Atrial fibrillation, anticoagulant stroke prophylaxis and bleeding risk with ibrutinib therapy for chronic lymphocytic leukaemia and lymphoproliferative disorders

Stephen P. Mulligan,[1,2] Christopher M. Ward,[2,3] David Whalley[2,4] and Sarah N. Hilmer[2,5]

[1]Department of Haematology, CLL Unit, [2]Kolling Research Institute, University of Sydney, [3]Department of Haematology, Haemostasis Unit, [4]Department of Cardiology, Electrophysiology Unit, and [5]Department of Clinical Pharmacology and Aged Care, Royal North Shore Hospital, Sydney, Australia

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Chronic lymphocytic leukaemia and ibrutinib

The management of chronic lymphocytic leukaemia (CLL) has been revolutionised over the last several years by the introduction of targeted inhibitors of the B-cell receptor signal and BCL2 pathways. Ibrutinib is the first in class covalent inhibitor of the Bruton Tyrosine Kinase (BTK) molecule, which it binds irreversibly at the BTK cysteine-481 ATP-binding site and inhibits phosphorylation of down-stream PLC-γ2, and B-cell receptor signalling (Byrd *et al*, 2013). Ibrutinib has been shown to improve progression free and overall survival in relapsed and refractory (R/R) CLL compared to ofatumumab (Byrd *et al*, 2014), and the combination of ibrutinib with bendamustine and rituximab (BR) is superior to BR (Chanan-Khan *et al*, 2016). Patients with R/R CLL therefore represent a high level of previously unmet need in CLL as they now achieve markedly superior outcomes than before ibrutinib was available. Sustained dose adherence may be important in maintaining response and optimal outcomes and avoiding the emergence of resistant clones (Jaeger *et al*, 2015). R/R CLL patients who are unable to tolerate ibrutinib have poor clinical outcomes and survival (Jain *et al*, 2015). More recently, ibrutinib has been compared to chlorambucil monotherapy in front-line CLL in patients deemed inappropriate for fludarabine-based therapy due to either comorbidity or advanced age. The results significantly favoured ibrutinib (Burger *et al*, 2015). Ibrutinib is now approved for relapsed and also front-line CLL therapy in the USA, and is therefore finding widespread use in CLL and other low-grade lymphoproliferative disorders.

Ibrutinib and atrial fibrillation

An unexpected adverse event that has emerged with ibrutinib is the occurrence of atrial fibrillation (AF). This occurred in 5–7.7% of patients on the initial three large randomised studies in CLL (Byrd *et al*, 2014; Burger *et al*, 2015; Chanan-Khan *et al*, 2016). A similar rate has been seen with ibrutinib in mantle cell lymphoma (MCL) (Dreyling *et al*, 2016; Lee *et al*, 2016) and Waldenstrom macroglobulinaemia (WM) (Treon *et al*, 2015; Gustine *et al*, 2016). A recent pooled meta-analysis of published data found the AF risk with ibrutinib is approximately four-fold higher than the comparator arms in published studies (Leong *et al*, 2016). A recent trial cohort in Bethesda had an incidence of 16% (14/85 patients) with follow-up of up to 26 months (Farooqui *et al*, 2015), most of whom (11/14 patients) were aged >65 years. In a report on ibrutinib-related AF in MCL, the cumulative incidence of AF at 6 months, 1 year and 2 years was 5.6%, 7.2% and 14.2% respectively (Lee *et al*, 2016). Hence, the risk of AF appears to be mainly early, but with a continuing risk with ongoing therapy. In this issue, Thompson and colleagues describe the clinical consequences of AF in CLL patients treated with ibrutinib and highlight the complexities of management in this setting (Thompson *et al*, 2016).

Ibrutinib and bleeding risk

Since the introduction of ibrutinib, a bleeding risk with the drug has been recognised (Lipsky *et al*, 2015). Ibrutinib induces a mild to moderate platelet function defect in approximately half of treated patients, usually presenting as cutaneous bruising or minor bleeding (Levade *et al*, 2014; Bye *et al*, 2015; Kamel *et al*, 2015; Alberelli *et al*, 2016). In most trials, the frequency of grade 3 or 4 bleeding events has been low at *c.* 3–4%. The antiplatelet effect of ibrutinib appears to vary among patients, but is exacerbated by other

Correspondence: Professor Stephen P. Mulligan, Department of Haematology, Royal North Shore Hospital, Pacific Highway, St Leonards, Sydney, NSW 2065, Australia.
E-mail: mulligan@sydney.edu.au

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medications (particularly aspirin, clopidogrel, non-steroidal anti-inflammatory drugs) and dietary supplements that affect platelet function. The utility of platelet function testing for patients on ibrutinib has not been established, but platelet aggregation responses to collagen (Kamel *et al*, 2015; Lipsky *et al*, 2015) and ristocetin are primarily affected (Kazianka *et al*, 2015). These acquired defects are consistent with an on-target inhibition of BTK signalling downstream from both the platelet collagen receptor glycoprotein (GP)VI, and the von Willebrand factor receptor, GPIb-V-IX (Quek *et al*, 1998; Bye *et al*, 2015; Rigg *et al*, 2016). However, routine platelet function studies in CLL patients may be confounded by thrombocytopenia and acquired platelet function defects reported in some CLL patients prior to the commencement of ibrutinib (Levade *et al*, 2014; Lipsky *et al*, 2015, 2016; Tam & Kamel, 2016).

Ibrutinib and hypertension

An increased incidence of hypertension of 3.5% has been observed in one major ibrutinib trial (Chanan-Khan *et al*, 2016) and 20% and 23% grade 3/4 hypertension at the 3-year follow-up in R/R and treatment-naïve patients, respectively (Byrd *et al* 2015). This is an additional risk factor for AF and should therefore be treated to minimize the contribution of this risk factor for AF.

Ibrutinib and drug interactions

Ibrutinib is metabolized by CYP3A4/5 and, to a lesser extent. CYP2D6, both members of the cytochrome P450 oxidizing enzyme superfamily (Scheers *et al*, 2015) (de Jong *et al*, 2015) (Lambert Kuhn *et al*, 2016; de Zwart *et al*, 2016). Therefore, the use of ibrutinib with CYP3A4 inhibitors, such as the moderate inhibitors diltiazem and verapamil that are commonly used for rate control in AF, can increase the patient's exposure to ibrutinib. There are also potential interactions with P-glycoprotein (https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf 05/2016). Ibrutinib inhibits P-glycoprotein and thus may increase exposure to P-glycoprotein substrates, many of which are used in the treatment of AF, such as digoxin, dabigatran and, to a lesser extent, apixaban and rivaroxaban. A recent assessment of 96 patients at the Mayo Clinic showed that two-thirds of CLL patients had potentially significant drug interaction at the time of commencing ibrutinib, and another 8% an ibrutinib dose-modifying interaction during the course of treatment (Finnes *et al*, 2015).

Drug interactions also include drug-disease interactions, where treatment of one condition may exacerbate another. In geriatric therapeutics, this is called 'therapeutic competition' and the risks and benefits on global health outcomes relevant to the patient are central to deciding whether to treat (Lorgunpai *et al*, 2014). Treatment of AF caused by ibrutinib can also be considered a prescribing cascade, which is the use of drugs to treat the side effects of other drugs and generally causes more harm than good due to cumulative side effects in older adults (Rochon & Gurwitz, 1997). Elderly patients, including patients with CLL, are commonly at risk of polypharmacy with a high prevalence of multimorbidity, and ongoing vigilance needs to be maintained in these patients to ensure that overall risk does not outweigh benefit (Hilmer *et al*, 2012; Scott *et al*, 2015).

Atrial fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia. It results in a fast and irregular heart rhythm and occurs in 1–2% of the general population. The risk increases with age with an incidence of <0.5% at age 40–50 years rising to 5–15% at age 80 years. Adults over 40 years have a 25% lifetime risk of developing AF. The causes are either cardiovascular (hypertension, heart failure, ischaemic heart disease and rheumatic valvular disease) or non-cardiovascular (such as sepsis and obstructive sleep apnoea) (Lip *et al*, 2016). AF is thought to require a 'trigger' for initiation in a cardiac 'vulnerable substrate' to maintain the arrhythmia (Lip *et al*, 2016). AF may be paroxysmal (self terminates <7 days), persistent (>7 days), long-standing persistent (>1 year) or permanent, and it typically becomes more persistent and resistant to rhythm control over time. Management may focus on rhythm control if AF is paroxysmal, but particularly on rate control for symptomatic tachycardia. The management of AF and its complications has been the subject of numerous large-scale clinical trials and extensive guidelines for management and is well beyond the scope of an editorial (Camm *et al*, 2010; January *et al*, 2014) (Lip *et al*, 2016) (Kirchhof *et al*, 2016).

Complications of AF

Atrial fibrillation is associated with a significant increase in morbidity and mortality, impaired quality of life, and more frequent admission to hospital. There is a five-fold increase in stroke, a threefold increase in heart failure, and a twofold increase in mortality. The stroke risk is increased whether the AF is persistent or intermittent.

Current cardiology guidelines do not recommend antiplatelet drugs for stroke prevention in AF (Camm *et al*, 2012). Given this, and the known anti-platelet effect of ibrutinib, there is probably no role for adding aspirin or clopidogrel to ibrutinib-treated CLL patients. The CHA_2DS_2-VASc [Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled) – Vascular disease, Age 65–74 years, and Sex category (female)] score can be used to identify the small number of truly 'low risk' community AF patients (*c.* 5%) who do not require anticoagulation; typically young patients, with lone AF and no risk factors (Camm *et al*, 2012). The vast majority of CLL patients with AF on ibrutinib will probably have a CHA_2DS_2-VASc score of at least 1 and therefore warrant

anticoagulation. European Society of Cardiology (ESC) guidelines (Camm *et al*, 2012) recommend anticoagulation with well-controlled warfarin or a non-vitamin-K oral anticoagulant (NOAC) for CHA_2DS_2-VASc score of 1 or more, irrespective of gender. As the median age of CLL exceeds 70 years, as will that of most patients with CLL with AF on ibrutinib, then the CHA_2DS_2-VASc score is likely to be less discriminating as an evaluation tool for most CLL patients.

The combination of ibrutinib and warfarin anticoagulants have been avoided to date due to bleeding risk concerns. The use of warfarin or vitamin K antagonists is a relative or absolute contraindication for ibrutinib use in clinical trials and early access settings. In the setting of AF however, the ongoing stroke risk justifies a reassessment of this position. The large AF trials [particularly RELY (Connolly *et al*, 2009) and ARISTOTLE (Granger *et al*, 2011)] showed that reduced doses of the direct thrombin inhibitor, dabigatran (110 mg bd), or the factor Xa inhibitor, apixaban (2.5 mg bd), respectively, offered similar protection against stroke to warfarin, but with lower bleeding rates than warfarin or full-dose NOAC (Ruff *et al*, 2014). However, it was recently shown that the safety advantage of apixaban over warfarin in the ARISTOTLE trial was significantly attenuated in participants with polypharmacy, which is likely to be highly prevalent in those treated for CLL and AF (Jaspers Focks *et al*, 2016). The addition of low-dose aspirin (100 mg) to NOACs was also permitted in these trials, with only a small increase in bleeding. If the antiplatelet effect of ibrutinib is similar to that of aspirin, these trial data suggest that combining ibrutinib with reduced dose NOAC may be a therapeutic strategy for CLL patients with concomitant AF. These combinations will need to be evaluated prospectively for safety in cohorts of CLL patients. From a clinical pharmacology perspective, in CLL patients with multiple interacting drugs that change over time, it could be argued that close monitoring and dose adjustment of warfarin within a tightly controlled window (e.g. International Normalized Ratio 2.0–2.5) might be preferred over NOACs. However, NOAC reversal agents are becoming available to mitigate some bleeding risk concerns (Pollack *et al*, 2015; Siegal *et al*, 2015). In the present setting in mid-2016, idarucizumab is already widely approved and available, providing immediate reversal of dabigatran. There are detailed, current guidelines for NOAC management (Heidbuchel *et al*, 2016), and with increasing use and data in the community AF population that unmonitored NOAC therapy appears comparable or safer than monitored warfarin (Nishtala *et al*, 2016). All these factors suggest that NOACs may be the longer term preferred option, provided safety could be confirmed in the ibrutinib treated patient.

Consequences of AF on ibrutinib

In this issue of the *British Journal of Haematology,* groups from MD Anderson, Houston, France and Australia have reported the clinical features and consequences of AF in 56 patients on ibrutinib in a retrospective study, the largest series reported to date (Thompson *et al*, 2016). All patients began on ibrutinib 420 mg/day, most were males (reflective in part of CLL patients who require therapy) and they had a median age of 70 years. The cumulative incidence of AF was 8.7% estimated from a subset of patients. Half of the patients developed AF quite early by 3.8 months, and 75% by 1 year. All were in sinus rhythm prior to ibrutinib, but 27% had a prior history of AF. Pre-existing risk factors of hypertension (64%), impaired left ventricular function (28%) and valvular dysfunction (25%) were common. Most AF was paroxysmal (64%), while 30% were continuous despite treatment. Although 35/56 reverted to sinus rhythm, 10 had recurrence. AF complications occurred in 4 patients; 3 developed cardiac failure (1 fatal) and 1 ischaemic stroke, the latter with 'silent' AF and not on thromboembolism (TE) prophylaxis. When TE prophylaxis was used, just under half were anti-coagulated with either warfarin ($n = 7$) or a NOAC ($n = 15$), while 22 received aspirin-based therapy, and 27% received no stroke prophylaxis. Of concern was the rate of grade 3/4 bleeding events, at 14%, significantly higher that previously reported. None of the 15 who bled appeared to have been anti-coagulated with a NOAC.

The authors highlight well the complex and interconnected management dilemma of CLL disease control, AF rate and rhythm control, AF complications of cardiac failure and thromboembolic risk, the need for thromboembolic and stroke prophylaxis in the setting of ibrutinib-induced platelet dysfunction, heightened bleeding risk, and an aging patient population, with many issues further complicated by multiple potential drug interactions. Perhaps not surprisingly, there was little uniformity of approach despite all patients being treated in academic medical centres.

It is important to emphasize that these patients were being treated with ibrutinib for their progressive CLL and 22 of them ultimately had their ibrutinib therapy stopped due to AF. Twice as many of the patients who stopped treatment had disease progression compared to continued treatment at either full or reduced ibrutinib dose.

Future directions

At present, clinicians should follow the current guidelines in the Prescriber Information for ibrutinib (https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf 05/2016), and the guidelines for the management of AF (Camm *et al*, 2010; January *et al*, 2014), and expert cardiology advice in their local institutions and clinical settings.

All patients for whom ibrutinib is planned should have a 12-lead electrocardiogram (ECG) prior to commencement of therapy. They should have clinical assessment of heart rate and rhythm at each follow-up, and consideration given to possible follow-up ECGs at perhaps 3, 6, 12 and 24 months following commencement to exclude the development of AF

while on therapy, particularly for those with 'silent' AF, for whom the stroke and thromboembolic risk is just as real as those that are symptomatic. There should be particular focus on patients aged 75 years and older who are more at risk of AF both in the general community and, it would appear from the available data, the group of patients on ibrutinib most at risk of developing AF.

Hypertension is a factor for consideration as it is both increased in incidence on ibrutinib (*c.* 2–3% annually) and also a risk factor for AF. Blood pressure should be monitored and optimised for patients on ibrutinib. Electrolytes and thyroid function studies should be checked and optimised pre-treatment as other potential contributing factors to AF risk.

Currently, the Prescriber Information for ibrutinib recommends dose reduction for adverse reactions of grade 3 or higher. However, in some reports, patients were able to maintain their dose of ibrutinib (Farooqui *et al*, 2015), while in others, a significant number of patients had either dose reduction or cessation of their ibrutinib, potentially adversely effecting their CLL-related disease outcomes (Jain *et al*, 2015); both of these were seen in the present study (Thompson *et al*, 2016). It would be useful to know if the occurrence of AF is ibrutinib dose-dependent or an idiosyncratic response.

In any event, it is important to capture all instances of AF, whether symptomatic or asymptomatic, as all are associated with thromboembolic risk. The current recommendations are based on AF symptom severity and type of therapy using clinical trial Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. It is imperative to record and report all AF grades whether grade 1/2 ('mild') or 3/4 ('severe') in future trials and reports. The data from the current study (Thompson *et al*, 2016) and the Bethesda group (Farooqui *et al*, 2015), suggest that dose reduction may not be necessary, at least once AF rate control is achieved, which would, in turn, enable patients to achieve the benefits of continued ibrutinib for their neoplastic disease control.

Consideration of baseline non-invasive assessment of left ventricular function and screen for underlying ischaemic heart disease may be appropriate for some patients prior to commencing treatment with either a stress echocardiogram or sestamibi perfusion scan. This would be principally relevant in patients for whom there have been suspicious symptoms. If left ventricular dysfunction or significant ischaemia is identified, then appropriate, optimal medical management of these conditions should be implemented prior to starting ibrutinib or as soon as practical. Whether these patients might benefit from prophylactic treatment with beta-blocker is one of many questions that need to be addressed. In an ideal world, a randomised controlled trial to assess whether this strategy is effective in decreasing the incidence of AF would be useful.

In the study reported by Thompson *et al* (2016), AF was persistent in over 60% of patients despite anti-arrhythmic drugs and cardio-version and one could argue that if patient's symptoms can be controlled medically with a simple strategy of rate control, such as with simple beta blockers and/or calcium channel blockers (with consideration of ibrutinib dose reduction if CYP3A4 inhibitors are used as described in the product information), then that may be safer than exposing them to the added risks of pro-arrhythmia and other non-cardiac toxicities of anti-arrhythmic drugs, such as flecainide, amiodarone and sotalol.

We endorse the authors' call for long-term follow-up of patients who commence on ibrutinib and develop AF so that systematic assessment and development of guidelines in this setting can be formulated. With up to 40% of patients discontinuing ibrutinib because of AF, and the intimately related issues of rate control, anticoagulant stroke prophylaxis and bleeding risk complicated by multiple drug interactions, there is a clear and pressing need to improve management of these patients and close cooperation between haematologists, cardiologists and clinical pharmacologists will be vital.

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