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LETTER TO THE EDITOR

WILEY

# Dabigatran in ibrutinib-treated patients with atrial fibrillation and lymphoproliferative diseases: Experience of 4 cases

The B cell receptor inhibitors, ie, ibrutinib and idelalisib, are significantly changing the treatment landscape of B cell lymproliferative diseases, able to induce long-lasting remission and associated with lower rates of infections and secondary cancers as compared with chemoimmunotherapy.[1,2] Particularly, ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase, is approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenstrom macroglobulinemia (WM).[3] However, ibrutinib carries a higher risk of both clinically significant bleedings via platelet inhibition[4] and atrial fibrillation (AF)[5] compared to standard chemotherapy. Atrial fibrillation in patients taking ibrutinib poses a unique challenge as the cumulative bleeding risk from the ibrutinib-related antiplatelet effects added to the anticoagulation can be dangerously high, as confirmed by clinical trials which found unacceptable bleeding rates when ibrutinib was used in combination with vitamin K antagonists.[4] Direct oral anticoagulants (DOACs) have been shown to cause fewer bleeding events than warfarin in multiple phase III trials, and are likely a safer class of anticoagulant to combine with ibrutinib.[3,4] However, current data regarding the combination of DOACs and ibrutinib is insufficient to draw strong conclusions and the management of AF in patients treated with ibrutinib is still controversial.[6]

We herein report the cases relating to 4 patients: 2 patients with CLL who developed ibrutinib-induced AF; 1 case of MCL and 1 of WM both presenting permanent AF who required treatment with ibrutinib. All 4 patients were effectively and safely managed with dabigatran.

Two heavily treated CLL patients, #1 and #2, harboring unfavorable prognostic markers (Table 1) developed persistent AF after 10 and 4 months of ibrutinib treatment, respectively. Both subjects had $CHA_2DS_2$-VASc and HAS BLED scores of 4 and 3, respectively, and a mild renal impairment; #1 also had a moderate thrombocytopenia ($58 \times 10^9$/L), and #2 suffers of arterial hypertension. Since ibrutinib primarily undergoes CYP3A4-mediated metabolism, and CYP3A4 inhibitors will increase ibrutinib exposure,[7,8] we opted for dabigatran, a DOAC without CYP3A4-mediated metabolism and with the possibility to be monitored by our laboratory. At AF onset, ibrutinib was transiently interrupted, antiarrhythmic drugs provided (#1 digoxin and #2 bisoprolol), and dabigatran was initiated at the lowest dosage (110 mg twice [BID]). Two weeks after its suspension, ibrutinib was reinitiated at the previous dosage with the recommendation to take it 4 to 6 hours after dabigatran. Dabigatran concentration (trough and peak levels) was monitored after other 2 and 4 weeks. Patient #1 showed high serum dabigatran levels (peak 332 μg/L [normal values (n.v.) 117-275 μg/L]—trough 160 μg/L [n.v. 61-143 μg/L]). After 4 weeks of combined treatment, she experienced grade 2 conjunctival hemorrhage which required the immediate suspension of dabigatran for 1 month. We decided to reinitiate dabigatran at a personalized reduced dosage (110 mg BID alternated with 110 mg once [QD]), and after an additional month, dabigatran levels were back within the normal range (peak 279 μg/L—trough 137 μg/L) (Table 1). Patient #2 showed dabigatran concentrations within the normal ranges in the 2 controls and developed self-remitting grade 1 petechiae after 3 months of concomitant therapy (Table 1).

Patient #3 had been affected by MCL from 2012 and received 6 cycles of R-BAC with complete response but relapsed after 5 years upon which ibrutinib was initiated at 560 mg/day. Her medical history revealed arterial hypertension, chronic thyroiditis, and ulcerative colitis. She was already on warfarin for chronic AF, and we decided to replace it with dabigatran 110 mg BID. During the follow-up, dabigatran levels always remain within the normal ranges (Table 1).

Patient #4 was an elderly woman who had previously received 4 lines of treatment for WM with $MYD88^{L265P}$ mutation. In July 2017, she initiated ibrutinib 420 mg/day for disease progression. Her medical history revealed hypertension, moderate renal impairment, and chronic AF for which she was currently taking warfarin which was replaced with dabigatran 110 mg BID. After 2 weeks, we observed a marked increase of dabigatran serum concentrations which later dropped to normal ranges after dose reduction (110 mg BID alternated with 110 mg QD) (Table 1).

After a median period of concomitant ibrutinib and dabigatran treatment of 10 months (range 5-15 months), no patient developed arterial ischemic events or major bleedings, though some minor bleedings episode occurred. Three out of 4 patients achieved partial remission, whereas ibrutinib was stopped after 5 months for patient #3 due to disease progression.

Most patients with B cell lymproliferative diseases who are eligible to ibrutinib are, as in our patients, elderly and likely to require anticoagulant or antiplatelet therapy due to age-related comorbidities such as AF or ischemic diseases. Phase 3 clinical trials clearly demonstrated that ibrutinib is an active and well-tolerated drug with an acceptable toxicity profile, albeit a higher risk of AF and bleedings.[3]

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**TABLE 1** Clinical and biological features of the 4 patients

| Variables | #1 | #2 | #3 | #4 |
|---|---|---|---|---|
| **Age (years)** | 68 | 74 | 81 | 74 |
| **Gender** | F | F | F | F |
| **Diagnosis** | CLL | CLL | MCL | WM |
| **Stage** | 4[b] | 2[b] | 4 | 4 |
| **Therapies before ibrutinib** | 3 | 2 | 1 | 4 |
| **$CHA_2DS_2$-VASc** | 4[a] | 4[a] | 5 | 5 |
| **HAS BLED** | 3[a] | 3[a] | 2 | 4 |
| **Ibrutinib[a] (mg)** | 420 | 420 | 560 | 420 mg |
| **Dabigatran (mg)** | 110 BID/110 QD | 110 BID | 110 BID | 110 BID/QD |
| **Months of ibrutinib and dabigatran** | 12 | 15 | 5 | 10 |
| **IGHV status** | Unmutated | Unmutated | Na | Na |
| **FISH** | Normal | del11q | t(11;14) | Na |
| **TP53 mutation** | Mutated | Unmutated | Unmutated | Unmutated |
| **Platelets (μL)** | 58 000[a] | 117 000[a] | 192 000 | 176 000 |
| **Cl. creatinine[a] (mL/min)** | 67[a] | 64[a] | 33 | 36 |
| **Dabigatran concentration (μg/L)[c]** | | | | |
| 2 weeks after ibrutinib start | Peak 332<br>Trough 160 | 118<br>86 | 126<br>- | 644<br>353 |
| 1 month after ibrutinib start | Peak 326<br>Trough 145 | 113<br>249 | 132<br>- | 524<br>- |
| 2 weeks after posology reduction | Peak 279<br>Trough 137 | - | - | 308<br>74 |

Abbreviations: F, female; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; WM, Waldenstrom macroglobulinemia; BID, *bis in die*; QD, once a day; na, not available.

[a]Variables at development of atrial fibrillation.

[b]Rai staging system.

[c]Normal values: peak 117 to 275 μg/L; trough 61 to 143 μg/L.

In a pooled analysis of 4 trials, the incidence of AF was 6.5% after a median follow-up of 16.6 months,[9] being highest in the first 6 months. Overall, 39% of these subjects had a bleeding event irrespectively to AF. Among the 49 patients with AF, 25 (51%) experienced bleeding complications: 9 of whom taking a single antithrombotic drug (1 aspirin, 5 DOACs, 3 heparin), 6 taking 2 antithrombotic medications, and 10 were not taking any antithrombotic medications.[9] As already mentioned, current data regarding the combination of DOACs and ibrutinib are insufficient to draw strong recommendations. Given the high rate of AF in patients requiring ibrutinib, we decide to perform an internal protocol in order to avoid as much as possible the risk of major bleeding complications. Among DOACs, dabigatran appears to be the most suitable at the moment, considering that its metabolism is not CYP3A4-mediated, the availability of a reversal agent (ie, idaracizumab), and the possibility to monitor its concentration (by dilute thrombin time or *ecarin* clotting time[10]). Although not recommended, monitoring plasma drug concentrations allowed us to reduce the posology in 2 out of our 4 patients, 2 of whom experienced minor bleedings (conjunctival hemorrhage and petechiae).

Based on this experience, dabigatran seems to be safe in ibrutinib-treated patients, and we would advise to monitor dabigatran levels at least twice in patients with a higher hemorrhagic profile (ie, impaired renal function, mild to moderate thrombocytopenia, and previous bleedings). The slight reduction of dabigatran dosage, tailored upon plasma levels, may be a solution for such fragile patients. Our experience supports the use of DOAC, in particular dabigatran, in patients with lymphoproliferative disease who require ibrutinib.

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## CONFLICT OF INTEREST

LT received research founding by Janssen and Gilead.

## AUTHORSHIP CONTRIBUTIONS

AV and EC designed the study, evaluated patients, and wrote the article; SI, ES, LS, and SP provided intellectual inputs and evaluated the patients during the follow-up; FP, PS, GS, and LT evaluated the

patients, provided intellectual inputs, and reviewed the article. All the authors have nothing to disclose.

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