved by Health Canada (HC) for WM in 2016 based on two non-randomized studies showing high response rates in heavily pretreated rituximab-refractory patients with sustained efficacy (86% progression-free survival (PFS) at 18 months) and acceptable tolerability[4,5]. Ibrutinib forms an irreversible covalent bond to the cysteine residue (C481) at the active binding site of BTK[6]. Patients with mutated MYD88 ($MYD88^{MUT}$), who represent over 90% of patients with WM, have a higher rate of response with ibrutinib than those without ($MYD88^{WT}$)[4,7,8]. Aside from its impressive efficacy, its oral administration offers a major advantage in terms of convenience for patients and lower administrative costs for publicly funded health care systems such as in Canada.

The toxicity of ibrutinib has become of greater concern with the ongoing emergence of trial data and real-world clinical experience with the drug. The indefinite duration of treatment results in extended exposure of a primarily elderly patient population to toxicities such as increased bleeding risk, atrial fibrillation, hypertension, and infection. Discontinuation of ibrutinib due to adverse events occurs at a higher rate in the real-world compared to clinical trials and has been associated with an inferior overall survival in WM[9].

Fortunately, several BTKis have recently emerged. Both acalabrutinib and zanubrutinib also bind irreversibly to BTK at C481, but both have more selectivity for targeting BTK than ibrutinib[6,10-12]. Data has demonstrated that tighter and more selective binding of BTK does translate into fewer adverse effects for patients[10,12]. The most informative study to date in this regard is the randomized phase 3 clinical trial comparing ibrutinib to zanubrutinib, the ASPEN study[10]. ASPEN is the largest multicentre phase 3 trial to date randomizing 201 patients with $MYD88^{MUT}$ WM to receive ibrutinib at 420 mg daily (n=99) vs. zanubrutinib 160 mg twice daily (n=102), with 37 patients being treatment-naïve and 164 being relapsed or refractory (R/R) with a median of 1 prior line of therapy (range 1-8). The median age at enrolment was 70 however

more patients randomized to zanubrutinib than to ibrutinib were >75 years old (33% vs 22%, respectively). Although not statistically significant, a higher rate of complete response (CR)/very good partial response (VGPR) was observed for zanubrutinib vs ibrutinib (28% vs 19%, respectively). With a median follow up of 19.4 months the major response rates (77% vs. 78%) and PFS (85% vs. 84% at 18 months) were also not statistically different in patients receiving zanubrutinib vs. ibrutinib, respectively. However, zanubrutinib was associated with a trend towards less toxicity. In particular, the incidences of all grade atrial fibrillation, diarrhea, bruising, muscle spasms, peripheral edema, and pneumonia were over 10% higher among ibrutinib-treated patients. The incidence of neutropenia was higher for zanubrutinib-treated patients (> 10% difference), although grade ≥3 infection rates were similar in both arms (1.2 and 1.1 events per 100 person-months). Further, more ibrutinib-treated patients required dose reductions (23% vs. 14%) and discontinued treatment (9% vs. 4%) due to adverse events. An analysis of quality of life (QoL) instruments demonstrated a trend towards greater improvement in the zanubrutinib arm, particularly in the subgroup of patients who achieved VGPR. These QoL improvements were most notable in validated instrument subscales encompassing appetite, dyspnea, fatigue, physical functioning and role functioning. The ASPEN trial formed the basis for recent approval of zanubrutinib for WM by HC. Although provincial funding is not yet in place, clinicians in Quebec can access zanubrutinib through the Patient d'exception mechanism.

As Canadian hematologists will be able to choose a BTKi for their patient with R/R WM, it is important to review the toxicities reported in trials. Toxicities of BTKis and their management will be discussed in this article.

Table 1 details adverse event rates in select trials and atrial fibrillation, hypertension and bleeding AEs are discussed below.

Atrial fibrillation

Atrial fibrillation (AFib) is one of the most problematic side effects associated with the use of BTKis. Although the consensus approach to AFib management is to continue treatment with the BTKi while medically managing the AFib, patients often require preventative anticoagulation depending on their additional risk factors for cerebrovascular accident (CVA), thus increasing the patient's risk of a major hemorrhage given the BTKis' antiplatelet effect.

In the original clinical trial using ibrutinib in previously-treated WM patients, the incidence of AFib increased to

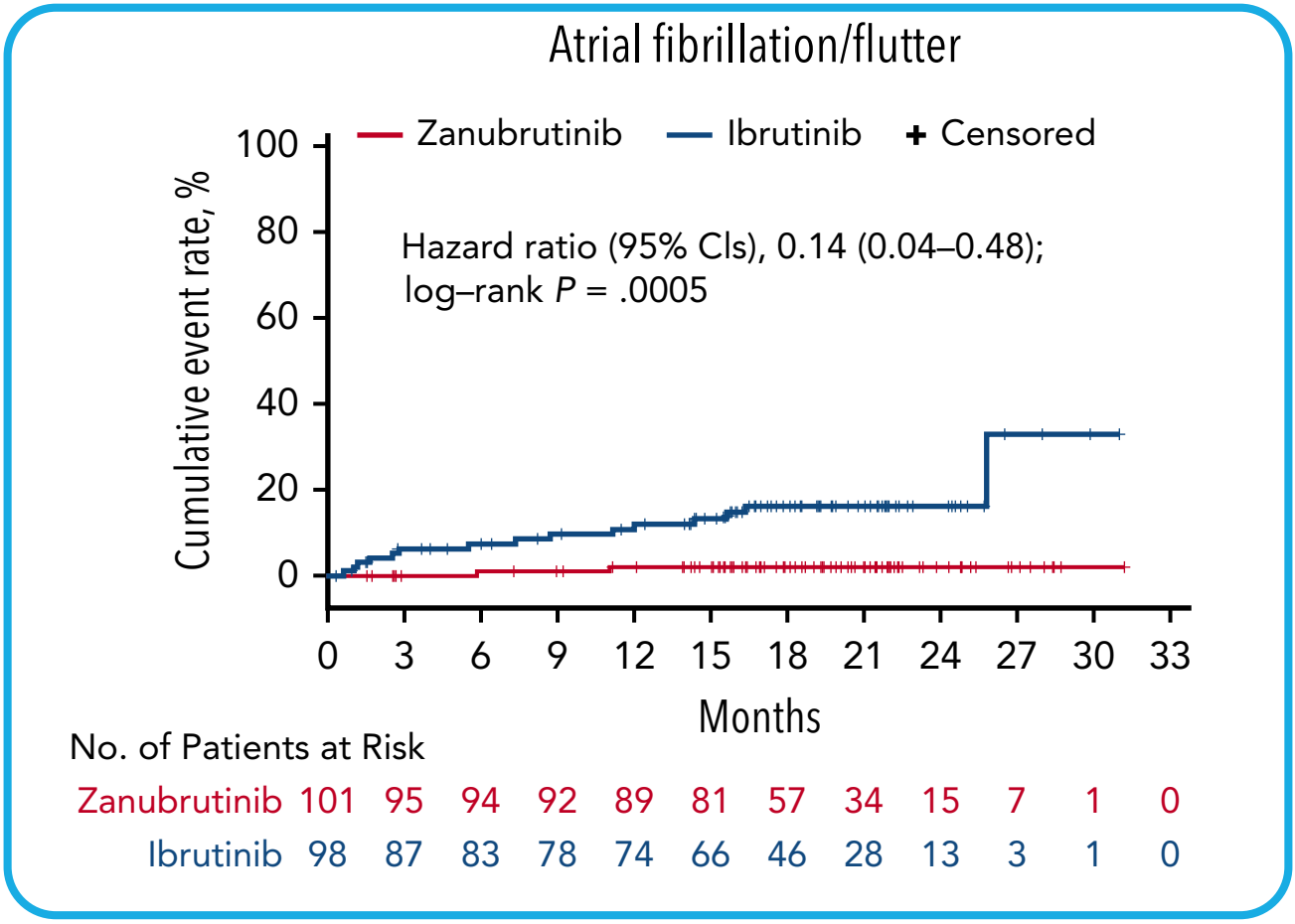

Figure 1. *Time to event analysis for atrial fibrillation/flutter; adapted from Tam et al*

13% with prolonged use, with the median time to onset of AFib at 15 months (range 3-38)[13]. Similarly, the phase 3 iNNOVATE trial reported a 15% AFib rate of any grade in the ibrutinib + rituximab arm vs. 3% placebo + rituximab[7]. In the ASPEN trial 15% of patients in the ibrutinib arm developed AFib (4% Grade ≥ 3) compared to 2% of those patients in the zanubrutinib arm (0% Grade ≥ 3)[10]. The incidence of AFib was approximately 10-fold higher with ibrutinib vs zanubrutinib (1.0 vs. 0.1 events per 100 person-months). The onset occurred predominantly in the first 6 months of ibrutinib (**Figure 1**). The AFib rate was similarly low with zanubrutinib in a phase 2 trial[11]. AFib occurred at a similarly low rate with acalabrutinib (5% with only one event grade 3, requiring cardioversion)[12].

Real-world evidence studies describing patients on monotherapy with ibrutinib for WM suggests that the rate of AFib with this agent is similar to that reported in trials[9,14,15]. In a relatively large cohort of 80 patients treated at Mayo Clinic, 84% of whom were R/R, the rate of AFib was 11% with most cases being new-onset (n=7). Patients with a prior history experience AFib more quickly after starting ibrutinib than those with no prior history[14]. Strikingly, the rate of discontinuation due to AFib in this RWE study was 16%, which is a large percentage of the overall rate of discontinuation for reasons other than disease progression (21%)[15]. Discontinuation for reasons other than disease progression has been shown to lead to inferior survival[9].

The management of BTKi-induced AFib requires an interdisciplinary team to assess the risk-benefit regarding continuation of the drug as well as evaluation of cardiovascular risk factors to control rate and initiate anti-coagulation therapy[6].

Hypertension

Hypertension is another problematic toxicity associated with the use of BTKis as it increases the risk of cardiovascular events; it is often asymptomatic and requires specific management. The incidence of hypertension was higher with ibrutinib vs. zanubrutinib in the ASPEN trial, with almost twice as many grade 3 or higher events (11% vs. 6%)[10]. Additionally, more ibrutinib-treated patients developed hypertension beyond 12 months (6 vs. 1 patient). The incidence of hypertension was particularly low with acalabrutinib[12].

The optimization of blood pressure prior to starting BTKis and routine monitoring in collaboration with primary care practitioners is recommended[6].

Bleeding

In iNNOVATE, bleeding events occurred more frequently in patients on ibrutinib + rituximab compared to placebo + rituximab (51% vs. 21%) but major hemorrhages occurred in only 3 patients (4%) in each arm[5]. Contusions and epistaxis (grade 1-2) were less common with zanubrutinib than ibrutinib[10]. In addition, the incidence of bleeding and major hemorrhage was also lower with zanubrutinib, although the comparison of exposure-adjusted incidence was not statistically significant (p=0.08). Researchers reported three grade 3-4 hemorrhage events with zanubrutinib, one requiring drug cessation[11]. In a single-arm study using acalabrutinib, 58% of patients had a bleeding event; three were grade 3-4 (1 dysfunctional uterine bleed, 1 retinal bleed, and 1 epistaxis), but one patient on apixaban died from an intracranial hematoma[12].

Patients on BTKis are recommended to hold their drug prior to and after surgical procedures to prevent bleeding and are also instructed to avoid supplements that may exacerbate bleeding risk (e.g. fish oils), as well as to avoid using concurrent warfarin and dual antiplatelet therapy[6]

Conclusions

With similar efficacy but improved tolerability, zanubrutinib is preferred over ibrutinib. Zanubrutinib is currently available only by compassionate access at the time of this supplement's release, but reimbursement has been recommended by both CADTH and INESSS. In addition, resistance to ibrutinib (and likely the newer BTKis) is known to occur with acquisition of mutations of BTK at the C481 site. As the treatment landscape for WM continues to evolve with the arrival of BTKis and other novel agents, it is imperative that clinicians have a good understanding of the potential AE profiles associated with these agents in order to optimize outcomes for patients.

Late Breaking ASPEN Trial Long-Term Data

At the recent 2022 ASCO and EHA meetings, researchers presented a poster on the long-term data from the ASPEN trial with a median follow up of 43 months. As previously outlined, patients in the ASPEN trial with $MYD88^{MUT}$ were assigned to cohort 1 and randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg. Patients without MYD88 mutations were assigned to cohort 2 and received zanubrutinib 160 mg twice daily. The median duration of treatment was 42 months (zanubrutinib) and 41 months (ibrutinib), with 67% and 58% remaining on treatment, respectively in this most recent analysis. Researchers report zanubrutinib being associated with higher CR + VGPR rate compared to ibrutinib. Zanubrutinib also demonstrated a clinically meaningful benefit vs ibrutinib in terms of long-term safety and tolerability as evidenced by lower rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death. This late-breaking poster continues to support earlier analysis showing that zanubrutinib demonstrates clinically meaningful efficacy in WM patients and consistent safety advantages with less off-target activity compared to ibrutinib.

Trial	Trial Type	TN/RR (%)	Agent	Bleeding	Atrial Arrhythmias	Hyper-tension	Neutropenia	Diarrhea	Med. Rx Duration (mos)	Rate discontinuation for AEs (%)
Treon et al.[4] (grade 1 AEs not reported)	2	0/100	Ibr	B 6.3/1.6	5/2	6/0	24/16	3/0	19.1	8
iNNOVATE[7]	3	45/55	Ibr+R	H 4/2.7	NR/12	13/13	NR/9	28/0	25.8	5
ASPEN[10]	3	18/81	Ibr	E 19/0 C 24/0 H 7/0.5*	15/4	16/11	13/8	32/1	18.6	9
		19/83	Zanu	E 13/0 C 13/0 H 4.4/0.3*	2/0	11/6	29/20	21/3	18.7	4
Trotman et al.[11]	1/2	31/69	Zanu	C 32.5/0 E 13/0 B 62.3/3.9 (4.5/0.1*)	5/1	16/4	18/16	20/3	(med f/u 36 mos)	13
Owen et al.[12]	2	13/87	Acala	C 29/0 E 10/1 B 58/3	5/1	5/3	17/16	31/2	(med f/u 27.5 mos)	7

Table 1. *Comparison of AE rates from select trials; courtesy of Anthea Peters, MD*

Acala, acalabrutinib; B, bleeding; C, contusion; E, epistaxis; H, hemorrhage; ibr, ibrutinib; TN, treatment-naïve; R, rituximab; RR, relapsed/refractory; zanu, zanubrutinib
**events per 100 person-months*
Numbers in table represent % all grade/grade ≥ 3 unless otherwise indicated

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