International consensus statement on the management of cardiovascular risk of Bruton’s tyrosine kinase inhibitors in CLL

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Bruton’s tyrosine kinase inhibitors (BTKis) have altered the treatment landscape for chronic lymphocytic leukemia (CLL) by offering effective and well-tolerated therapeutic options. However, since the approval of ibrutinib, concern has risen regarding the risk of cardiovascular (CV) adverse events, including atrial fibrillation (AF), hypertension, and heart failure. Newer BTKis appear to have lower CV risks, but data are limited. It is important to understand the risks posed by BTKis and how those risks interact with individual patients, and we convened a panel of physicians with expertise in CLL and CV toxicities in oncology to develop evidence-based consensus recommendations for community hematologists and oncologists. Care providers should thoroughly assess a patient’s CV risk level before treatment initiation, including established CV diseases and risk factors, and perform investigations dependent on preexisting diseases and risk factors, including an electrocardiogram (ECG). For patients with high CV risk, BTKi treatment is often appropriate in consultation with a multidisciplinary team (MDT), and more selective BTKis, including acalabrutinib and zanubrutinib, are preferred. BTKi treatment should generally be avoided in patients with a history of heart failure. Ibrutinib should be avoided in patients with a history of ventricular arrhythmias, but the risk of newer drugs is not yet known. Finally, an MDT is crucial to help manage emerging toxicities with the goal of maintaining BTKi therapy, if possible. Optimizing heart failure, arrhythmia, and hypertension control will likely improve tolerance and maintenance of BTKi therapy. However, additional studies are needed to identify the most optimal strategy for these drugs.

Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the developed world, with a growing global incidence of 91 per 1000 in 2017.1 Against the backdrop of this increase, the development of Bruton’s tyrosine kinase inhibitors (BTKis) has transformed the treatment landscape of CLL. Preclinical
studies showed inhibition of BTK by ibrutinib, a first-in-class oral nonreversible inhibitor of BTK, interfered with B-cell antigen receptor signaling and caused the selective apoptosis of B cells without affecting T-cell survival.\(^2,3\) Multiple phase 3 clinical studies in patients with CLL have demonstrated ibrutinib has dramatically better efficacy than traditional chemoimmunotherapies (CITs) and is well tolerated.\(^4,6\)

However, BTKis are given daily until disease progression or discontinuation because of toxicity, and accumulating data have revealed multiple adverse events (AEs) that are specifically associated with ibrutinib, including cardiovascular (CV) AEs such as atrial fibrillation (AF) and other arrhythmias, hypertension (HTN), and non-CV AEs such as bleeding, infection, diarrhea, and arthralgias in long-term follow-up.\(^4,10\) After potential signals of CV toxicities in clinical trials, further evidence from meta-analyses, observational studies, and pharmacovigilance data has confirmed the heightened risk.\(^11-15\) For example, retrospective data from 778 case-control pairs in a recent Canadian study suggest that the 3-year risk for AF and heart failure is roughly doubled in patients receiving ibrutinib therapy compared with matched control samples,\(^16\) and a long-term follow-up in patients treated with ibrutinib monotherapy (median, 87 months) reported HTN of grade ≥3 in 28% of subjects.\(^17\) This is consistent with multiple previous reports documenting a higher incidence of these AEs in patients treated with ibrutinib.\(^1,13,15,18\) It is apparent, however, that many of these patients with some elevated CV risk can still safely benefit from BTKi therapy.\(^19,20\) Therefore, it is crucial to minimize the CV risk in patients through careful monitoring and early toxicity management.

There are now multiple irreversible BTKis in development with greater selectivity for BTK (hereafter referred to as second-generation BTKis), including acalabrutinib, which has been recently approved by the European Union, the US Food and Drug Administration, and the Japanese Ministry of Health, Labor, and Welfare for treating patients with CLL. Zanubrutinib, another second-generation irreversible inhibitor, is approved for other B-cell malignancies and is being evaluated for use in patients with CLL.\(^21,22\) Because they are more selective and have fewer “off-target” effects, it was hoped these agents would retain the benefits of ibrutinib while producing fewer CV AEs. Randomized trials of ibrutinib and second-generation BTKis, including the ELEVATE-RR, ALPINE, and ASPEN studies, have allowed the hypothesis of fewer CV toxicities to be tested in phase 3 trials for the first time. The publication of these data provides a good opportunity to reexamine and reevaluate standards of care for treating patients with BTKi therapy. We provide a management guideline for CV toxicities of BTKi developed by an international expert panel focusing on the treatment of patients with hematologic malignancies and risk of cardiovascular disease (CVD), with a focus on patients with CLL.

**Methods**

**Steering committee**

An international steering committee of 12 physicians was convened to discuss the current clinical evidence regarding the CV toxicities of BTKis and other approved treatments for CLL. The committee included hematologists, oncologists, and cardio-oncologists with a specialist interest in CV toxicities to provide a diversity of clinical experience. The committee sought to make practical recommendations on the optimal selection of treatment for patients and effective ways to mitigate CV toxicities. Multiple in-person virtual sessions were conducted, various management domains were generated and discussed at length, and verbal and written comments were collated and presented as specific recommendations.

**Literature search and selection**

We searched the published medical literature on Medline using the PubMed website (pubmed.ncbi.nlm.nih.gov) from inception through January 2021. The search terms were general in nature and intended to search broadly for clinically relevant CLL and cardio-oncology publications (supplemental Material 1 in the data supplement). In addition, references of relevant nonsystematic review articles were scanned to identify additional relevant studies. The evidence considered was confined to peer-reviewed articles only.

**Current therapies for CLL**

**BTKis**

Guidelines recommend BTKis, including ibrutinib or acalabrutinib, for treating both fit and unfit patients with treatment-naïve CLL.\(^23,24\) Anti-CD20 therapy may be added to BTKi treatment, although adding rituximab to ibrutinib has not shown a survival advantage over ibrutinib alone.\(^8,25\) In addition, the ELEVATE-TN study, which tested acalabrutinib plus obinutuzumab, was not statistically powered to detect a difference between the combination treatment and acalabrutinib monotherapy.\(^26\) BTKi monotherapy is also recommended for patients with relapsed or refractory (RR) CLL. Because every phase 3 study that has been done on ibrutinib in patients with CLL or Waldenström’s macroglobulinemia (WM) has shown an excess of AF in patients treated with ibrutinib,\(^5,6,8,9,27,28\) the guidelines suggest alternative options for ibrutinib, including second-generation BTKis, such as acalabrutinib or zanubrutinib, with lower risks of this AE.\(^29,30\)

**Ibrutinib.** As the first-in-class BTKi to be approved for CLL, ibrutinib offers the richest source of long-term data on CV risks with these drugs. The RESONATE trial first tested ibrutinib against ofatumumab in patients with RR CLL.\(^9\) At a median follow-up time of 9.4 months, AF was observed in 10 (5%) patients in the ibrutinib group, including 6 (3%) with grade ≥3 AF, whereas a single patient in the ofatumumab group had AF of grade 1 or 2 (Table 1). Long-term follow-up results of patients in the RESONATE trial receiving ibrutinib showed that after a median of 41 months of therapy, the most common AEs associated with ibrutinib were consistent with previous studies and decreased over time, with the exception of HTN and bruising.\(^10\) HTN was reported in 41 (21%) patients during long-term follow-up, including 18 (9%) grade ≥3 events, and AF occurred in 24 (12%) patients, including 12 (6%) grade ≥3 (Table 1). Other CV AEs consisted of congestive heart failure (CHF) in 9 (5%) patients, including 5 (3%) of grade ≥3, and ventricular arrhythmia in 2 (1%) patients.\(^10\)

In the RESONATE-2 study, patients with treatment-naïve (TN) CLL or small lymphocytic lymphoma (SLL) aged ≥65 years were randomized to receive either ibrutinib monotherapy or chlorambucil.\(^8\) Patients in the ibrutinib group were treated for a median of 17.4 months, and 8 (6%) developed any grade AF, including 2 (1%) with grade 3 AF (Table 1). There was a single case of AF in the chlorambucil arm and no grade ≥3 HTN. AF was managed with
discontinuation of the study drug in 2 of these 8 patients, whereas the rest continued without dose modification. In the ibritinib arm, HTN was observed in 19 (14%) patients, including 6 (4%) with grade 3 events, and all 6 were successfully managed with antihypertensive drugs and without reducing the dose of ibritinib. The 5-year follow-up showed any grade AF was reported in 22 (16%) patients, including 7 (5%) with grade 3 AF, and HTN was observed in 35 (26%) patients, including grade 3 HTN in 12 (9%) patients and no grade 4 or 5 events (Table 1). The majority of incidents of grade 3 AF were in the first 3 years and declined in years 4 and 5, consistent with previous studies showing a decline in this AE over time with BTKi therapy. In contrast, rates of grade 3 HTN remained fairly consistent throughout the 5-year study period.

**Table 1. Cardiovascular adverse events in phase 3 trials of BTKis**

| Study             | N Treatment Arm | Study Population | Median Follow-up, mo | Atrial Fibrillation, n (%) | Hypertension, n (%) | Ventricular Arrhythmias, n (%) |
|-------------------|-----------------|------------------|----------------------|-----------------------------|---------------------|-------------------------------|
|                   |                 |                  |                      | All grades | Grade ≥3 | All grades | Grade ≥3 | All grades | Grade ≥3 |
| Ibrutinib         | RESONATE       | RR CLL           | 9.4                  | 10 (5)       | 6 (3)    | NR         | NR       | NR         | NR       |
|                   | 195 ibrutinib  |                   |                      | 1 (0)       | 0 (0)    | NR         | NR       | NR         | NR       |
|                   | 191 ofatumumab |                   |                      |             |          | NR         | NR       | NR         | NR       |
| Long-term follow up | 195 ibrutinib | RR CLL           | 41.0                 | 24 (12)     | 12 (6)   | 41 (21)    | 18 (9)   | 2 (1)      | 0 (0)    |
| RESONATE-2      | 135 ibrutinib  | TN CLL/SLL; ≥65 yr | 17.4               | 8 (6)        | 2 (1)    | 19 (14)    | 6 (4)    | NR         | NR       |
|                   | 132 chlorambucil |                   |                      | 1 (1)       | 0 (0)    | NR         | 0 (0)   | NR         | NR       |
| Long-term follow-up | 135 ibrutinib | TN CLL/SLL; ≥65 yr | 57.0               | 22 (16)     | 7 (5)    | 35 (28)    | 12 (9)   | NR         | NR       |
| ECOG1912      | 352 ibrutinib + | TN CLL/SLL; ≥70 yr | 33.6               | NR          | 13 (4)   | NR         | 66 (19)  | NR         | 1 (0)    |
|                | rituximab      |                   |                      |             |          |            |          |            |          |
| 158 FCR        |                 |                   |                      | 5 (3)       | 2 (1)    | NR         | 13 (8)   | NR         | 0 (0)    |
| HELIOS         | 287 ibrutinib  | RR CLL/SLL       | 17.0                | 21 (7)      | NR       | NR         | NR       | NR         | 3 (1)    |
|                | 287 BR         |                   |                      | 7 (2)       | NR       | NR         | NR       | NR         | 0 (0)    |
| Alliance A041202 | 180 ibrutinib | TN CLL; ≥65 yr   | 38.0               | 31 (17)     | 17 (9)   | NR         | 53 (29)  | NR         | 1 (1)    |
|                | monotherapy    |                   |                      |             |          |            |          |            |          |
| 176 BR         | 181 ibrutinib + | TN CLL/SLL       | 25 (14)             | 10 (6)      | NR       | 61 (34)   | NR       | 0 (0)      |          |
|                | rituximab      |                   |                      |             |          |            |          |            |          |
| ILLUMINATE     | 113 ibrutinib + | TN CLL/SLL; ≥65 yr | 31.3               | 8 (7)       | 6 (5)    | 15 (13)   | 4 (4)    | NR         | NR       |
|                | obinutuzumab   | or unfit          |                      |             |          |            |          |            |          |
| 115 Cit-O      |                 |                   |                      | 0 (0)       | 0 (0)    | 5 (4)      | 4 (3)    | NR         | NR       |
| Acalabrutinib  | ASCEND         | RR CLL           | 16.1                | 8 (5)       | 2 (1)    | 5 (3)      | 3 (2)    | 0 (0)      | 0 (0)    |
|                | 154 acalabrutinib |                   |                      |             |          |            |          |            |          |
|                | 118 idelalisib + | RR CLL           | 4 (3)               | 1 (1)       | 5 (4)    | 1 (1)     | 0 (0)    | 0 (0)      |          |
|                | rituximab      |                   |                      |             |          |            |          |            |          |
| 35 BR          | 179 acalabrutin | —                 | 7 (4)               | 0 (0)       | 8 (4)    | 4 (2)     | 0 (0)    | 0 (0)      |          |
|                | monotherapy    |                   |                      |             |          |            |          |            |          |
| ELEVATE-TN     | 178 acalabrutin | —                 | 6 (3)               | 1 (1)       | 13 (7)   | 5 (3)     | 0 (0)    | 0 (0)      |          |
|                | obinutuzumab   |                   |                      |             |          |            |          |            |          |
| 177 Cit-O      | 265 ibrutinib  | RR CLL with del17 | 40.9               | 42 (16)     | 9 (3)    | 60 (23)   | 23 (9)   | 1 (0)      | 1 (0)    |
|                | or del11 mutations |               |                      |             |          |            |          |            |          |
|                | 268 acalabrutin |                   |                      | 25 (9)      | 12 (4)   | 23 (9)    | 11 (4)   | 0 (0)      | 0 (0)    |
| Zanubrutinib   | ALPINE         | RR CLL/SLL       | 15.0                | 21 (10)     | NR       | NR         | NR       | NR         | NR       |
|                | 208 ibrutinib  |                   |                      |             |          |            |          |            |          |
|                | 207 zanubrutin | WM                | 5 (2.5)             | 0 (0)       | 6 (4)    | 5 (3)     | 0 (0)    | 0 (0)      |          |
| ASPEN          | 98 ibrutinib   |                   | 37.0                | 15 (15)     | 4 (4)    | 16 (16)   | 11 (11)  | NR         | NR       |
|                | 101 zanubrutin |                   |                      | 2 (2)       | 0 (0)    | 11 (11)   | 6 (6)    | NR         | NR       |

BR, bendamustine plus rituximab; Cib-O, chlorambucil plus obinutuzumab; FCR, fludarabine, cyclophosphamide, and rituximab; SLL, small lymphocytic lymphoma; TN, treatment-naïve. Italics denote the non-BTKi comparator arm of the trial.

IBRUTINIB COMBINATIONS The E1912 trial (NCT02048813) tested ibritinib plus rituximab vs fludarabine, cyclophosphamide, and rituximab (FCR) in patients with TN CLL who were ≤70 years. Cardiac toxicities of grade ≥3 were reported in 23 (6%) patients who received ibritinib–rituximab, including 13 (4%) cases of atrial fibrillation or flutter, 3 cases of cardiac chest pain, 2 cases of supraventricular tachycardia, 2 cases of nonfatal heart failure, 2 cases of pericardial perfusion, 1 case of sinus bradycardia, 1 case of ventricular tachycardia, 1 case of cardiac arrest (nonfatal), and 1 case of myocardial infarction. In patients receiving CIT with FCR, there were 3 patients with grade ≥3 cardiac events, including 2 cases of AF. Grade ≥3 HTN was observed in 66 (19%) patients in the ibritinib–rituximab group and 13 (8%) patients receiving FCR (Table 1).
A regimen of ibrutinib plus bendamustine plus rituximab (BR) was tested against BR only in the HELIOS trial in patients with previously treated CLL/SLL.27 AF was reported in 7 (2%) patients in the BR group but in 21 (7%) of the ibrutinib group. Of 25 patients with a history of AF, 7 developed AF during the study. In total, 58 (87%) patients in the ibrutinib group who had continuing cardiac comorbid conditions and untreated CLL or SLL, and any grade AF was observed more often in patients receiving ibrutinib and none who received BR only, and the number of ventricular arrhythmias, cardiac, and sudden deaths in the ibrutinib arm (7 [2.4%]) was significantly higher than in the control arm, which recorded none (P = .025).38 The Alliance A041202 trial also tested ibrutinib therapy, with and without rituximab, against BR but enrolled patients aged ≥65 years with untreated CLL.6 AF was reported in 31 (17%) patients, including 17 (9%) of grade ≥3 in the ibrutinib monotherapy group. In comparison, there were 25 (14%) patients with AF in the ibrutinib–rituximab group (10 [6%] with grade ≥3) and 5 (3%) patients in the BR arm with AF, all with grade ≥3 (Table 1). Notably, the rates of grade ≥3 HTN reported in this trial were quite high, including 53 (29%) patients receiving ibrutinib, 61 (34%) in the ibrutinib–rituximab group, and 25 (14%) of those in the BR arm. Grade 5 AEs were reported in 9% of patients treated with BR, 13% of those receiving ibrutinib monotherapy, and 12% of those receiving ibrutinib plus rituximab. Finally, the ILLUMINATE trial tested ibrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab (Clb-O) in patients ≥65 years old or who were <65 and with coexisting conditions and untreated CLL or SLL, and any grade AF was reported in 8 (7%) patients treated with ibrutinib plus obinutuzumab, including 6 (5%) with grade ≥3 events. In addition, 15 (13%) patients experienced HTN of any grade, and 4 (4%) patients had grade ≥3 HTN.4 The number of cases of grade ≥3 HTN was similar in patients receiving Clb-O, but there were no cases of AF in this group.

**Acalabrutinib.** Acalabrutinib is a second-generation irreversible BTKi with fewer off-target effects than ibrutinib,34,35 and it was hoped that this agent would provide an alternative to ibrutinib with fewer CV risks. The ASCEND study randomized patients with RR CLL to acalabrutinib monotherapy or the investigator’s choice of idealisib plus rituximab or BR.36 In the acalabrutinib group, 8 (5%) patients experienced AF events (Table 1). There were 5 (3%) cases of AF in the comparator groups, including 2 (1%) with grade ≥3. The investigators also reported 5 (3%) patients with HTN in the acalabrutinib group, including 3 (2%) with grade ≥3 HTN, while there were 5 (4%) cases of HTN in the idealisib plus rituximab group, 1 of which (1%) was grade ≥3 and none in the BR arm. Next, the ELEVATE-TN study evaluated acalabrutinib with or without obinutuzumab in comparison with Clb-O in patients with TN CLL, excluding those with significant CV disease.26 The authors reported any grade AF events in 13 (4%) patients receiving acalabrutinib either as monotherapy or with obinutuzumab, including a single event of grade ≥3, whereas 1 case of AF was reported in the Clb-O group (Table 1). HTN was reported in 21 (6%) patients in either acalabrutinib treatment group, including 9 (3%) with grade ≥3, compared with 5 (3%) patients in the Clb-O group with grade ≥3 HTN. No ventricular arrhythmias were reported in this study.

With the publication of the ELEVATE-RR study results, the first data from a phase 3 comparison of ibrutinib monotherapy with acalabrutinib monotherapy in patients with CLL became available. This study was conducted in patients with RR CLL and confirmed del(17)(p13.1) or del(11)(q22.3) mutations.29 After a median follow-up time of 40.9 months, the incidence of all cardiac events was higher in the ibrutinib group (n = 79 [30%]) than in the acalabrutinib group (n = 64 [24%]). Likewise, the incidence of AF of any grade was significantly higher in the ibrutinib group (42 [16%]) than in the acalabrutinib group (25 [9%]; P = .02). In addition, the analysis showed the median time to AF was longer in patients treated with acalabrutinib (29 months) than ibrutinib (16 months), and a lower proportion of patients without a prior history of AF had an AF event during the study in the acalabrutinib group (15 patients [6%]) than in the ibrutinib group (37 patients [15%]).29 Most patients who experienced AF had relevant risk factors, including being ≥75 years old or having a history of AF and/or HTN. The exposure-adjusted frequency of any grade AF or atrial flutter was twofold lower with acalabrutinib than ibrutinib (hazard ratio, 0.52; 95% confidence interval, 0.32-0.86). Treatment discontinuation because of cardiac AEs was over fivefold higher in patients receiving ibrutinib than those receiving acalabrutinib. Other notable cardiac AEs reported included 1 case of grade 4 ventricular fibrillation and 1 case of sudden cardiac death in the ibrutinib group and none in the acalabrutinib group. Any grade HTN was observed more often in patients in the ibrutinib group (n = 60 [23%]) than in the acalabrutinib group (n = 25 [9%]), as was grade ≥3 HTN (Table 1).

**Zanubrutinib.** Zanubrutinib is another irreversible BTKi designed for greater selectivity and fewer off-target effects than ibrutinib that has been approved in the United States for use with WM and is undergoing phase 3 testing for use in CLL.37 The open-label ASPEN study tested ibrutinib and zanubrutinib in 199 patients with RR WM for a median treatment duration of just over 18.5 months. Patients in the ASPEN study treated with ibrutinib had significantly more AF events of any grade (n = 15 [15%]) than those treated with zanubrutinib (n = 2 [2%]; P = .0004), and AF events of grade ≥3 were also significantly more common in the ibrutinib group (n = 4 [4%]) than the zanubrutinib group (n = 0 [0%]; P = .02).30 All grade and grade ≥3 HTN were also more common in the ibrutinib treatment group than in the zanubrutinib group, but this difference did not reach significance (Table 1). Moreover, more patients treated with ibrutinib developed HTN later in the treatment course.30 Like the ELEVATE-RR study in patients with CLL, these results showed the second-generation BTKi was associated with fewer CV AEs than ibrutinib. The ongoing phase 3 ALPINE study is a head-to-head trial of zanubrutinib and ibrutinib monotherapy in RR CLL/SLL.22 Although the data are not yet mature and have not been published in a peer-reviewed form, public results presented at the 2021 meeting of the European Hematology Association showed that after a median treatment time of 15 months, a significantly lower incidence of AF was observed in the zanubrutinib arm (2 [2.5%]) than the ibrutinib arm (21 [10%]; P = .0014),38 whereas an initial release of the final response analysis showed HTN was reported in 13% of patients treated with zanubrutinib and 10% of those receiving ibrutinib (P value not reported).39 More broadly, the rates of any grade cardiac disorders were lower with zanubrutinib (13%) than ibrutinib (25%), as were grade ≥3 cardiac disorders,
The 2019 approval of venetoclax, an orally available BCL-2 antagonist, added another effective treatment option for treating CLL. Venetoclax has the benefit of being time-limited, unlike BTKis, and is effective in both mutated and unmutated IGHV CLL, although BCL-2 antagonists are associated with their own risks, including tumor lysis syndrome and hepatic AEs. The CLL14 trial of venetoclax and obinutuzumab in TN CLL did not reveal any CV risks associated with BCL-2 antagonism through 2 years following treatment cessation. The MURANO trial (NCT02005471), likewise, did not reveal any signal for CV toxicities from treatment with venetoclax plus rituximab for RR CLL through 2 years of treatment or after 4 years of follow-up. Clb-O. However, the role of these agents is being redefined in the era of BTKis and BCL-2 antagonists. While a number of AEs have been associated with CIT, clinical trials have shown little evidence of CV effects for the FCR or BR regimens when used as a frontline treatment for CLL.

Practical recommendations for BTKi therapy

Pretreatment workup

The pretreatment workup for all patients should include a comprehensive patient history and targeted CV examination, including an electrocardiogram (ECG) and a blood pressure measurement to identify the main risk factors present, including AF and HTN (Table 2). Beyond these basic measures, an echocardiogram can be considered for patients with high CV risk or established CV disease. Additional items to consider when deciding on a course of treatment for CLL include concomitant medications; a history of valvular heart disease, particularly mitral valve disease or other conditions that increase the risk of AF substantially; a history of ventricular arrhythmias, clinical heart failure, or left ventricular dysfunction/reduced ejection fraction. Even patients with these risk factors may often safely receive BTKi therapy and benefit from its therapeutic effects. But clinicians should consider more intense cardiac screening and monitoring in those with established CVD because of their increased risk.

Selecting a course of treatment

Based on the evidence available in clinical trials discussed and the relatively lower incidence of events in patients without baseline risk factors, younger patients (<70 years) with no CV risk factors at the initiation of therapy can be treated with either ibrutinib or a second-generation BTKi. The lower overall rate of AEs, particularly AF, associated with second-generation BTKis is most important to consider for patients with existing risk factors, and acalabrutinib or zanubrutinib are generally preferred over ibrutinib for patients with established CVD, such as well-controlled AF, HTN, heart failure, or valvular heart disease.

Patients with a history of AF. In most cases, patients with a history of AF and no additional risk factors should be treated with the typical standard of care for BTKi therapy used in patients without a history of AF (Table 3). It is important to note that prior AF may present with a spectrum of risk on the basis of the specifics of earlier AF events, existing comorbidities, or other risk factors, and if clinicians are concerned about the CV risk of any patients, other options should be strongly considered, including the second-generation BTKis or Bcl-2 antagonists.

In patients with ongoing AF, BTKi therapy is still often possible. After undertaking the baseline CV risk factor assessment and controlling ongoing AF either through primary care or in consultation with a multidisciplinary team, including a cardio-oncologist or cardiologist with expertise in hematologic malignancies, it is reasonable to proceed with the typical standard of care, including BTKis. The second-generation BTKis are preferred over ibrutinib for this population because of their lower risk of AF as well as evidence of less effect on platelet function than ibrutinib in preclinical work.

### Table 2. Pretreatment recommendations

| Initial workup                                      |
|----------------------------------------------------|
| Comprehensive patient history                       |
| Blood pressure measurement                          |
| Electrocardiogram                                   |
| Concomitant medications                             |
| CV risk factor assessment: the presence of diabetes, obesity, hypertension, dyslipidemia, chronic renal disease |
| History of valvular heart disease                    |
| History of arrhythmias, heart failure, or left ventricular dysfunction/reduced ejection fraction |
| History of ischemic heart disease                    |
| For patients with high CV risk or established CV disease |
| Echocardiogram                                      |
| Baseline cardiac biomarkers                          |
| Consider using FRS-CVD score for stratification     |

**Treatment selection**

- Patients with no CV risk factors
  - Any approved BTKi
  - If other safety concerns, favor more selective drugs (acalabrutinib or zanubrutinib) or Bcl-2 inhibitors
  - Patients with CV risk (eg, well-controlled AF, HTN)
  - Consider second-generation BTKis (acalabrutinib or zanubrutinib)

**FRS-CVD**, Framingham risk score-cardiovascular disease.

BCL-2 antagonists

The 2019 approval of venetoclax, an orally available BCL-2 antagonist, added another effective treatment option for treating CLL. Venetoclax has the benefit of being time-limited, unlike BTKis, and is effective in both mutated and unmutated IGHV CLL, although BCL-2 antagonists are associated with their own risks, including tumor lysis syndrome and hepatic AEs. The CLL14 trial of venetoclax and obinutuzumab in TN CLL did not reveal any CV risks associated with BCL-2 antagonism through 2 years following treatment cessation. The MURANO trial (NCT02005471), likewise, did not reveal any signal for CV toxicities from treatment with venetoclax plus rituximab for RR CLL through 2 years of treatment or after 4 years of follow-up.
Table 3. Recommendations for patients with CV risk

| Atrial fibrillation                      |
|----------------------------------------|
| Determine whether the patient is high or low risk |
| Low-risk cases may be safely treated with BTKis |
| Favor more second-generation BTKis (acalabrutinib or zanubrutinib) or alternative treatments |
| BTKi treatment may be continued in consultation with MDT for patients with: |
| Permanent/persistent AF                |
| HTN                                    |
| History of myocardial infarction        |
| BTKis NOT recommended for patients with: |
| History of ventricular arrhythmia        |
| Family history of sudden cardiac death   |
| Severe, uncontrolled HTN                |
| Severe or uncontrolled congestive heart failure (LVEF <30%) |

**Hypertension**

If HTN is well-controlled, BTKi therapy may be used

- Monitor blood pressure at least biweekly for the first 3-6 mo of BTKi therapy
- Maintain early threshold for treatment during BTKi therapy

**CHF**

- Examine with echocardiogram
- Restrict to <2 g daily sodium intake
- Monitor weight daily
- Monitor blood pressure twice weekly
- Manage care with MDT (preferred) or in collaboration with a cardio-oncologist

**Ventricular arrhythmias**

- Ibrutinib should be avoided
- The risk of second-generation BTKis (acalabrutinib or zanubrutinib) is not currently known

LVEF, left ventricular ejection fraction; MDT, multidisciplinary team.

Should any CV toxicities develop, they can be diagnosed rapidly, and the multidisciplinary team (MDT) can come to a collaborative decision as to how best to alter treatment to mitigate risk. In those with difficult-to-tolerate CVD, it may be reasonable or necessary to hold BTKi therapy, at least temporarily. If treatment options are limited and CVD is controlled, rechallenge may be considered. However, if the patient has difficult-to-manage AF, recent acute coronary syndromes, or difficult-to-control heart failure, alternatives to BTKi treatment, including venetoclax, should be considered.

**Patients with HTN.** Patients with a history of HTN can be successfully treated with BTKi therapy, although the entirety of a patient’s CV risk should be considered to determine appropriate treatment (Table 3). When using BTKi therapy in this patient population, the recommended adjustments to standard care include close initial clinical monitoring of blood pressure, including at least biweekly checks.

Clinicians should maintain an early threshold for treatment in patients with HTN at the initiation of BTKi therapy, especially if they have other relevant CV risk factors. If pharmacologic management of HTN is required, initiate treatment according to current HTN treatment guidelines. If grade 3 or 4 toxicity occurs, interrupt BTKi therapy and reduce the dose by 140 mg per day for ibrutinib or by 100 mg per day for acalabrutinib.

**CHF.** In general, BTKis should be avoided in patients with active CHF, but this is a relative contraindication, not an absolute one. In cases of concern to the clinician, a BCL-2 antagonist may be a better option because of the lower risk of CV events, although patients need to be able to tolerate high volume hydration to prevent possible tumor lysis syndrome with venetoclax as well as its medical management. If BTKi therapy is pursued, a second-generation BTKi should be used to minimize the risk of AF (Table 3). Patients with well-controlled CHF (European Hematology Association score of 1 or 2) can be supported on BTKi therapy if it is well planned in advance and CV treatment is optimized before beginning hematological therapy. However, it is strongly recommended to treat such patients as an MDT, or at least in collaboration with a cardiologist or cardio-oncologist.

Before initiating treatment, patients with CHF should undergo an echocardiogram, ECG, and Holter monitoring to identify any arrhythmias at baseline. Repeat the ECG at 3 months and continue with ongoing cardiology reviews. During treatment, limit patients with CHF taking BTKis to <2 g of daily sodium intake, monitor their weight daily, and check their blood pressure twice a week and at each clinical visit. Assess renal function and systolic function (by echo or cardiac magnetic resonance imaging) regularly in these patients, and work in collaboration with a cardiologist or cardio-oncologist to optimize heart failure therapy according to current guidelines. Finally, optimize treatment of CHF and arterial HTN according to guidelines and in collaboration with the cardiologist or cardio-oncologist.

**Ventricular arrhythmias.** The use of BTKis, especially ibrutinib, should be avoided in patients with a history of ventricular arrhythmias and cardiac arrest. Ibrutinib has been shown to increase the incidence of ventricular arrhythmias and sudden cardiac death.

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Table 4. Managing CV toxicities during BTKi treatment

| Emerging atrial fibrillation |
|------------------------------|
| Manage care using an MDT    |
| If other risk factors are limited (eg, CHA2DS2-VASc score = 0 or 1), BTKi therapy can be continued |
| Warfarin less preferred to alternative anticoagulant therapies |
| If recurrent events on ibrutinib, trial with acalabrutinib |

**Emerging HTN**

- Begin regular home blood pressure monitoring
- New treatments for HTN or adjustments to ongoing treatments should be decided in conjunction with MDT
- Follow management guidelines and avoid CYP3A4 inhibitors where possible
- Non-ACEi in the first instance
- Use combination therapy if needed to attain systolic blood pressure control

**Emerging CHF**

- Initiate ACEi/ARB/ARNI plus β-blockers as tolerated and according to guidelines
- Periodic echocardiogram or other EF assessment every 6-12 mo in the setting of active CHF

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor.
Although data are not yet available regarding whether second-generation BTKis are also associated with these events, a Bcl-2 antagonist is preferred to any BTKi in these patients.

Managing CV toxicities during treatment

For patients who experience emerging AF after beginning BTKi therapy, an MDT is often helpful for balancing the benefits of ongoing therapy with the management of AF as well as the patient's risk of bleeding and stroke (Table 4). Patients with limited risk factors often are appropriate candidates for continued BTKi treatment, including patients with scores of 0 or 1 according to CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 and sex category [female]) scores of 0 or 1 or comparable scores on other risk assessments. Several treatment strategies have been investigated for patients with multiple CV risk factors. Clinical trials routinely exclude warfarin, and warfarin is less preferred in patients receiving BTKis, but the current data do not clearly support a single approach, with some research supporting discontinuing BTKi and initiating anticoagulation, while other data recommend stopping drugs temporarily and reinitiating therapy once control of AF is achieved. Patients who experience recurrent events with ibrutinib despite dose hold and reductions on ibrutinib can be trialed on acalabrutinib with caution since there is data to suggest that it may be better tolerated with a lower incidence of recurrent events.

A prospective study of AF incidence in patients treated with ibrutinib showed that the majority of patients who developed ibrutinib-related AF were also with a variety of anticoagulants, and no major bleeding events resulted, suggesting that anticoagulant treatment often does not require stopping BTKi treatment. More recently, interim results from the phase 3 FLAIR trial of ibrutinib and rituximab vs FCR in TN CLL suggested previous treatment with angiotensin-converting enzyme inhibitors (ACEIs) was positively correlated with the risk of ventricular tachycardias and sudden cardiac death in patients receiving ibrutinib and rituximab. At a median treatment time of 52.7 months, sudden cardiac death had occurred in 7 of 47 (15%) patients receiving ACEI treatment at trial entry vs 1 of 336 (0.3%) patients who did not take ACEIs at trial entry (P < .0001). This potential association of ACEI treatment with ventricular tachycardia and sudden cardiac death in patients receiving BTKis has not been previously reported and may indicate a new safety consideration. However, these data are immature and require confirmation, and comprehensive data on the risk of ventricular tachycardia associated with BTKis does not yet exist. For the present, it should be presumed that second-generation BTKis may present a similar risk in patients who have previously used or are using an ACEI and monitor such patients closely.

If patients experience emergent HTN during BTKi therapy, it is recommended to begin regular home blood pressure monitoring. It is important to involve the MDT in decisions about initiating new treatment to manage HTN or adjusting existing HTN treatments. Options for management should follow published guidelines, and CY3A4 inhibitors should be avoided. For patients with emerging CHF, stop BTKi immediately and initiate treatment with ACEi/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor plus β-blockers as tolerated and according to current guidelines. For patients with active CHF, monitor with periodic echocardiograms or other assessments of ejection fraction every 6 to 12 months.

When to refer to cardio-oncology

Cardio-oncologists can be invaluable members of a patient's MDT; however, there are still too few of these specialists to consult on all CLL patients with CV risk factors. It is therefore important to refer the most challenging cases, including patients with a history of ventricular tachycardia or arrhythmia or difficult-to-manage CHF, before beginning BTKi treatment. Providers should also consider referring patients with a history of substantial CV disease, including AF or CHF, difficult-to-control hypertension (>2 medications needed), or ongoing cardiac complications that require referral to a cardio-oncologist in cases of concern, but it is not necessary to do so routinely. In many cases, ongoing management by the patient’s own cardiologist is the most appropriate course of action. Additionally, a cardio-oncologist may be required to consult if there are any red flags in the initial workup, particularly AF on baseline ECG.

Conclusions

BTKi therapy has changed the CLL treatment in substantial ways, but these drugs also present CV risks. New second-generation BTKis have now been developed that are more selective for BTK and appear to have fewer off-target effects, providing the potential to reap the benefits of BTK inhibition while lessening the CV risks. The recommendations presented here take into account the available phase 3 data for BTKis in order to promote their safe and effective use. Optimizing heart failure, ventricular arrhythmia, and HTN control will likely improve tolerance and maintenance of BTKi therapy. However, additional studies are needed to identify the most optimal strategy across this growing class of drugs.

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