Management of cardiovascular complications of bruton tyrosine kinase inhibitors

Chloe Pek Sang Tang,[1,*] Gregory Y.H. Lip,[2,3,*] Terry McCormack,[4] Alexander R. Lyon,[5] Peter Hillmen,[6] Sunil Iyengar,[7] Nicolas Martinez-Calle,[8] Nilima Parry-Jones,[9] Piers E.M. Patten,[10] Anna Schuh,[1] and Renata Walewska[11], on behalf of the BSH guidelines committee, UK CLL Forum

[1]Oxford University Hospitals NHS Trust, Oxford, [2]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK, [3]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark, [4]Hull York Medical School, Hull, [5]Royal Brompton NHS Trust, London, [6]Leeds Teaching Hospital NHS Trust, Leeds, [7]Royal Marsden Hospital NHS Trust, Sutton, [8]Nottingham University Hospitals NHS Trust, Nottingham, [9]Aneurin Bevan University Health Board, Abergavenny, [10]Comprehensive Cancer Centre, Kings College London, London, and [11]University Hospitals Dorset NHS Trust, Poole, UK

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Methodology

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Literature review

Literature search was peformed using PubMed on 2 June 2020, with search terms ibrutinib, Bruton Tyrosine Kinase Inhibitor, atrial fibrillation, hypertension, sudden cardiac death and cardiovascular complications, and confined to publications in English.

Review of the manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haemato-Oncology Task Force, the BSH Guidelines Committee and the Haemato-Oncology sounding board of BSH. It has also been reviewed by UK CLL Forum Executive and British Cardiology-Oncology Society.

Correspondence: BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
Email: bshguidelines@b-s-h.org.uk
*These authors made an equal contribution

Introduction

Bruton tyrosine kinase inhibitors (BTKi) have revolutionised the treatment of chronic lymphocytic leukaemia (CLL). Cardiovascular (CV) adverse events associated with BTKi therapy may interfere with continuation of best possible care, induce life-threatening CV complications or lead to long-term morbidity including worse CLL-related outcomes if optimal BTKi treatment is withheld.[1,2] Correct understanding, interpretation and management of BTKi-related CV adverse events are required and should be placed within the context of the overall care of the individual patient. We aim to provide practical management recommendations for BTKi-associated cardiac toxicity to enhance maintenance on BTKi therapy with minimal disruption.

Hypertension

Hypertension is a common cardiovascular adverse event in oncology patients, as recently reviewed.[3] In general, BTKi-associated hypertension has an incidence of 30% (systolic blood pressure [BP] ≥ 160 mmHg or diastolic BP ≥ 100 mmHg in 5%), and is proportional to duration of therapy.[4–6] In the larger phase 3 randomised controlled trials (RCT), the rate of new hypertension across all ages is double that in the non-ibrutinib arm.[7–10] Dickerson *et al.*[11] reported an increased risk of developing major adverse cardiovascular events (MACE; hazard ratio [HR], 2·17; 95% CI, 1·08–4·38) and of arrhythmia (HR 3·18; CI, 1·37–7·37) with ibrutinib-related hypertension compared to patients with stable or no hypertension. Antihypertensive initiation lowered MACE risk (HR 0·40; 95% CI, 0·24–0·66), suggesting the interaction of hypertension and ibrutinib could increase the risk of atrial

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fibrillation (AF) and other cardiovascular events.[11] Drug treatment should be considered in patients aged over 80 with ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) BP > 145/85 mmHg.[12]

Recommendations

- Blood pressure should be measured at every clinic visit. Patients with systolic BP > 140 mmHg or diastolic BP > 90 mmHg should be offered ABPM/HBPM (1A).
- In patients aged over 80 years with ABPM/HBPM > 135/85, strongly consider commencing antihypertensive treatment, especially in those with target organ damage or diabetes. Drug treatment should be considered in patients aged over 80 years with ABPM/HBPM BP > 145/85 mmHg (1B).
- We recommend using angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor-blockers (ARB) as first line treatment of BTKi-related hypertension due to the benefit on left ventricular and renal function and the lack of drug-drug interactions (DDI). When combining antihypertensives, it is preferable to avoid medications that inhibit CYP3A4, e.g., verapamil (1C).
- Second line antihypertensive strategies for BTKi-related hypertension include carvedilol, spironolactone, hydralazine and oral nitrates. Verapamil and diltiazem may be considered in patients with AF intolerant of betablockers if left ventricular ejection fraction (LVEF) is more than 50%, but care is needed given potential drug interactions with ibrutinib. Diuretics should be considered if there is clinical evidence of fluid retention (2C). Cardiology advice may be prudent.
- In patients with asymptomatic severe hypertension (clinic BP of 180/120 mm Hg), assess for target organ damage and initiate an antihypertensive immediately whilst withholding BTKi until BP is adequately controlled (1C).
- Dose modification of BTKi can generally be avoided with aggressive treatment of hypertension to avoid further complications, such as AF and heart failure. It is reasonable to reduce the dose of BTKi when optimal control of BP is not achievable despite the use of maximal antihypertensive therapy (2C).
- Patient education regarding the risks of hypertension and AF risk is recommended for all patients who have started using BTKis (4D), with advice regarding home blood pressure and heart rate monitoring.

Atrial fibrillation

The incidence of new-onset AF is increased in patients with CLL on BTKi therapy, reported at 6%.[13–15] A nationwide Swedish population study demonstrated that the prevalence of AF was already 8% (66/828) at the time of commencement of first line therapy.[16] The association between ibrutinib and AF is evident from two meta-analyses demonstrating a higher pooled rate of AF (5·77 per 100 person-years) compared to the age-matched population in the Framingham study (1·8 per 100 person-years).[15,17–19] The median time of onset of AF from initiation of therapy was 2·8 months (range 0·3–17·5). The cumulative rate of AF at 36 months was 11·2% (95% CI: 11·2, 16·8), with new cases of AF occurring at a continuous low rate over time.[20] Older age, male sex, past history of AF, hyperlipidaemia, hypertension and valvular heart disease were identified as risk factors for AF development.[13,20–22]

Baseline CV risk assessment prior to initiation of BTKi is recommended. Baseline and serial electrocardiograms (ECGs) are recommended, particularly during the first 12 months of treatment.[23,24] A baseline transthoracic echocardiogram should be considered for patients with pre-existing AF, coronary artery disease, heart failure or cardiomyopathy, and hypertension.[25–27] Prior history of AF is not a contraindication to BTKi initiation, with the exception of the following: recurrent decompensated cardiac failure secondary to AF, or a contraindication to anticoagulation due to a history of a life-threatening bleed or uncontrolled bleeding. Alternative anti-CLL therapy such as conventional chemotherapy or BCL2 inhibitor (e.g., venetoclax) may be used. BTKi dose modification is not warranted unless a patient has new onset, symptomatic grade 3 AF or haemodynamic instability. Early cardiology opinion should be sought for high-risk patients, ideally from a specialist cardio-oncology service. The side-effect of AF appears to be a class effect, albeit potentially of lower frequency in second generation BTKi (Table I). This hypothesis will be confirmed or refuted in the ongoing ALPINE (zanubrutinib vs. ibrutinib) and ACE-CL-006 (acalabrutinib vs. ibrutinib) RCTs.[28]

In patients with suspected paroxysmal AF undetected by standard 12 lead resting ECG recording, a 48-hour ambulatory ECG monitor, seven-day event recorder or 7–14 day ECG patch recording device should be used based on the frequency of suspected symptomatic episodes.[29,30] A confirmed diagnosis of AF should prompt a cardiology or cardio-oncology referral so that joint decision-making regarding the need for anticoagulation and/or need for interruption of BTKi, rate versus rhythm strategy and pharmacological/non-pharmacological treatment of symptoms can occur. Transthoracic echocardiography (TTE) should be performed to exclude concomitant structural cardiac abnormality and establish cardiac function. If ischaemic heart disease is suspected then a myocardial perfusion scan should be considered, avoiding dobutamine as the stressor.

Both the CHA_2DS_2-VASc (Table II) and HAS-BLED (Table III) scores should be calculated in AF patients, to assess AF-related stroke and bleeding risks, respectively.[31,32] Limited evidence for these scores in cancer patients are available, and specifically in CLL patients receiving BTKi

Table I. Rate of atrial fibrillation and grade 3 bleeding in second generation of BTKi.

Trial	Phase	No. of patients	Setting	Atrial fibrillation (all grade)	Grade 3 bleeding
ASCEND Acala vs. IR vs. BR (Ghia *et al.*, 2020)[76]	3	398	RR	3% vs. 0	1% vs. 0
ELEVATE Acala vs. Acala-G vs. Chl-G (Sharman *et al.*, 2020)[77]	3	675	TN	4% vs. 3% vs. 1%	2% vs. 2% vs. 0
Acala monotherapy (Byrd *et al.*, 2020)[78]	2	134	RR	7%	5%
Acala-G (Woyach *et al.*, 2020)[79]	2	19TN 26 RR	TN and RR	2%	4%
SEQUOIA – zanubrutinib arm C result (Tam *et al.*, 2019a)[80]	3	109	TN	0	2·8%
Zanubrutinib monotherapy (Tam *et al.*, 2019b)[81]	1/2	122	TN	3%	2%

B-R, bendamustine plus rituximab; Chl-G, chorambucil plus obinutuzumab; I-R, idelalisib plus rituximab; RR relapsed/refractory; TN, treatment naive.

Table II. The CHA2DS2VASc Risk Score for Predicting Stroke in non-Anticoagulated Patients with non Valvular Atrial Fibrillation.

Abbreviation	Risk Factor	Score
C	Congestive heart failure (or left ventricular dysfunction)	1
H	Hypertension	1
A2	Age ≥ 75 years	2
D	Diabetes mellitus	1
S2	Prior stroke or TIA or thromboembolism	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, and aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (female sex)	1
	Maximum score	9

TIA, transient ischaemic attack.

Table III. The HAS-BLED risk score for predicting bleeding in anticoagulated patients with atrial fibrillation.

Abbreviation	Clinical characteristic	Score
H	Hypertension (uncontrolled, > 160 mm Hg systolic)	1
A	Abnormal renal or hepatic function	1–2
S	Stroke	1
B	Bleeding history or predisposition (anaemia)	1
L	Labile INR (TTR < 60%)	1
E	Elderly (age > 65 years)	1
D	Drugs (antiplatelet agents and NSAIDs) or alcohol (1 point each)	1–2

Maximum Score – 9, High risk ≥ 4- Annual bleeding risk ≥ 8%, Moderate risk 2–3- Annual bleeding risk 2–4%, Low risk if score 0–1- Annual bleeding risk < 2%.
INR, international normalised ratio; NSAID, nonsteroidal anti-inflammatory drugs; TTR, time in therapeutic range.

therapy.[33–35] Although neither score is fully validated in the CLL patients *per se*, they are a simple and practical guide to aid risk assessment and decision-making regarding the requirement and safety of anticoagulation for stroke prophylaxis. The HAS-BLED score is the best validated bleeding risk score in AF, while the $CHADS_2$ and CHA_2DS_2VASc are the best validated common stroke risk scores in AF.[36] Both stroke and bleeding risks are dynamic, changing with ageing and incident comorbidities, risk re-assessment should thus be considered at every AF patient contact.[37]

In general, stroke prevention with oral anticoagulation (OAC) is recommended in patients with a CHA_2DS_2-VASc score of ≥ 2 in males or ≥ 3 in females, taking the potential cancer-related risks of serious bleeding into consideration.[38,39] Oral anticoagulation should preferably be with a direct oral anticoagulant (DOAC). The HAS-BLED score should be appropriately used to address the modifiable bleeding risk factors (e.g., uncontrolled blood pressure, labile international normalised ratios (INRs) if on vitamin K antagonists (VKA), excessive alcohol or concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin, and to 'flag up' the high bleeding risk patients for early review and follow-up.[40] Such an approach has been shown to mitigate modifiable bleeding risks, leading to lower bleeding rates and an increased OAC uptake, at least in a general AF population.[41] A high HAS-BLED score is not a reason to withhold OAC, as the net clinical benefit balancing stroke reduction against serious bleeding is even greater with high HAS-BLED scores.[42]

There is a dearth of robust data in assessing the safety of combining BTKi and anticoagulants in CLL patients with an inherent high bleeding risk.[43–45] Furthermore, substantial DDI occur between anticoagulants and BTKi via CYP3A4 and p-glycoprotein pathways.[46] In an integrated analysis of 15 ibrutinib clinical trials including four RCTs, reported low-grade haemorrhage was common (35% vs. 15% in comparator arms) but the incidence of major haemorrhage (MH) was similar between the ibrutinib arm and comparator arm with longer follow-up (3·2 vs. 3·1 per 1000 person-months).[47] In multivariate analysis, the use of antiplatelet or anticoagulant (AP/AC) was associated with an increased risk of MH in the total ibrutinib pool (HR, 1·7; 95% CI, 1·0–2·7; $P = 0·041$) but not in the total randomised pool.[48] The risk

of MH with the concomitant use of anticoagulants and/or antiplatelets (AP/AC) and ibrutinib from retrospective cohort studies was much higher (16–18%),[21,49,50] underscoring the need for thejudicious use of these agents in the more vulnerable group.[51]

Each individual DOAC manifests a different risk-benefit profile, but we recommend the use of a label-adherent dose of DOAC due to its superior safety and efficacy relative to warfarin.[52–59] Dabigatran is a reasonable option given the reduced potential of CYP3A4 interaction and availability of an antidote,[60] although a specific reversal agent (adexanet alpha) for the oral factor Xa inhibitors is now available.

Patients with AF and concomitant coronary disease are complex, and the topic has been recently reviewed.[61,62] The use of dual antiplatelets and OAC in combination should be used for a minimal duration in high thrombotic risk AF patients with a recent coronary stent; in high bleeding risk patients, dual therapy with OAC plus a P2Y12 inhibitor (clopidogrel) may be used judiciously.[62,50] Patients with a stable vascular disease can be managed with an OAC alone in long-term treatment (more than 12 months). The management of these niche patients should be discussed in a multidisciplinary team meeting (MDT) involving the treating haematologist, cardiologist and the haemostasis and thrombosis specialist.

Rate control with beta blockade is recommended as the first-line approach in the symptomatic treatment of haemodynamically stable AF for several reasons. First, it is unlikely a rhythm-control strategy will be successful in the face of ongoing long term BTKi therapy. Second, there are multiple drug interactions between ibrutinib and antiarrhythmic agents used for rate and rhythm control (amiodarone, digoxin, verapamil and diltiazem) via CYP3A4 hepatic metabolism.[63–65] Atrial fibrillation ablation targeting the pulmonary veins is not recommended as it rarely offers long term AF-free survival. If AF rate control is not possible pharmacologically, then atrioventricular node (AVN) ablation and cardiac resynchronisation therapy (CRT) pacemaker implantation may be considered for symptomatic fast AF when CLL-related prognosis is more than one year.[66,67]

Recent studies have shown that the leading cause of death for AF patients already treated with appropriate anticoagulation is heart failure. This may include the direct myocardial toxicity of BTKis, hence the cornerstone of treatment should be directed at prevention and management of cardiac failure.[68–70] Other associated cardiovascular risk factors and comorbidities should also be proactively managed, and a holistic and integrated approach to AF care such as the ABC pathway (i.e., 'A' Avoid stroke; 'B' Better symptom management and 'C' Cardiovascular and comorbidity risk optimisation) is recommended in the new 2020 ESC Guidelines for AF management, and importantly, ABC pathway-adherent care has been associated with improved clinical outcomes in general AF populations.[71,39] A suggested algorithm for management of BTKi related AF is outlined below (Fig 1 and Table IV).

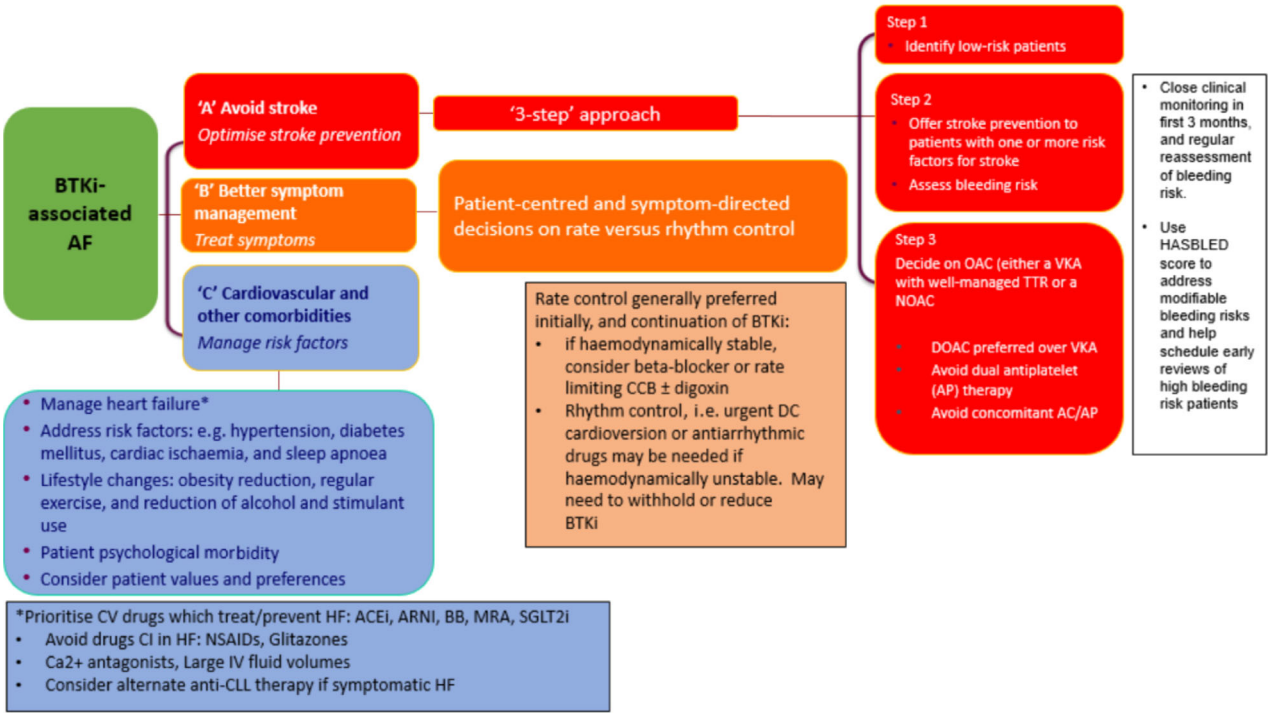

Fig 1. BTKi associated atrial fibrillation. [Colour figure can be viewed at wileyonlinelibrary.com]

Table IV. Recommended pre-BTKi cardiac assessment.

Pre-BTKi assessment
1. History: cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes mellitus), personal history of arrhythmia, family history of inherited cardiomyopathy and sudden cardiac death, bleeding disorder, recent surgery or history uncontrolled or major bleeding to be elicited.
2. Blood pressure measurement and 12-lead ECG. Patients with systolic BP >140 mmHg or diastolic BP > 90 mmHg should be offered ABPM or HBPM.
3. Assess for target organ damage for severe hypertension-left ventricular hypertrophy, chronic kidney disease, hypertensive retinopathy or increased urine albumin: creatinine ratio.
4. Close collaboration with a general practitioner to ensure good control and monitoring of blood pressure whilst on BTKi.
5. Baseline transthoracic echocardiogram is recommended for patients with pre-existing AF, heart failure, diabetes, coronary artery disease and hypertension.
6. Referral to cardiologist is encourgaged for patients with history of atrial fibrillation for optimisation of cardiovascular risk factors, discussion of appropriate anticoagulation for stroke prevention and control of symptom.

ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation; BP, blood pressure; BTKi, bruton tyrosine kinase inhibitors; ECG, electrocardiogram; HBPM, home blood pressure monitoring.

Recommendations

- Baseline and serial (3–6 monthly) ECG should be performed during the first 12 months of therapy (1C).
- Baseline transthoracic echocardiogram is recommended for patients with pre-existing AF, heart failure, diabetes, coronary artery disease and/or hypertension (1C).
- In patients with new atrial fibrillation during BTKi treatment, a prompt cardiology referral should be made for joint decision-making regarding the need for anticoagulation and pharmacological/non-pharmacological treatment of symptoms which can occur (1B).
- A holistic and integrated approach to AF care is recommended based on the ABC pathway, i.e., 'A' Avoid stroke; 'B' Better symptom management and 'C' Cardiovascular and comorbidity risk optimisation (1A).
- The use of DOAC is preferred to VKA due to superiority of efficacy and safety. Label-adherent dosing of DOAC is recommended. Dose reduction of DOAC can be considered during the period of full dose BTKi for those patients with particularly high-bleeding risk (2C).
- A rate control strategy for AF should be used first in haemodynamically stable AF. We recommend the use of a beta blocker licensed for heart failure for rate control (bisoprolol, carvedilol or nebivolol) (1A).
- Temporary dose reduction of BTKi may be used to alleviate fast AF not controlled optimally with a beta blocker (2C).
- Cessation of BTKi is strongly recommended in patients who develop significant worsening of heart failure until they are stabilised and a specialist cardio-oncology opinion guides cautious reintroduction with appropriate surveillance (1C).

Ventricular arrhythmia and sudden cardiac death

Isolated infrequent ventricular ectopics on ECGs may simply merit observation, especially if there are no/minimal symptoms and no other significant comorbidities.

There is emerging evidence of a causal relationship between ventricular arrhythmia (VA) and sudden cardiac death (SCD) with ibrutinib in recent clinical trials (Table V) and an earlier case report.[72] Longitudinal data (2009–2016) from US-based Comprehensive Cancer Registry revealed an increased idiopathic VA 100,000 person-year incidence rate of 596 compared to 48·1 in non-ibrutinib treated patients. This corresponds to a relative risk of 12·4 ($P < 0{\cdot}001$) and an absolute excess risk of 548. The VA incidence rate rises to 617 per 100 000 person-year in ibrutinib patients with underlying coronary artery disease and heart failure. Over a median follow-up of 32 months, 11 patients developed symptomatic VA with a median time to event of 16 months.[73] Cheng *et al.* reported 33 cases of ibrutinib-associated VA published through the FDA Adverse Events Reporting System between 2013–2017, the majority of which had no underlying cardiac history. The consequences of VA were serious: fatal in five patients, and a further 10 had life-threatening events.[74] Based on this analysis, the FDA has updated the prescribing information for ibrutinib to include information about cardiac arrhythmias and ventricular tachyarrhythmias. A study of mouse models has shown that administration of a high dose of ibrutinib increased susceptibility to both AF and VA induced by intracardiac pacing.[75] The rare, but real risk of VA should be included in routine patient consultations, and symptoms of palpitations, dizziness, and syncope must be investigated in detail, including echocardiography and cardiac rhythm monitoring.[1]

[1]A recent alert from an unpublished clinical trial (FLAIR: a phase III, randomised controlled trial comparing the use of ibrutinib and rituximab [IR] versus FCR versus ibrutinib and venetoclax in treatment naïve CLL patients) reported that patients in the ibrutinib and rituximab (IR) arm have an elevated risk of sudden cardiac death if they were on ACE inhibitor treatment at study entry versus patients not on ACE inhibitors at study entry. Pending further data, patients currently receiving both ibrutinib and an ACE inhibitor should consider stopping the ACE inhibitor and changing to an alternative antihypertensive treatment. Decisions to stop ibrutinib should be clinically driven, with monitoring of disease status when ibrutinib is ceased.

Table V. Rate of sudden cardiac death and ventricular arrhythmia in ibrutinib clinical trials.

Trial	No of patients	Median Age (years)	Median follow up (months)	TN or RR	Sudden cardiac death
FCG + ibrutinib (Jain *et al*., 2019)[82]	45	60	34·2	TN	one (aged 26 with no cardiac RF; died from worsening CCF)
Alliance I vs. IR vs. BR (Woyach *et al*., 2018)[9]	364 in ibrutinib arm	71	38	TN	11 in ibrutinib arms vs. one; one G4 cardiac arrest
IR vs. FCR (ECOG ACRIN) (Shanafelt *et al*., 2019)[7]	354 in ibrutinib arm	58	33·6	TN	one death with hx of AF; one G4 cardiac arrest; one G3 VT
Illuminate IG vs. Chlr-G (Moreno *et al*., 2019b)[83]	113 in ibrutinib arm	70	31·3	TN	one sudden death, one cardiac arrest, three unknown cause of death, one died after cross over to ibrutinib arm
HELIOS (Ibrutinib and BR vs. BR) (Chanan-Khan *et al*., 2016)[84]	287	64	14·7 mo	RR	three sudden cardiac death and four G3, VA and cardiac arrests in ibrutinib arm vs. none in comparator arm

ACRIN, American College of Radiology Imaging Network; BR, bendamustine plus rituximab; CCF, congestive cardiac failure; Chl-G, chorambucil plus obinutuzumab; ECOG, Eastern Cooperative Oncology Group; FCG, fludarabine, cyclophosphamide and obinutuzumab; IG, immunoglobulin; I-R, idelalisib plus rituximab; RF, radiofrequency; RR, relapsed/refractory; TN, treatment naive; VA, ventricular arrhythmias; VT, ventricular tachycardia.

Recommendations

- The risks of VA and sudden cardiac death should be included in routine patient consent for treatment with BTKi (https://www.cancerresearchuk.org/sites/default/files/cancer-stats/cll_ibrutinib_v1/cll_ibrutinib_v1.pdf). In patients with CLL and a previous history of ventricular arrhythmias, a structural cardiomyopathy associated with SCD, a genetic cardiac arrhythmia syndrome (e.g., long QT, Brugada) or a family history of an inherited cardiomyopathy, appropriate counselling and risk: a benefit assessment should be made regarding BTKi therapy, and alternative anti-CLL therapy should be considered if available (1C).
- Patients presenting with symptoms of syncope, dizziness or palpitations should prompt further investigations with electrocardiogram, and referral to cardiology for echocardiography and cardiac rhythm monitoring (1B).
- Serious cardiovascular events including ventricular arrhythmia, unexplained death and sudden cardiac death should be carefully adjudicated and reported in clinical trials to gain deeper insight into the real incidence and pathophysiology of the disease (1C).
- Given the high mortality rate associated with VA, BTKi therapy should be discontinued in patients with idiopathic VA. Urgent cardiology referral should be made to exclude underlying cardiac disease (1C).
- In patients who are deemed to have another underlying reversible cause for VA, continuation of BTKi therapy needs to be carefully considered once the cause is rectified, with close monitoring and collaboration with treating haematologists and cardiologists. Dose modification of BTKi may be required due to the high frequency of DDI between BTKi and antiarrhythmic agents (2C).

A range of other CV complications of ibrutinib have been reported including heart failure and cardiac conduction disease, but these are rarer than hypertension, AF and VAs. Consideration for a causative link if CLL patients present with HF or cardiac conduction disease whilst taking a BTKi should be considered.

Summary

Bruton tyrosine kinase inhibitors has transformed the treatment landscape of CLL but led to an unfortunate rise in targeted therapy-associated CV complications, including hypertension, AF and ventricular arrhythmias with related SCD. A multidisciplinary input with haematologists and cardiologists is recommended to provide personalised, risk-adapted treatment whilst employing appropriate risk mitigation strategies in order to improve patient outcomes.

Referral of complex cases to specialist cardio-oncology services, where available, is recommended, and further preclinical and clinical research is needed to understand the pathophysiology and strategies to prevent and manage BTKi-related CV toxicities.

We include, with this good practice paper on management of cardiovascular complications of BTKi, an information sheet for use by Primary Care Physicians (Supplementary) to aid patient management.

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Conflict of Interests

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Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website https://b-s-h.org.uk/guidelines.

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