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Ibrutinib and Bruton's Tyrosine Kinase Inhibitors in Chronic Lymphocytic Leukemia: Focus on Atrial Fibrillation and Ventricular Tachyarrhythmias/ Sudden Cardiac Death

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Abstract

Background: The natural history of chronic lymphocytic leukemia (CLL) was dramatically improved by the introduction of ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor. In this review, we aimed to summarize and critically evaluate the association between first- and second-generation BTK inhibitors and the risk of atrial fibrillation (AF) and ventricular arrhythmias (VA). ***Summary:*** Since the first clinical experience, the development of AF was observed as the result of off-target effects that likely combined with patient's predisposing risk factors and concomitant cardiac morbidities. More recently, both ibrutinib dose reduction and arrhythmia management allowed long-term treatment, with positive effects on progression-free survival and reduced all-cause mortality as well. Second-generation BTK inhibitors, acalabrutinib, and zanubrutinib have been tested and validated in CLL. A lower occurrence of AF as compared with ibrutinib has been found, although AF has always been a secondary endpoint of all studies that probed these agents. ***Key Messages:*** For this reason, caution should be exercised before concluding that second-generation BTK inhibitors are safer than ibrutinib. Recent data on the effectiveness of ibrutinib over a follow-up of 8 years show a remarkable benefit on all-cause mortality, which is of great value also for interpreting the clinical impact of the few cases of VA and sudden cardiac death (SCD) reported for ibrutinib, independently of QT lengthening. Since a risk of VA and SCD has been recently reported also during treatment with second-generation BTK inhibitors, it appears that this risk, usually reaching its maximum size effect at long-term follow-up, likely denotes a class effect of BTK inhibitors.

Introduction

Cancer per se is associated with an increased risk of atrial fibrillation (AF). Patients with cancer were in fact shown to carry a 20% higher adjusted risk of AF as compared to noncancer patients, regardless of active cancer treatment [1]. Similarly, to noncancer patients, new-on-

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set AF is associated with an increased risk of thromboembolic events and heart failure, requiring appropriate management [2, 3]. The effects on ventricular function have been object of many studies starting from the introduction of anthracyclines in chemotherapy [4]. More recently, the issue of AF and ventricular tachyarrhythmias became of interest both as the results of cancer itself or new chemotherapy agents. The association between anticancer therapies and AF is well known, with many factors being involved in complex interactions [5–11].

In recent years, Bruton tyrosine kinase (BTK) inhibitors have been used to treat lymphoid malignancies significantly improving clinical outcomes [12]. However, these agents have been associated with an increased risk of AF [4, 13]. The aim of the present review is to summarize and critically evaluate the association between first- and second-generation BTK inhibitors and the risk of AF and ventricular arrhythmias (VA) by analyzing data from randomized controlled trials and large observational studies.

Hematological Malignancies and AF: A Strict Association

Although any type of cancer can be associated with an increased incidence of AF compared to the general population, some types of malignancies are associated with a significantly higher risk as is for lung cancer according to data from a long-term epidemiological study [14]. High rates of incident AF have also been reported for skin, esophageal, and hematologic malignancies [15]. As far as hematological malignancies are concerned, the risk of AF appears particularly high in patients affected by chronic lymphocytic leukemia (CLL). A study from the Mayo Clinic [16] evaluated the prevalence of AF at baseline and the incidence of AF during follow-up in 2,444 patients with newly diagnosed CLL [16]. In this analysis, a prior history of AF was present in around 6% of the patients, and among the 2,292 patients without a history of AF, 6.1% developed incident AF during follow-up (incidence of approximately 1%/year) [16].

The Mayo Clinic cohort study [16] provided important information also on the risk factors associated with incident AF in CLL patients. Older age, male sex, valvular heart disease, and hypertension were identified as clinical factors significantly associated with an increased risk of incident AF. The prevalence of AF showed an age-dependence in both CLL patients and control adult populations, with a higher prevalence in any age strata of CLL patients. The risk of developing incident AF along with time, modeled at 10 years, was highly variable according to the combination of risk factors, ranging from 4%–33%, thus providing an interesting background for interpreting the occurrence of AF in CLL patients, independently of the effects of pharmacologic treatments [16].

CLL treatment has been revolutionized by the advent of BTK inhibitors, of which ibrutinib was the only to be approved and marketed at the time when the Mayo Clinic study [16] was published. Ibrutinib therapy is associated with an increased risk of AF, and the literature actually refers to ibrutinib as the typical "targeted" drug that causes AF [17]. Here, it is worth noting that the cohort study included only 72 patients treated with ibrutinib [16]. Therefore, the study provided an unbiased assessment of the association between CLL and both prevalent and incident AF, also with respect to a known perpetrator of incident AF.

AF and Anticancer Drugs

Many anticancer drugs, both old generation and novel agents, may be associated with AF [5, 6, 8, 15]. However, the association between anticancer drugs and the occurrence of AF is not of easy analysis. Many confounders and competing factors may influence the occurrence of AF during a trial, and even more in daily practice. The type and stage of cancer, concurrent surgical or diagnostic interventions, electrolyte abnormalities, the development of hypertension, and metabolic alterations, all interact through complex pathways. The intrinsic effects of specific drugs, whether used alone or in combination, may also result in modulation of molecular pathways and ionic effects at cardiac level that eventually lead to an increased risk of arrhythmias, specifically of AF. In this perspective, a multidimensional assessment of AF risk is much more appropriate than just considering the association of AF with a given drug in isolation [17].

Data regarding anticancer drug-associated AF have variable sources and only in part are derived from randomized clinical trials (RCTs). The vast majority of data are retrieved from real-world datasets or pharmacovigilance reports [15]. RCTs have some limitations in assessing the risk of AF associated with cancer drugs or multimodality treatments since they are neither aimed nor powered for assessing these outcomes. Efficacy is the main endpoint of randomized pivotal trials of cancer drugs, and in many cases the trials exclude patients at higher risk of AF onset, such as subjects with cardiovas-

cular risk factors, established cardiac abnormalities, or history of prior AF. Moreover, RCTs have no specific diagnostic methods for identifying AF with high sensitivity, leaving AF detection and management to the investigator's clinical assessment.

In the light of these limitations, pharmacovigilance reports recently analyzed the issue of AF in patients treated with cancer drugs. Using the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a publicly available pharmacovigilance tool provided by the FDA, which collects adverse event (AE) reports from the USA and other countries, Ahmad et al. [18] analyzed the top 30 cancer drugs associated with AF case, reporting up to February 2021. The highest number of AEs was reported for lenalidomide, while nilotinib accounted for the highest proportion of reported cardiac AEs (15.6% of the total reported drug AEs), followed by trastuzumab (14.5%), ibrutinib (12.8%), carfilzomib (12.5%), and doxorubicin (11%). Taking into account AF as a percentage of all reported drug AEs, ibrutinib accounted for the highest percentage (5.3%), followed by venetoclax (1.6%), bortezomib (1.6%), carfilzomib (1.5%), and nilotinib (1.4%). The proportional reporting ratio was used to measure disproportionality in reporting of drug AEs, with the highest values for AF, reading ibrutinib first (5.96, 95% confidence interval [CI]: 5.70–6.23), followed by bortezomib (1.65, 95% CI: 1.52–1.79), venetoclax (1.65, 95% CI: 1.46–1.85), carfilzomib (1.53, 95% CI: 1.33–1.77), and nilotinib (1.46, 95% CI: 1.31–1.63) [18].

Another pharmacovigilance study, reported by Alexandre et al. [15] and based on the WHO dataset VigiBase, identified 19 cancer drugs associated with AF. Fourteen of the 19 drugs analyzed (74%), were used to treat hematologic malignancies. The association with AF was an unprecedent finding for 9 drugs (45%), including immunomodulators (lenalidomide, pomalidomide), kinase inhibitors (nilotinib, ponatinib, midostaurin), antimetabolites (azacytidine, clofarabine), docetaxel (tubulin-active taxane), and obinutuzumab (anti-CD20 monoclonal antibody).

Overall, these data suggest that the occurrence of AF in patients with cancer, and especially in patients with hematological malignancies, is a general problem particularly in patients aged more than 65 years [15], deserving a careful analysis. Many drugs may increase the risk of AF during cancer treatment, thus requiring a specific decision-making aimed at avoiding treatment interruption [12, 15].

Treatment of CLL with Ibrutinib and Risk of AF

Ibrutinib is effective in treating CLL, mantle cell lymphoma, and Waldenstrom macroglobulinemia as monotherapy and in combination [19]. In CLL patients, including those at high-risk, ibrutinib improves response rate, progression-free and overall survival in relapsed/refractory (R/R), and treatment-naïve patients [20–23]. In the registration clinical trials, ibrutinib had a favorable safety profile and in general was well tolerated, even in older patients. Data at long-term follow-up confirm the overall efficacy and safety profile of ibrutinib in CLL. Among the reported AEs, an increased risk of AF was reported. In detail, in phase III CLL trials, there was a 5–7% incidence of AF, which was mostly graded 1–2 by CTCAE criteria. Grade 3–4 AF incidence was 0–3% [20, 21, 23, 24]. A detailed overview regarding AF in ibrutinib and control patients enrolled in RCTs or large observational studies of CLL is shown in Table 1.

A systematic review and meta-analysis of RCTs of ibrutinib versus chemotherapy, monoclonal antibody, or combinations, showed an incidence of serious AF (and/or atrial flutter) of 3.03% for ibrutinib versus 0.8% for the comparator(s) (risk ratio 3.80) [25]. The incidence of any grade AF (and/or atrial flutter) was 8.2% for ibrutinib versus 0.9% for comparators (risk ratio 8.8) [25]. In real-world settings (UK and Ireland), the incidence of AF in R/R CLL patients treated with ibrutinib was 5.1% [26]. Overall, AEs in clinical trials, including AF and bleeding, were manageable in most patients through an appropriate risk stratification for stroke, appropriate decision-making for anticoagulation, and control of cardiac rate and/or rhythm.

As expected, ibrutinib-related risk of AF was increased by the same risk factors as those identified in the general population and for other drugs (older age, male sex, valvular heart disease, hypertension) [15, 18, 27]. It follows that cause-and-effect relationships between ibrutinib and AF, and a precise definition of ibrutinib as an independent determinant or contributing cause of AF, cannot be obtained in isolation from a context where many other factors predispose patients to AF and aggravate AF risk.

Regardless of how precisely AEs develop, preventability and clinical manageability of AEs determine the actual risk-benefit ratio of ibrutinib. Patients' candidate for ibrutinib should undergo a comprehensive clinical evaluation aimed at identifying baseline risk factors, informing patients about their correct management, and providing practical guidelines to avoid interactions between ibrutinib and other drugs [12]. AF exposes patients to the risk of stroke, requiring anticoagulant treatment to decrease

Table 1. AF and VT/SCD in trials or large observational studies (>100 patients) on BTK inhibitors in CLL patients

Study, year, ref	Type of study and type of CLL patients enrolled	Treatment arms, *N* patients	Age of the patients, years	Patients with prior AF included	Follow-up	AF during follow-up, *N* patients (%)		Ventricular tachyarrhythmias/ SCD during follow-up, *N* patients (%)		Effect on all-cause mortality (vs. control)
						any grade	grade ≥3	any grade	grade ≥3	
Ibrutinib										
RESONATE, 2014 [19]	RCT on RR CLL	195 ibrutinib	67 (range 30–86)	NR	9.4 months	10 (5)	6 (3)	NR	NR	With ibrutinib HR 0.43; 95% CI: 0.24–0.79) for all-cause death
		191 ofatumumab	67 (range 37–88)	NR		1 (1)	NR	NR	NR	
RESONATE long-term follow-up, 2019 [56]	RCT on RR CLL	195 ibrutinib	67 (range 30–86)	NR	41 months	24 (12)	12 (6)	2 (1)	0	With ibrutinib HR: 0.64; 95% CI: 0.42–0.98 for all-cause death
		191 ofatumumab	67 (range 37–88)	NR		NR	NR	NR	NR	
RESONATE-2, 2015 [20]	RCT on untreated CLL/SLL	135 ibrutinib	73 (range 65–89)	NR	18.4 months	8 (6)	2 (1)	NR	NR	With ibrutinib HR 0.16; 95% CI: 0.05–0.56 for all-cause death
		132 chlorambucil	72 (range 65–90)	NR		1 (1)	0	NR	NR	
RESONATE-2, long-term follow-up, 2022 [55]	RCT on untreated CLL/SLL	135 ibrutinib	73 (range 65–89)	NR	8 years	7% in years 7–8	8 (6)	NR	NR	The 7-year survival estimate was 78% (HR vs. chlorambucil: 0.45; 95% CI: 0.28–0.74)
		132 chlorambucil	72 (range 65–90)	NR		NR	NR	NR	NR	
ECOG-1912, 2019 [57]	RCT on untreated CLL/SLL	352 ibrutinib + rituximab	56.7±7.5	1 patient	33.6 months	26 (7.4)	Grade 3: 9 (2.6) Grade 4: 2 (0.6)	NR	VT: 1 patient Cardiac arrest (non fatal): 1 patient	With ibrutinib HR 0.17; 95% CI: 0.05–0.54 for all-cause death
		158 fludarabine, cyclophosphamide + rituximab	56.7±7.2	NR		5 (3.2)	Grade 3: 1 (0.6) Grade 4 1 (0.6)	NR	NR	
HELIOS, 2016 [22]	RCT on RR CLL/ SLL	287 ibrutinib + bendamustine-rituximab	64 (range 31–86)	25 (8.7)	17 months	21 (7)	NR	NR	3 (1)	With ibrutinib HR 0.63, 95% CI: 0.39–1.02 for all-cause death. After adjustment for crossovers: HR 0.58, 95% CI: 0.35–0.96 for all-cause death
		287 bendamustine + rituximab	63 (range 36–83)	22 (7.6)		7 (2)	NR	NR	0	
ALLIANCE, 2018 [58]	RCT on untreated CLL	180 ibrutinib	71 (range 65–89)	NR	38 months	31 (17)	17 (9)	NR	1 patient	No significant difference among the three treatment groups with regard to overall survival
		181 ibrutinib + rituximab	71 (range 65–86)	NR		25 (14)	10 (6)	NR	0	
		176 bendamustine-rituximab	70 (range 65–86)	NR		5 (3)	5 (3)	NR	0	
ILLUMINATE, 2019 [59]	RCT on untreated CLL/SLL	113 ibrutinib + obinutuzumab	70 (IQR 66–75)	NR	31.3 months	Grade 1–2: 8 (7)	6 (5)	NR	NR	Median overall survival not reached in either group (HR 0.92; 95% CI: 0.48–2.77)
		115 chlorambucil + obinutuzumab	72 (IQR 66–77)	NR		0	0	NR	NR	
Omi et al., 2022 [60]	Prospective post marketing surveillance study on RR CLL/ SLL	289 patients newly initialed with ibrutinib	72 (range 33–92)	26 (9%) prior history of arrhythmia	1 year	7 (2.4)	NR	1 (0.3)	NR	With ibrutinib overall survival rates of 79.1%

Table 1 (continued)

Study, year, ref	Type of study and type of CLL patients enrolled	Treatment arms, *N* patients	Age of the patients, years	Patients with prior AF included	Follow-up	AF during follow-up, *N* patients (%)		Ventricular tachyarrhythmias/ SCD during follow-up, *N* patients (%)		Effect on all-cause mortality (vs. control)
						any grade	grade ≥3	any grade	grade ≥3	
GIMEMA LLC1114 study, 2022 [61]	Prospective, phase 2, single-arm on untreated CLL	146 patients treated with ibrutinib + rituximab	73 (range 37–88)	NR	49.1 months	16%	6%	NR	NR	With ibrutinib 48-month overall survival rate of 90% (95% CI: 84.7–95.3)
CLL 12 trial, 2022 [62]	RCT on CLL in Binet stage A without treatment indication	182 ibrutinib	64 (range 38–85)	NR	31 months	9/158 (5.7)	8/158 (5.1)	NR	NR	With ibrutinib HR for progression or death 0.18, 95% CI: 0.12–0.27
		181 placebos	64 (range 36–80)	NR		1/155 (0.6)	1/155 (0.6)	NR	NR	
Akpinar et al. 2021 [63]	Retrospective study on RR CLL	200 ibrutinib	68 (range 39–86)	NR	17 months	5 (2.8)	0	NR	NR	With ibrutinib HR for overall survival 0.136; 95% CI: 0.079–0.259
IBRORS-LLC Study, 2021 [64]	Retrospective study on CLL	269 ibrutinib	70.9 (range 63.1–77.4)	19 (7.1%)	19.2 months	8 (3)	4 (1.5)	NR	NR	Median overall survival was not reached irrespective of the line in which ibrutinib was used
Abdel-Qadir et al., 2021 [65]	Case-control study on CLL	778 ibrutinib-treated patients	Mean 72.9	79 (10.2)	19 months	137 (17.6)	NR	NR	NR	Survival at 3 years was estimated at 73.9% (95% CI: 69.4–77.9) in ibrutinib-treated patients and 77.2% (95% CI: 73.0–80.8) in controls ($p = 0.84$)
		778 ibrutinib-naïve CLL controls	Mean 73.0	79 (10.2)		71 (9.1)	NR	NR	NR	
GENUINE, 2021 [66]	RCT on RR CLL/ SLL	64 ublituximab plus ibrutinib	66 (IQR 62–74)	NR	41.6 months	3 (5)	5 (7.8)	NR	SCD: 1 (2)	NR
		62 ibrutinib	67 (IQR (62–74)	NR		0	0	NR	SCD: 1 (2)	
Acalabrutinib										
ASCEND, 2020 [39]	RCT on RR CLL	154 acalabrutinib	68 (range 32–89)	NR	16.1 months	8 (5)	2 (1)	0	0	With acalabrutinib monotherapy (HR for risk of progression or death: 0.31; 95% CI: 0.20–0.49)
		118 idelalisib + rituximab	67 (range 34–90)	NR		4 (3)	1 (1)	0	0	
		35 bendamustine-rituximab		NR		1 (3)	1 (3)	0	0	
ELEVATE – TN, 2022 [67]	RCT on untreated CLL/SLL	179 acalabrutinib	70 (IQR 66–75)	NR	46.9 months	11 (6.1)	2 (1.1)	NR	NR	Overall survival: acalabrutinib-obinutuzumab versus obinutuzumab-chlorambucil (HR: 0.50; 95% CI: 0.25, 1.02) acalabrutinib-obinutuzumab versus acalabrutinib (HR: 0.53; 95% CI: 0.26, 1.06) acalabrutinib versus obinutuzumab-chlorambucil (HR 0.95; 95% CI: 0.52–1.74)
		178 acalabrutinib + obinutuzumab	70 (IQR 65–75)	NR		7 (3.9)	1 (0.6)	NR	NR	
		177 chlorambucil + obinutuzumab	71 (IQR 67–76)	NR		1 (0.6)	0	NR	NR	

Table 1 (continued)

Study, year, ref	Type of study and type of CLL patients enrolled	Treatment arms, *N* patients	Age of the patients, years	Patients with prior AF included	Follow-up	AF during follow-up, *N* patients (%)		Ventricular tachyarrhythmias/ SCD during follow-up, *N* patients (%)		Effect on all-cause mortality (vs. control)
						any grade	grade ≥3	any grade	grade ≥3	
ELEVATE-RR, 2021 [40]	RCT on RR CLL with del17 or del 11 mutations	268 acalabrutinib	66 (range 41–89)	10/25 (40.0)	40.9 months	25 (9.4)	13 (4.9)	1 (0.4)	1 (0.4)	Observed deaths: 63 patients (23.5%) with acalabrutinib and 73 (27.5%) with ibrutinib (HR, 0.82; 95% CI: 0.59–1.15)
		265 ibrutinib	65 (range 28–88)	5/42 (11.9)		42 (16.0)	10 (3.8)	3 (1.1)	3 (1.1)	
Zanubrutinib										
ALPINE, 2021 [68]	RCT on RR CLL/ SLL	207 zanubrutinib	Age ≥65 years: 62.3% NR		15.0 months	5 (2.5)	NR	NR	NR	NR
		208 ibrutinib	Age ≥65 years: 61.5% NR			21 (10)	NR	NR	NR	
SEQUOIA, 2022 [43]	RCT on untreated CLL/SLL	241 zanubrutinib	70 (IQR 66–75)	NR	26.2 months	8 (3.3)	1 (0.4)	2 (0.8)	2 (0.8)	No significant difference in overall survival between groups (HR 1·07, 95% CI: 0.51–2.22; $p = 0.87$)
		238 bendamustine-rituximab	70 (IQR 64–74)	NR		6 (2.6)	3 (1.3)	0	0	

Reports from pharmacovigilance and cohort study focused on the VT and SCD are not included in this comprehensive table but are reported in the text. CI, confidence interval; AF, atrial fibrillation; CLL, chronic lymphocytic leukemia; HR, hazard ratio; IQR, interquartile range; NA, not applicable; NR, not reported; RCT, randomized controlled trial; RR, relapsed refractory; SCD, sudden cardiac death; SLL, small lymphocytic lymphoma; VT, ventricular tachyarrhythmias.

thromboembolic complications, and specific clinical indications have been released in accordance with literature and consensus of experts [28, 29]. The timetable for a periodic assessment may be guided by appreciating that AF risk is higher over the first 2 years of treatment [12]. A reasonable approach might be to perform an ECG every 1 or 2 months during the first 6 months and every 6 months thereafter [12]. An ECG should be promptly performed in patients reporting symptoms suggestive of AF (palpitations, light-headedness or syncope, dyspnea, or other symptoms of heart failure potentially associated with AF) [12]. The QTc interval should be accurately measured to rule out a pathologic lengthening.

The occurrence of AF in patients receiving ibrutinib therapy is a clinical issue manageable through a multidisciplinary dialogue between hematologists and cardiologists. Drug interruption is not required in the majority of cases, provided that patients are closely managed, particularly with regard to the choice of anticoagulant and anti-arrhythmic drugs and the prevention and surveillance of bleeding risk [12]. Data from an international study of ibrutinib in CLL showed that patients who had ibrutinib interrupted at the time of AF onset had a significantly worse progression-free survival compared with those who had a reduction of ibrutinib dose without interruption or those who continued full dose ibrutinib [30]. Following earlier suggestion that ibrutinib dosage could be reduced and ibrutinib therapy continued in the interest of patient oncologic outcome [12], the same strategy was adopted also by the group of the Mayo Clinic [16]. The vast majority of patients with treatment-emergent AF were able to continue ibrutinib, with dose reduction being required in 43% of them [31].

Pharmacokinetic and pharmacodynamic considerations support the feasibility and efficacy of reducing ibrutinib dose in appropriately selected cases [32]. In fact, ibrutinib therapy causes an early decline in BTK protein levels in CLL, which makes lower doses of ibrutinib still provide nearly complete occupation of the residual BTK as well as inhibition of downstream proliferation signals [33]. These mechanisms were successfully confirmed in a proof-of-concept study [34].

New BTK Inhibitors: Acalabrutinib and Zanubrutinib and Risk of AF

Acalabrutinib and zanubrutinib are second-generation irreversible BTK inhibitors. Acalabrutinib seems to cause fewer off-target effects than ibrutinib [35, 36]. A

detailed overview of AF in acalabrutinib and zanubrutinib and control patients enrolled in the RCTs performed on CLL patients is shown in Table 1. The improved safety profile of acalabrutinib was originally attributed to its increased specificity for BTK, sparing the activity of other kinases otherwise inhibited by ibrutinib [37]. However, this interpretation has been questioned on the basis of shoulder-to-shoulder comparisons between acalabrutinib and ibrutinib in terms of kinase binding-inhibition-dissociation kinetics [38].

Acalabrutinib was tested in the ASCEND study in patients with R/R CLL versus idelalisib plus rituximab or bendamustine plus rituximab [39]. At a follow-up of 16.1 months, AF was observed in 5% of patients treated with acalabrutinib versus 3% in the comparator groups [39]. In the ELEVATE-RR study results, ibrutinib monotherapy was compared to acalabrutinib monotherapy in patients with R/R CLL [40]. At a median follow-up of 40.9 months, incidence of any grade AF was 16% in ibrutinib-treated patients and 9% in acalabrutinib-treated patients ($p = 0.02$). However, it should be noted that despite all-grade AF incidence was significantly lower with acalabrutinib compared to ibrutinib, the occurrence of grade ≥3 AF during the follow-up was quite similar [40]. The median time to AF was longer in patients treated with acalabrutinib (29 months) than ibrutinib (16 months), and incident AF in patients without a prior history of AF was lower in acalabrutinib-treated patients (6%) than ibrutinib-treated patients' group (15%). Overall, risk factors for developing AF were, as expected, age of 75 years or older, hypertension, and history of AF [40]. In view of these findings, the recent guidelines on cardio-oncology of the European Society of Cardiology in collaboration with other associations, such as the European Hematology Association and the International Cardio-Oncology Society, report that there are not enough data to recommend different monitoring strategies during treatment with these BTK inhibitors [4].

Zanubrutinib is another irreversible BTK inhibitor more selective than ibrutinib and has initially been tested in Waldenstrom macroglobulinemia [41]. In the ongoing phase 3 ALPINE study, zanubrutinib is compared with ibrutinib monotherapy in R/R CLL, and in a preliminary analysis with a follow-up of 15 months, AF was found to occur in 10% of ibrutinib-treated patients and 2% of zanubrutinib-treated patients [42]. Recently, the SEQUOIA trial showed that zanubrutinib was associated with a 3% rate of AF, in line with the results of the ALPINE trial (Table 1) [43].

These data show that also more selective second-generation BTK inhibitors can induce AF in CLL patients, thus denoting that AF may be a class effect. The available data from RCTs point to a reduced incidence of AF from acalabrutinib or zanubrutinib compared to ibrutinib, but an open question remains about what the actual incidence would have been had the three analogues been compared at a longer follow-up. Things might further change in real-life settings, where both the burden of comorbidities and the expectation of prolonged treatment set the stage for a possible late onset of AF and other AEs in patients treated with acalabrutinib or zanubrutinib. If confirmed, these different patterns of AE development should be compared with the rather well-established characteristics of ibrutinib-related AE, which occurs early during therapy but does not significantly increase over time.

In daily practice, clinical decision-making on the choice of a specific BTK inhibitor in patients affected by CLL should be guided by a medical need for efficacy, in terms of disease remission at long and very long-term. The occurrence of AF, whose risk depends on many factors, including patient age and underlying cardiovascular disease, can be appropriately managed through a strict collaboration between hematologists and cardiologists [12]. This includes a clinically-oriented pretreatment assessment, as already mentioned, and careful choice of cardiovascular medications (anticoagulants and anti-arrhythmics, if needed) and regular monitoring.

BTK Inhibitors and Risk of Ventricular Tachyarrhythmias and Sudden Cardiac Death

There is a growing interest in evaluating the risk of VA and sudden cardiac death (SCD) in patients treated with BTK inhibitors. An early report analyzed cases of polymorphic ventricular tachycardia and ventricular fibrillation during treatment with ibrutinib and found that these events were unrelated to a lengthening of the QTc interval [44]. Indeed, from the safety viewpoint, the assessment of drug effects on repolarization through QTc analysis is a key step in the development of anticancer agents and ibrutinib did not show evidence of pathologic effects on the QTc [44]. It is noteworthy that in a study of healthy subjects, administration of ibrutinib did not cause pathologic and harmful prolongations of the QT/QTc interval even after high, supratherapeutic dosages (840 and 1,690 mg) [45]. In analyzing this complex topic, different sources of information can be considered: RCTs, case reports

and case series, observational studies, and analysis of pharmacovigilance reports.

In reviewing published trials of ibrutinib, Lampson et al. [44] identified a total of 10 cases of sudden death or cardiac arrest among ~1,000 enrolled patients, with a calculated weighted incidence rate of 788 events per 100,000 person-years. They also reported, for a comparison, that the rates of SCD for 65-year-old subjects can be estimated in the range of 200–400 events per 100,000 person-years. In an analysis of data from a large US-based Comprehensive Cancer Center registry cohort of consecutive patients treated with ibrutinib from 2009 to 2016, Guha et al. [46] explored the rate of incident new symptomatic VA among patients treated with ibrutinib for a hematologic malignancy. This analysis showed that over a median follow-up of 32 months, 11 patients developed symptomatic VA, of which 7 (including one ventricular fibrillation/SCD and two recurrent sustained ventricular tachycardias) had at least probable association with ibrutinib, with a median time-to-event of 16 months (range 0.7–57.6) [46]. Another analysis of pharmacovigilance datasets was reported by Salem et al. [17], who evaluated reports on ibrutinib using VigiBase updated to January 2018. Disproportionality analysis showed that for ibrutinib, as compared to other drugs of the database, there was an increased reporting of VA, with a median time from drug initiation of 70 days, but not an increased reporting of cardiac death or shock or torsades de pointe/QT prolongation [17]. In discussing these data, the authors mentioned case reports of polymorphic ventricular tachycardia associated with normal QTc interval and no short-long-short coupling pattern at arrhythmia initiation [47, 48]. These findings may suggest alterations in cardiac sarcoplasmic reticulum Ca^{2+} homeostasis associated with cardiac ryanodine receptor (RyR2)-calmodulin-dependent protein kinase (CaMKII) pathways [17].

In the most recent analysis of VigiBase, updated to January 1, 2019, Salem et al. [49] reported that the number of cases of long QT, torsades de pointe, and ventricular tachyarrhythmias related to cancer drugs markedly increased. For ibrutinib, as for other anticancer agents, including CAR-T cell (axicabtagene ciloleucel), a signal was found for a risk of ventricular tachyarrhythmias and sudden death, independently of QT lengthening [49].

A very recent report focused on acalabrutinib and analyzed a large contemporary US-based Comprehensive Cancer Center cohort of 290 consecutive patients treated with acalabrutinib for B-cells malignancies (89% for CLL) between 2014 and 2020 [50]. The primary end point, by including ventricular fibrillation, ventricular tachycardia, and symptomatic premature ventricular contractions, was actually a mixture of sustained and nonsustained ventricular tachyarrhythmias, with variable outcome implications. The median age of the 290 patients included in the cohort was around 64 years, and 26.6% had been previously treated with ibrutinib. Over a median follow-up of around 42 months, 10 patients developed symptomatic ventricular tachyarrhythmias, including 1 sudden death/ventricular fibrillation, and 1 recurrent sustained ventricular tachycardia. Eighty percent of these arrhythmic events were judged to have had at least a probable association with acalabrutinib treatment, with a median time-to-event of 14.9 months (range 1.1–55.8), which was fully identical with that previously reported for ventricular tachyarrhythmias in ibrutinib-treated patients [46, 50]. Of note, among patients not previously treated with ibrutinib and without coronary artery disease or heart failure, the weighted average incidence of ventricular tachyarrhythmias during acalabrutinib treatment was 394 per 100,000 person-years compared to a reported incidence of 48.1 among similar-aged non BTK inhibitors-treated subjects, with a relative risk 8-fold higher than expected. Except for age, no cardiac or electrocardiographic variable was found as significantly associated with occurrence of ventricular tachyarrhythmias during follow-up.

As far as zanubrutinib is concerned, recent data derived from the SEQUOIA trial [43]. The trial compared zanubrutinib with bendamustine-rituximab in 590 patients with CLL or SLL showing that the risk of AF and ventricular tachyarrhythmias in the zanubrutinib arm was not negligible [43].

Taken together, these initial data on second-generation BTK suggest a class effect also for ventricular tachyarrhythmias, to be confirmed by larger trials and real-world registries. As known, no trial has been powered for these events, and therefore, any conclusive consideration appears premature.

There are important limitations in retrospective analyses of datasets, and trial data as well, with regard to classifying and reporting VA, which can be either sustained or nonsustained, with marked different significance. More in general, there may be problems with an appropriate labeling of sudden deaths as SCDs due to life-threatening ventricular tachyarrhythmias. Indeed, in the cardiology field there is a substantial concern on the validity of a proper assignment of deaths as "sudden cardiac deaths," since in many cases, documentation of the arrhythmic event is lacking. Post hoc adjudication, also on the basis of autopsy studies, revealed that the role of ventricular tachyarrhythmias was overestimated. Many

deaths, originally classified as SCD, could more appropriately reinterpreted as noncardiac deaths [51, 52]. All-cause mortality appears to be a more proper end point, since it is independent of subjectivity in adjudicating the event and provides a balanced assessment of drug efficacy and safety. All-cause mortality should therefore be preferred in any clinical setting evaluating therapeutic interventions, even in case of interventions with a direct impact on ventricular tachyarrhythmias, such as implantable cardioverter defibrillators [53, 54].

Taking all these considerations in a due account, it is of great clinical value to consider that in the setting of CLL, ibrutinib afforded a reduction of all-cause mortality. In detail, in the landmark phase 3 RESONATE trial [19] evaluating patients with R/R CLL or small lymphocytic lymphoma, randomized to treatment with ibrutinib or ofatumumab, overall survival was improved in ibrutinib-treated patients (hazard ratio for death, 0.43; $p = 0.005$ at a median follow-up of 9.4 months). Also, in another landmark phase 3 trial, RESONATE-2 [20], comparing ibrutinib and chlorambucil in previously untreated old patients, ibrutinib significantly improved overall survival (hazard ratio, 0.16; 95% CI: 0.05–0.56; $p = 0.001$ at a median follow-up of 18.4 months). More recently, an improvement of overall survival in ibrutinib-treated patients versus patients treated with chlorambucil was demonstrated by the long-term follow-up of RESONATE-2 [55]. These data, derived from double-blind controlled trials, indicate that independently of potential effects on ventricular tachyarrhythmias, the net benefit of ibrutinib treatment in CLL patients is undisputedly positive, with a marked improvement of survival from all-cause mortality. As a matter of fact, while waiting for more data, the reported cases of ventricular tachyarrhythmias and sudden death during ibrutinib do not appear to influence the benefit of this treatment on survival in CLL, as compared with alternative treatments.

A risk of VA and SCD has been recently reported also during long-term treatment with acalabrutinib. It appears that this risk, usually appearing at long-term, may be common also to second generation BTK inhibitors [46]. In this regard, long-term data on zanubrutinib are waited for a more complete assessment.

Conclusions

The natural history of CLL was dramatically improved by the clinical use of ibrutinib, a BTK inhibitor. According to the results of RCTs, this agent was found effective in both untreated and relapsed refractory CLL. Since the first experience with ibrutinib was gained, development of AF was observed and attributed to off-target effect(s) that made ibrutinib synergize with risk factors that are common in CLL patients, such as age and concomitant cardiac morbidities. Management of AF requires appropriate risk stratification for systemic thromboembolism/stroke and institution of oral anticoagulation in the at-risk patients. In the first experience, the occurrence of AF was often associated with ibrutinib discontinuation, but more recently both ibrutinib dose reduction and management of the arrhythmia allowed long-term treatment with ibrutinib, thus achieving the positive effects of this treatment demonstrated by trials in terms of progression-free survival and also reduced all-cause mortality.

More recently, second-generation BTK inhibitors, acalabrutinib and zanubrutinib, have been tested and validated in CLL with evidence of improved progression-free survival at midterm. A lower occurrence of AF as compared with ibrutinib has been found, although AF has always been a secondary end point of all studies, validating these new therapeutic regimens. For this reason, caution should be exercised before concluding that second-generation BTK inhibitors are safer than ibrutinib. The pathophysiological foundations of AEs associated with this class of agents are in fact complex enough to require longer follow-up and more mature data from both clinical trials and "real-world" observational studies, registries, and pharmacovigilance reports.

Recent data on the effectiveness of ibrutinib over a follow-up of 8 years, showing a benefit on all-cause mortality, are of great value for interpreting the clinical impact of the few cases of ventricular tachyarrhythmias and SCD reported for ibrutinib, independently on QT lengthening. As a matter of fact, while waiting for more data, these cases do not appear to influence the benefit of this treatment on survival in CLL as compared with alternative treatments. A risk of VA and SCD has been recently reported also during treatment with acalabrutinib and zanubrutinib, commonly portrayed as being a more selective BTK inhibitor than ibrutinib. It thus appears that this risk may be common also to second-generation BTK inhibitors, with a high likelihood of being a class effect of BTK inhibitors. However, these data need to be confirmed by dedicated studies, and at present any conclusive consideration cannot be drawn. Management of the cardiovascular adverse effects of BTK inhibitors requires a strict collaboration between onco-haematologists and cardiologists in order to allow treatment continuation for achieving at long-term the full benefits of available treatments.

Conflict of Interest Statement

Giuseppe Boriani received small speaker's fees from Bayer, Boston, Boehringer Inghelheim, Bristol-Myers Squibb, Daiichi-Sankyo, and Janssen, outside of the submitted work. The other authors declare no conflict of interest.

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Conception and design of the work: Giuseppe Boriani and Giorgio Minotti. Interpretation of data of the work: Giuseppe Boriani, Pierantonio Menna, Riccardo Morgagni, Giorgio Minotti, and Marco Vitolo. Drafting the work and/or revising it critically for important intellectual content: Giuseppe Boriani, Pierantonio Menna, Riccardo Morgagni, Giorgio Minotti, and Marco Vitolo. Final approval of the version to be published: Giuseppe Boriani, Pierantonio Menna, Riccardo Morgagni, Giorgio Minotti, and Marco Vitolo.

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