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## Original Article

# Ibrutinib pharmacokinetics in B-lymphoproliferative disorders discloses exposure-related incidence of hypertension

Loïc Ysebaert<sup>a,b</sup>, Caroline Protin<sup>a</sup>, Lucie Obéric<sup>a</sup>, Guillaume Beziat, Sandra De Barros<sup>c</sup>, Baptiste Bonneau<sup>c</sup>, Ben Allal<sup>d</sup>, Malika Yakoubi<sup>d</sup>, Anne Quillet-Mary<sup>b</sup>, and Fabien Despas<sup>c,e</sup>

**Objective:** Ibrutinib has been the first Bruton tyrosine kinase inhibitor (BTKi) authorized for the treatment of B-cell lymphoproliferative disorders (B-LPDs). Numerous publications have confirmed the efficacy of this orally administrated drug in chemo-free regimens for B-LPDs. They also reported several adverse events (AE) associated with ibrutinib treatment. Whether these AEs depended on ibrutinib exposure has however been seldom explored.

**Methods:** In the study reported here, the incidence of AE was recorded in 92 patients with B-LPD (mostly chronic lymphocytic leukemia  $n = 79$ ) for whom ibrutinib alone was proposed as first line therapy. Moreover, a pharmacokinetics (PK) exploration was planned over one day after 1 month treatment. PK assays included drug and metabolite (DHD-ibrutinib) mean/median and maximal plasmatic concentrations as well as areas under the curve (AUE) data.

**Results:** This PK evaluation was analyzed regarding AEs recorded over the first year of therapy, which were similar as in published reports. PK data disclosed a significant impact of ibrutinib exposure on infections but mostly on the occurrence of hypertension. The latter was mostly related to dihydrodiol-ibrutinib (DHD-ibrutinib) exposure.

**Conclusions:** These data suggest that a DHD-ibrutinib assay after one month of treatment could be interesting to consider a lower dosage for patients above maximal concentration thresholds for the drug, its metabolite or the sum of both. Whether this can be applied to newer BTKi remains to be explored but it could be important for patients to whom ibrutinib is proposed.

**Keywords:** chronic lymphocytic leukemia, hypertension, ibrutinib, Lymphoproliferative disorders, pharmacokinetics

**Abbreviations:** AE, adverse event; AUC, area under the curve; B-LPDs, B-cell lymphoproliferative disorders; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; DHD-ibrutinib, dihydrodiol-ibrutinib; EMA, European Medicine Agency; FCR, fludarabine, cyclophosphamide and rituximab; FDA, Food and Drug Administration; MCL, mantle cell lymphoma; MTD, maximal tolerated dose; PK, pharmacokinetic; TEAE, treatment-emergent adverse event; TEC, tyrosine kinase expressed in hepatocellular carcinoma; WM, Waldenström macroglobulinemia

## INTRODUCTION

Since initial clinical trials, in 2009, the first Bruton tyrosine kinase (BTK) inhibitor (BTKi), ibrutinib, has raised increasing interest in treatment regimens for B-lymphoproliferative disorders (LPD) [1–3] because of the crucial role of BTK in B-cell physiology and in the development of LPDs [4]. This orally administered small molecule came as a promising alternative to the classical immunochemotherapy schedule associating fludarabine, cyclophosphamide and rituximab (FCR) in chronic lymphocytic leukemia (CLL) [5]. Authorization from the Food and Drug Administration (FDA) [6] and European Medicine Agency (EMA) [7] as well as country-specific authorities [8] was rapidly granted as early as in 2013 for patients with refractory/relapsed (R/R) CLL as well as in first line for CLL patients with *TP53* mutation/del(17p) [6–8]. It was also authorized for patients with mantle cell lymphoma (MCL) or Waldenström macroglobulinemia (WM) [6–8]. This paved the way for newer chemo-free oral treatment approaches that soon blossomed and are now considered standard of care [9]. Several studies have shown that, although safety was acceptable, it was however important to monitor adverse events (AEs). Indeed, BTK, besides B-cells, is expressed in many cell-types together with other members of the Tec family (named for the tyrosine kinase

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expressed in hepatocellular carcinoma: TEC) [4]. Tec kinases can thus be impacted by ibrutinib, leading to off-target AEs.

Musculoskeletal AE, reported by the patients as sustained pain, can be a cause of treatment interruption but the underlying mechanisms remain unknown [10]. Bleeding AE have been demonstrated to be caused by the impairment of platelet binding to collagen in clot formation, since platelets express both BTK and TEC [11–13]. Because blockade of these tyrosine kinases interferes with proper functioning of Fc $\gamma$ RII on platelets but also on neutrophils [14], this is a plausible reason for the infectious AEs following ibrutinib therapy [15]. Macrophage-dependent phagocytosis has also been reported to be altered and thus is similarly likely to contribute to infections [16]. Neutropenia could be related to the impact of BTKi on myeloid differentiation [4]. Gastro-intestinal AEs, mostly benign and manageable, but also more worrisome cardiac AEs are likely related to interference with the endothelial growth factor receptor (EGFR) [17]. Cardiovascular toxicity, with hypertension (HTN) and a risk for atrial fibrillation, led to recommendations in patient management after ibrutinib initiation [18,19].

Through its rapid absorption, ibrutinib reaches a maximal plasmatic concentration peak 1 to 2 h after administration and is rapidly undetectable (half-life of 4–6 h) [20,21]. It must be noted, however, that these plasmatic halftimes do not consider the strong irreversible binding of ibrutinib to its target cysteine on the BTK molecule, which leaves a large part of the drug within cells [21].

Nonetheless, following pharmacokinetic (PK) studies in a phase I trial with dose escalation [20] that did not reach the maximal tolerated dose (MTD), a standard dosage was recommended, at 420 mg/day (d) for CLL and WM patients and 560 mg/d in case of MCL. Of note, ibrutinib is metabolized in dihydrodiol-ibrutinib (DHD-ibrutinib), which is supposed to be 15 times less active than the whole molecule [21,22], despite having but has an extended half-time of 6–11 h. Furthermore, our group has published a PK-POP model of activity of ibrutinib and its metabolite, suggesting that DHD-ibrutinib accounts for 50% of the global antikinase effect of the drug [23]. Again, this should be considered in the light of drug-target binding, and important PK interpatient variability.

As reported by our group [23], however, there are important inter-individual PK variations in patients receiving ibrutinib. This could impact both the response to treatment (too low exposure) and the incidence of AEs (overexposure) but has seldom been documented. Here, PK analyses were planned in an open, nonrandomized trial with ibrutinib as a single drug for patients with B-LPD. One-day kinetics of ibrutinib and its metabolite was assessed after 1 month therapy. These results were correlated both with response to therapy and AEs at 1 year.

## PATIENTS AND METHODS

A single-drug treatment with ibrutinib was proposed for a duration of 2 years to patients (all Caucasians) with B-LPDs (CLL, MCL or WM), with a PK follow-up (clinicaltrials.gov NCT02824159) in Toulouse (France) University Hospital.

The trial had also been approved and was supported by the French National Agency for the Safety of Medicines and Health Products (ANSM: AAP-2015-073).

The protocol planned clinical and-biological assessments at inclusion, then at months 1, 2, 3, 6, 12, 18 and 24. Additionally, as per current procedure in the investigating center, a nurse specialized in ambulatory therapy and telemedicine remained in close contact with all patients by telephone. Follow-up was carried on for the planned 2 years or until treatment cessation.

PK was scheduled to be performed over 1 day after one month of treatment, upon stabilization of drug levels. During that day, blood was collected on ethylenediaminetetraacetic acid (EDTA) just before the daily drug intake then after 30 min and 1, 2, 4 and 6 h. Plasmas were forwarded for drug and DHD-ibrutinib analysis by ultra-performance liquid chromatography followed by mass spectrometry (UPLC-MS-MS). Four criteria were retained to assess exposure, both for the drug and for DHD-ibrutinib (metabolite), respectively mean concentration, maximal concentration residual drug concentration and area under the curve (AUC). Combined drug and metabolite AUC was added as a ninth parameter.

Ibrutinib is essentially metabolized by cytochrome P450 (CYP3A). In order to investigate the possible role of CYP3A polymorphism in PK variations, saliva was collected at inclusion to analyze germinal DNA. Single nucleotide polymorphisms of CYP3A4 and CYP3A5 were evaluated as described elsewhere [24]. Real time polymerase chain reactions were performed on a Fluidigm-BioMark (Fluidigm, Salk Institute, La Jolla, CA) chip and Fluidigm SNP Genotyping Analysis was used for data interpretation.

All AEs were collected over the first year of the study and graded according to common terminology criteria for adverse events V4.0 (CTCAE) [25]. Correlations between AEs, treatment duration and level of drug exposure (as measured by PK assays) were investigated. Treatment-emergent (TEAE) were also singled out.

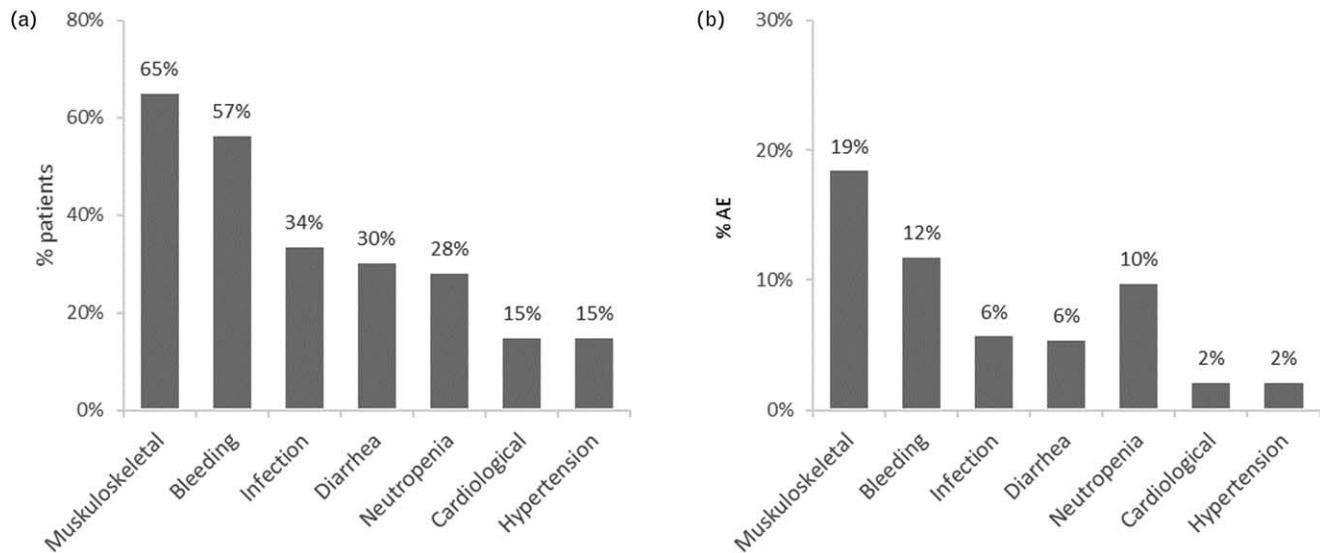
Blood pressure was measured, and HTN diagnosed and classified by CTCAE criteria [25]. These measurements were performed by each patient hematologist or general practitioner. Mean arterial pressure assessments were performed to confirm HTN by self-measurement at home. Most patients (10/14, 71.4%) benefited from a monitoring with nephrology/cardiology specialists after the diagnosis of HTN.

Data are expressed as percentages, means or medians. For univariate analyses, values were considered using base 1 or base 10 (variation of 1 or 10 units), and base 100 for AUC. Statistics were performed with R software for univariate and multivariate analyses. Results are presented as odd ratios (OR) with 25–75% interquartile range (IQR). *P* values  $\leq 0.05$  were considered statistically significant. SAS and Medcalc (Ostend, Belgium) were used for ROC curves, Forest plots and comparison graphs.

## RESULTS

Between April 2016 and April 2019, 92 patients were enrolled. All of them had provided informed consent.

## Hypertension and ibrutinib exposure



**FIGURE 1** Partition of adverse events in the first year of treatment with ibrutinib. (a) Proportion of patients with at least one treatment-emergent adverse event. (b) Proportions of treatment-emergent adverse events.

Patient characteristics are given in Table S1, Supplemental Digital Content, <http://links.lww.com/HJH/C610>. Briefly, these subjects had a mean age of  $68.3 \pm 9.4$  years, 71% were males and 64% were in relapse. Most of them ( $n = 79$ , 86%) had been diagnosed with CLL among whom 20 were eligible for first line treatment because of mutated *TP53*. The other patients were 2 WM and 11 MCL. The latter received ibrutinib at a dosage of 560 mg/d while it was 420 mg/d for CLL and WM patients. The effective treatment duration exceeded 1 year for 66 (71.7%) patients and continued after 2 years for 54 (58.7%).

During the first year of treatment, a total of 724 AEs was observed in 97.8% of the patients with a median of 8 per patient. They were Severe AEs in 15.2% of the patients ( $n = 17$  SAEs). Cardiac AEs, mostly atrial fibrillation, were observed in 15.2% of the patients enrolled, but were the first cause of severe AEs (8.7%) and the most frequent cause of treatment cessation (4.3% of the patients) during the first year. AEs resulted in dosage adjustment for 58.7% of the patients and in definitive treatment cessation for 8.7%. Of note, no ibrutinib discontinuation was due to HTN only.

Figure 1 shows the partition of TEAEs. The most frequent of the latter, besides AEs of the hematologic and lymphatic systems (29% AE, not shown), were musculoskeletal (19%).

Correlations between all AEs and treatment were also investigated. The two highest significances, in univariate analysis, were that stopping treatment before 1 year was associated with less musculoskeletal AEs and less bleeding ( $P$  values respectively 0.005 and 0.003). Conversely, more infections occurred in patients with musculoskeletal or bleeding AEs ( $P$  values respectively 0.01 and 0.005). However, in multivariate analysis, only less than one year of treatment remained statistically significant for these two events.

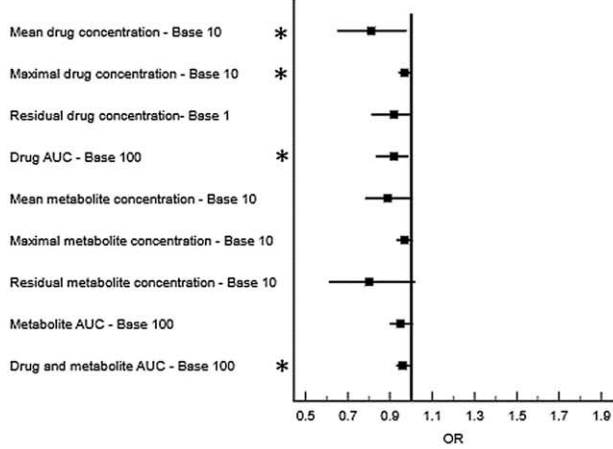
Additionally, because this study included PK assessments, the occurrence of AEs could be analyzed according to levels of treatment exposure at one month. Data reported in Table S1, Supplemental Digital Content, <http://links.lww.com/HJH/C610>

and the Forest plots in Fig. 2 show the associations between PK data and AEs. They indicate that neither drug nor metabolite exposures had any significant incidence on the risk of bleedings, neutropenia nor cardiological AEs (FA/Flutter). Conversely, relationships were found between PK data, musculoskeletal AEs, infections and, most interestingly, HTN. Overall, statistically significant differences were observed for 8/9 tested criteria of exposure to drug and/or metabolite. Drug concentrations significantly impacted the incidence of musculoskeletal AEs (mean and maximal drug concentration,  $P = 0.043$  and  $0.04$ ; drug and drug/metabolite AUC  $P = 0.043$  and  $0.036$ ) and infections (drug  $C_{max}$   $P = 0.027$ ). However, HTN was more significantly impacted by metabolite levels (mean and maximal concentrations and AUC,  $P$  values of 0.01, 0.037 and 0.01 respectively) than by drug exposure (drug  $C_{max}$ ,  $P = 0.046$ ). This translated in a significant impact of the drug and metabolite AUC ( $P = 0.012$ ) on the development of early onset HTN. This notion was retained as significant in multivariate analysis (Table 1,  $P = 0.0012$ ).

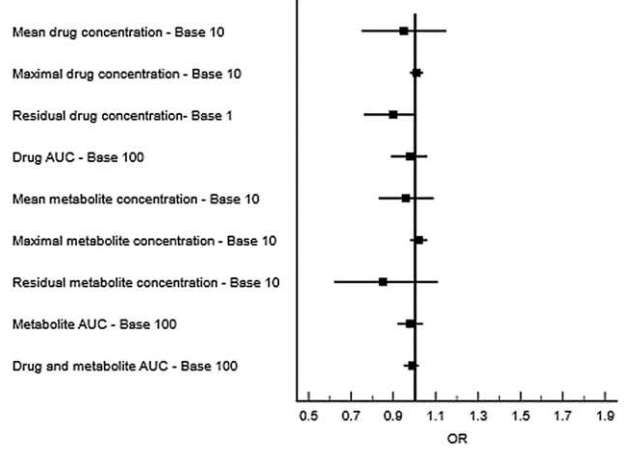
Figure 3 illustrates the significant differences between patients who developed hypertensive AEs or not, highlighting the large dispersion of data. Ibrutinib median  $C_{max}$  was respectively 256 (IQR 167–317) ng/ml in HTN patients vs. 142 (IQR 72–230) ng/ml in patients without HTN ( $P = 0.046$ ). The medians of DHD-ibrutinib mean concentrations were respectively 83 (IQR 73–108) ng/ml and 62 (IQR 41–87) ng/ml ( $P = 0.01$ ) while median  $C_{max}$  of metabolite were 289 (IQR 245–311) ng/ml and 187 (IQR 122–263) ng/ml ( $P = 0.04$ ). The median AUC of combined drug/metabolite were respectively 2807 (IQR 2438–3654) ng/ml·h and 2037 (IQR 1302–2871) ng/ml·h. This was even more significant considering only the subgroup of CLL patients at 2764 (IQR 2402–3322) ng/ml·h and 1936 (IQR 1200–2720) ng/ml·h ( $P = 0.006$ ). Of note, in this subgroup, all PK variables of metabolite and combined drug-metabolite significantly associated with hypertension. Of note, creatinine clearance levels were similar in both groups

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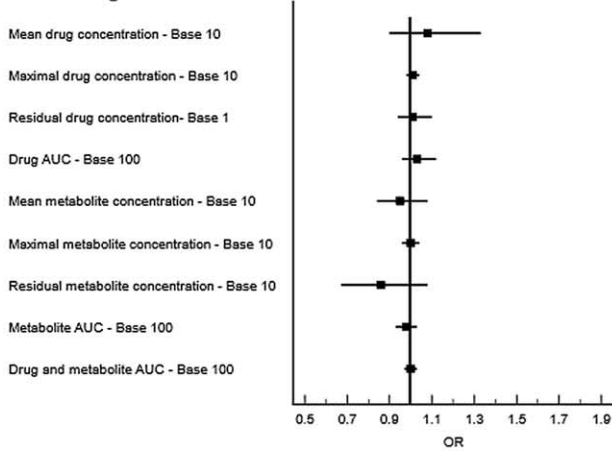
**Musculo skeletal**



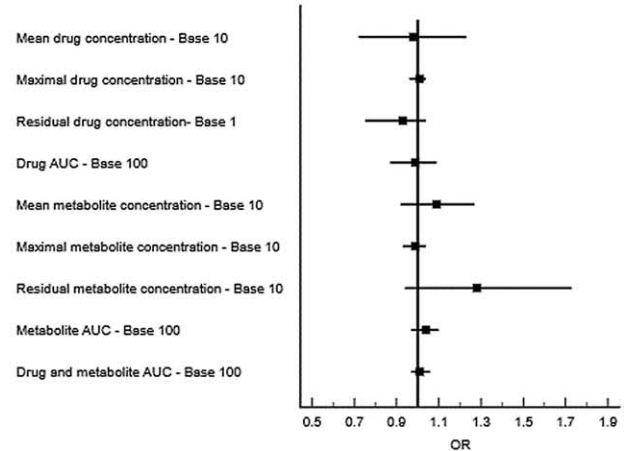
**Neutropenia**



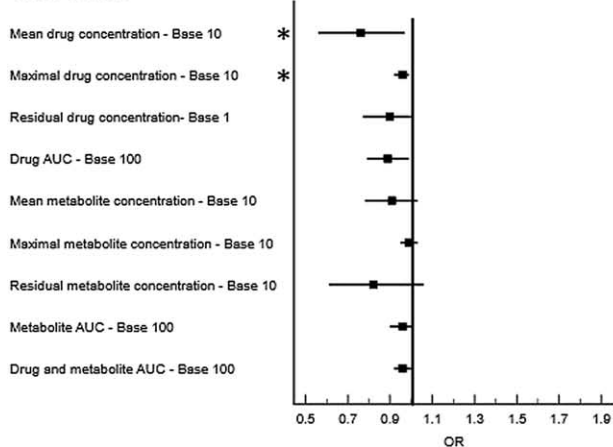
**Bleeding**



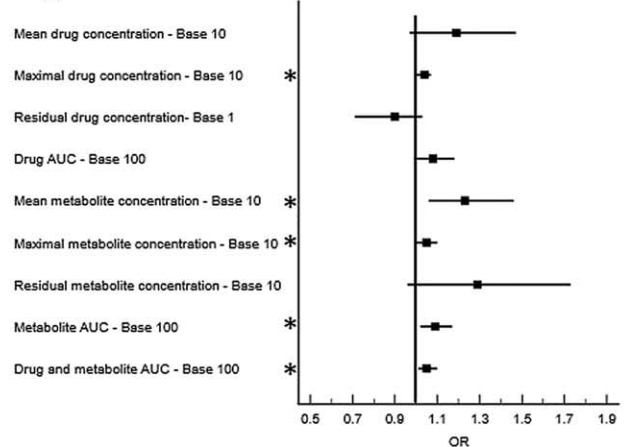
**Cardiological**



**Infection**



**Hypertension**



**FIGURE 2** Pharmacokinetics and adverse events. Forest plots of factors influencing the types of AE collected. Asterisks indicate statistical significance. Full data in Table S1, Supplemental Digital Content, <http://links.lww.com/HJH/C610>. AE, adverse events.

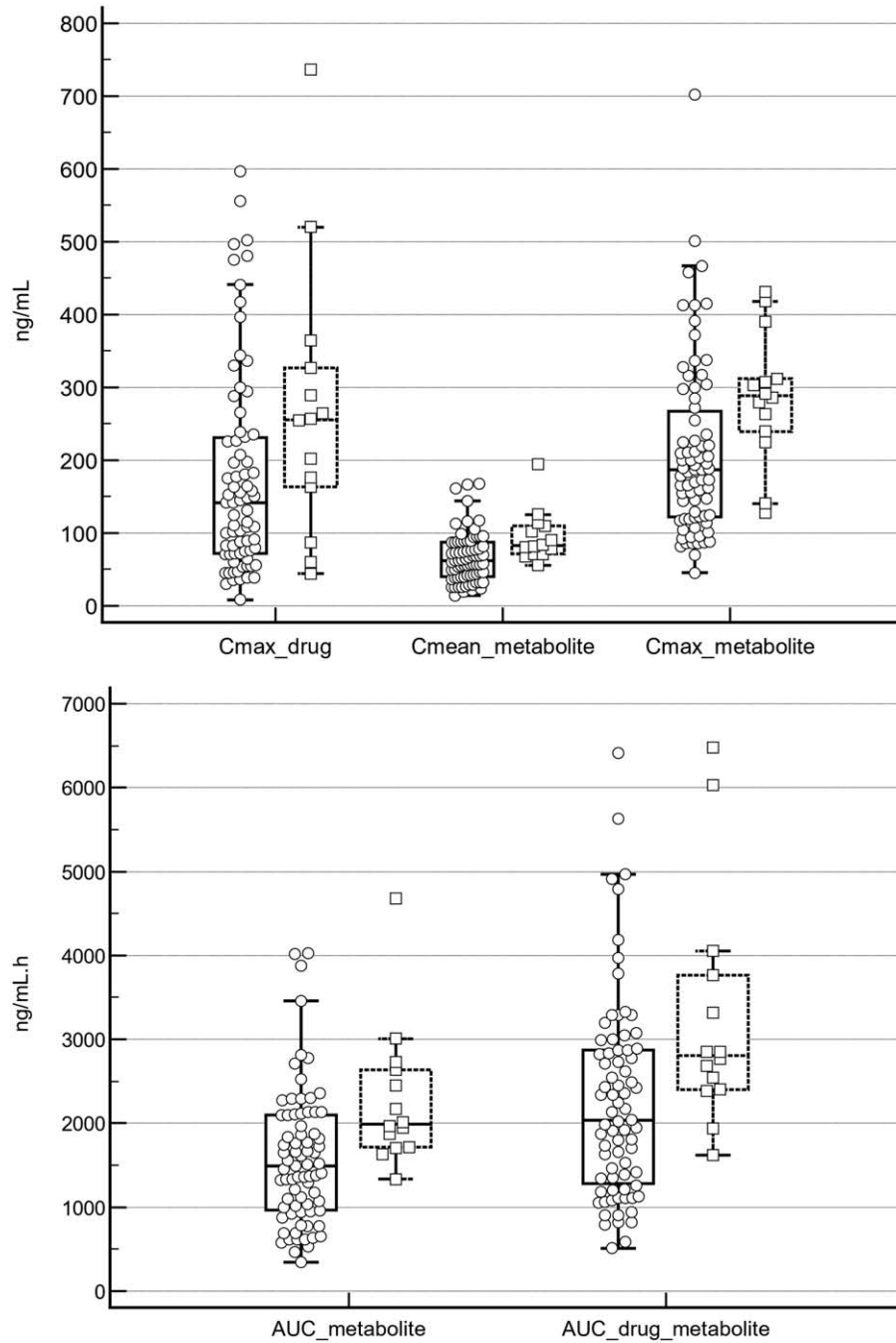
(with or without HTN), from the date of ibrutinib initiation up to 12 months of exposure at 65.5 (27–81) vs. 64.5 (35–81) ml/min, respectively.

From a practical point of view, were these parameters to be applied in current practice, threshold levels should be

established. This was investigated through ROC curves analyses. As shown in Fig. 4, a maximal drug threshold of 163.4 mg/l yields a sensitivity of 78.6% and a specificity of 61.3% ( $P=0.03$ ) for the risk of HTN. These values are respectively 85.7% and 70.7% for a metabolite threshold

**TABLE 1. Multivariate analysis of occurrence of hypertension during 1 year of follow-up**

Variable	Reference	N	Multivariate analysis			
			OR	2.5%	97.5%	P
Clearance (binary)	≥60	89	3,24	0,85	13,60	0,091
Disease state	First line		0,22	0,05	0,96	0,044
AUC drug and metabolite – base 100			1,07	1,02	1,12	0,007



**FIGURE 3** Pharmacokinetics and hypertension. Significant differences between patients without (circles) or with (squares) hypertension AE. Values expressed as ng/ml. AE, adverse events.

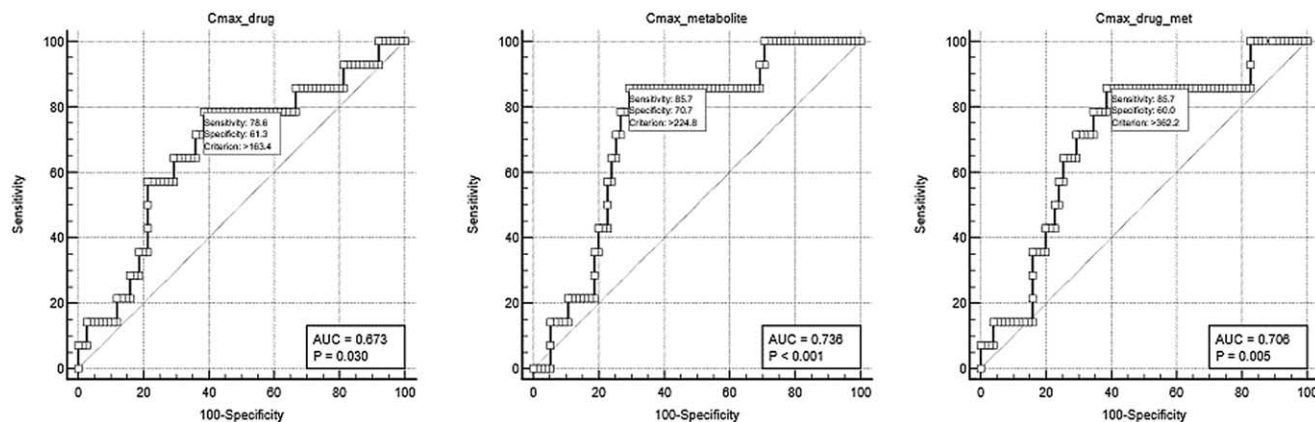
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FIGURE 4 ROC curves. Drug (left) metabolite (middle) and drug + metabolite (right) maximal concentrations.

of 224.8 mg/l ( $P < 0.001$ ). For the sum of drug + metabolite maximal concentration, sensitivity and specificity are 85.7% and 60% respectively for a cumulative threshold of 362.2 mg/l ( $P = 0.005$ ).

Finally, analysis of cytochrome P450 polymorphism disclosed a majority of patients with CYP3A4\*1/\*1 (88.9%) and CYP3A5\*1/\*3 (94.4), the others harboring CYP3A4\*1/\*22 (10.6%) and CYP3A4\*3/\*3 (5.4%). There was no relationship between CYP3A5 and PK data. Conversely, patients with CYP3A4\*1/\*22 had significantly higher drug and metabolite AUC ( $P = 0.031$  and  $P = 0.046$  respectively).

## DISCUSSION

This study, conducted in a cohort of patients with B-LPDs (mostly CLL but also a group with MCL), disclosed, at one year, the occurrence of treatment cessation and AEs with incidences similar to those reported in previous studies [17,26,27]. The originality of this work resides in the PK study performed after one month of treatment. No relationship was disclosed between AE and drug exposure, but several significant associations were observed with less severe AEs. These could be due to off-target binding of ibrutinib or to overexposure in some individuals. In a previous study, our group had already shown different incidences of bleeding between patients treated with the same dosage of ibrutinib [28]. In this more specific work, the large dispersion of data confirms that individual responses are an important factor liable to impact the occurrence of AEs.

Bleeding, which remained the most frequent EA, was not impacted by PK variations, suggesting that the irreversible covalent binding of ibrutinib to BTK and TEC in platelets [11,13], well demonstrated to be the mechanism impairing platelet-collagen interactions, does not depend on the trough of ibrutinib or its metabolite. Consequently, at the dosage used, PK had no incidence on bleeding. The same can be hypothesized for the absence of impact of ibrutinib exposure on neutropenia or cardiovascular events.

Conversely, musculoskeletal AEs and infections were impacted by drug exposure. A recent study by Rhodes *et al.* [10] has suggested, by showing a prevalence of this type of AE in younger and female patients, that ibrutinib

could interfere with auto-immune disorders. This information was not collected here. Yet, since musculoskeletal AEs are less frequent with new generation BTKi [29], which are more BTK-specific, it can be suspected that they are related to off-target ibrutinib binding. Infections, as mentioned previously are likely due to impairment of myeloid cells, potentially also through ibrutinib binding on other tyrosine kinases [14–16].

The most striking relationship was observed between ibrutinib PK and HTN, a type of ibrutinib-related AE well recognized [30,31] but of unknown mechanisms. Although Dickerson *et al.* [30] reported no relationship between ibrutinib dosage and the occurrence or worsening of HTN, the PK analysis performed here brings a new view on the topic. It also sheds light on the interest of the use of other BTKi [32]. Indeed, acalabrutinib and zanubrutinib bind BTK with different affinity and selectivity than ibrutinib, suggesting again that hypertensive AEs could be related to an off-target effect of ibrutinib. One such target could be the C-terminal Src kinase (CSL) [32,33], reported as an important regulator of blood pressure [34]. Other potential targets, RIPK2 and ERBB4 have recently been identified in an *in silico* study [35]. Another important point is that in the present study, although not significantly, drug exposure (not shown) was higher for all PK parameters assessed in patients with hypertensive AEs. This is consistent with the fact that lowering the dosage or temporarily halting ibrutinib therapy is clinically associated with decreased HTN (and less musculoskeletal pain). Because such dose reductions were performed, no patient with HTN had to discontinue ibrutinib in this study (the cessation of ibrutinib before one year of exposure is correlated to adverse OS in both registration trials and real-life studies). This is at variance with the recent report by Samples *et al.* [36] where ibrutinib dose-reduction was performed for 9 patients only while this treatment was discontinued in 44 patients (26 with prior HTN and 18 without HTN), among a cohort of 196 patients treated with BTKi. This adds strength to the main conclusion of our manuscript: since HTN appears to be dose-dependent. Therefore, dose reduction is preferable rather than early discontinuation. No specific anti-HTN medication can however be proposed, due to the small size of the cohort reported.

Finally, it is striking that, at variance with other types of AEs, HTN was mostly related to metabolic parameters. Ibrutinib is metabolized by CYP3A [21]. Polymorphism analysis in this series identified a statistically significantly higher exposure to both ibrutinib and DHD-ibrutinib for individuals with CYP3A4\*1/\*22. This phenotype, present in 5.3% of Caucasians is associated with slower metabolism [37]. Could thus low metabolizers [35,37,38] be the most at risk of developing/increasing hypertension? Would DHD-ibrutinib have an even higher affinity than ibrutinib for other kinases than BTK, for instance EGFR or VEGFR? This remains to be demonstrated.

Taken together, these data suggest that although treatment with ibrutinib, alone or in combination, has become a gold standard in the management of patients with LPDs, caution is recommended in the prevention of AE, and especially hypertension [18,19]. The conclusion that can be drawn would be to monitor concentrations of ibrutinib and DHD-ibrutinib after one month, in order to decrease dosage in patients with high exposure.

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## Conflicts of interest

None of the authors have conflicts of interest to declare related to the design, management nor interpretation of the study.

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