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BRIEF COMMUNICATION

Australian data on the utilisation and duration on treatment of ibrutinib with a proton pump inhibitor in patients with relapsed or refractory chronic lymphocytic leukaemia

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Abstract

In Australia, over half of patients with relapsed/refractory chronic lymphocytic leukaemia treated with ibrutinib use concomitant proton pump inhibitors (PPIs). High gastric pH reduces the bioavailability of some Bruton tyrosine kinase inhibitors. There was no difference in duration on ibrutinib with or without concomitant PPI (unadjusted $P = 0.61$; adjusted hazard ratio: 1.23, 95% confidence interval: 0.75–2.02, $P = 0.411$). PPI use does not affect ibrutinib treatment persistence.

The treatment of chronic lymphocytic leukaemia (CLL) has been transformed with the advent of small-molecule inhibitors, including the Bruton tyrosine kinase (BTK) inhibitors.[1] Three covalent BTK inhibitors are available in Australia: ibrutinib, acalabrutinib and zanubrutinib.[2–4] Ibrutinib was the first BTK inhibitor approved for the treatment of CLL in Australia and has extensive clinical trial[2,5,6] and real-world evidence (RWE)[7] to support its use in patients with relapsed/refractory (R/R) CLL. Zanubrutinib is not currently approved for the treatment of CLL.[4]

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Conflict of interest: R. Salvaris notes honoraria from AstraZeneca, Roche and AbbVie. S. Mulligan notes honoraria/advisory or speaker services from Janssen, AbbVie and AstraZeneca. S. Opat notes consultancy for AbbVie, AstraZeneca, Janssen and Roche, research funding from AbbVie, AstraZeneca, BeiGene, Gilead, Janssen, Pharmacyclics, Roche, Sandoz and Takeda, and honoraria from AbbVie, AstraZeneca, Celgene, CSL Behring, Gilead, Janssen, Merck, Roche and Takeda. A. Puig and M. McGeachie are employees of Janssen-Cilag Pty Ltd Australia.

Clinical trial populations are highly selected and may not reflect those patients seen in the 'real-world' clinical practice, where patients are likely to be older with more comorbidities. Recent RWE from Australia indicates that proton pump inhibitors (PPIs) are commonly prescribed medications, particularly in older patients with CLL.[7–10] However, high gastric pH reduces the bioavailability of some BTK inhibitors, which rely on an acidic environment for absorption.

Ibrutinib, acalabrutinib and zanubrutinib differ in their pharmacokinetic (PK) and pharmacodynamic properties.[2–4] The solubility of ibrutinib is pH-dependent. As such, there is a theoretical risk that co-administration with PPIs may decrease ibrutinib exposure.[2] However, a PK study showed that while concomitant administration of omeprazole decreased the maximum concentration (C_{max}) of ibrutinib, it only marginally affected the area under the plasma drug concentration-time curve (AUC). As AUC is deemed a more relevant measure of ibrutinib activity, co-administration with a PPI is unlikely to have a clinically relevant effect.[11] Administration of acalabrutinib with a PPI may decrease its plasma concentrations and therefore should be avoided, as detailed in the prescribing information.[3] Moreover, because of the long-lasting effects of PPIs, separation of acalabrutinib and PPI dose administration may not eliminate the

interaction.[3,12] A population PK analysis of zanubrutinib in healthy volunteers and patients with B-cell malignancies showed no statistically significant difference in the PKs of zanubrutinib when co-administered with PPIs.[4,13] However, the impact of co-administration of acalabrutinib or zanubrutinib with a PPI on treatment persistence in a real-world setting has not been adequately studied given these BTK inhibitors have not been in clinical practice for an extensive period of time. In contrast, ibrutinib has been approved, reimbursed and available to patients with R/R CLL through the Australian government-subsidised Pharmaceutical Benefits Scheme (PBS) since December 2017.

Therefore, the aim of this study was to compare real-world outcomes of patients with R/R CLL treated with ibrutinib with or without a PPI in Australia. Ibrutinib is a treat-to-progression drug[2]; duration of therapy may be indicative of ibrutinib's effectiveness and tolerability in a real-world setting.

A retrospective cohort analysis of patients with CLL was undertaken using the PBS 10% sample, a nationally representative, standardised, longitudinal extract containing PBS dispensing data for a random 10% sample of Australians from December 2017 to December 2021.[14,15] Information was accessed through the data custodian, Services Australia, and Prospection Pty Ltd performed the analysis under a licence agreement (EREC RMS2321).

Patients receiving ibrutinib for CLL were identified using PBS item code 11213E. Exclusion criteria were: less than 18 years of age at index date (date of the first ibrutinib prescription) or used ibrutinib as first-line treatment (ibrutinib is not PBS listed for first-line use). Duration on ibrutinib was defined as the time, in consecutive days, from the date of first prescription of ibrutinib until the last date that ibrutinib was dispensed. A patient was considered to have discontinued ibrutinib if there was a period of 6 months or more between drug dispensations. Patients were divided into two mutually exclusive cohorts. The ibrutinib with concomitant PPI cohort included patients who had had at least one PBS reimbursed PPI script dispensed within 90 days prior to ibrutinib index date. The second cohort, ibrutinib without concomitant PPI, included patients who did not have any PPI script dispensed within 90 days prior to ibrutinib index date. The median duration of treatment was calculated using Kaplan–Meier methods, and differences between cohorts were assessed using log-rank tests. Cox Proportional Hazards modelling was used to assess the impact of age, sex, time since first CLL treatment, and first-line and later therapy on the duration of treatment.

Between 1 December 2017 and 31 December 2021 (first date of PBS-reimbursed ibrutinib availability to date of censor), 193 patients dispensed ibrutinib for CLL in the 10% PBS data set. Of these, 103 patients (53%) received ibrutinib with concomitant PPIs. Patient characteristics are presented in Table 1.

The median duration on ibrutinib treatment in the ibrutinib with concomitant PPI cohort was 41 months (95% confidence interval (CI): 32 months, upper limit not reached). The median of the cohort taking ibrutinib with no concomitant PPI was not reached (95% CI: 34 months, upper limit not reached; $P = 0.61$). There was no difference in the duration on ibrutinib in those taking concomitant PPI compared to those not taking concomitant PPI (unadjusted $P = 0.61$, Fig. 1; adjusted hazard ratio: 1.23, 95% CI: 0.75–2.02, $P = 0.411$). At 48 months, just under half (46.8%, 95% CI: 35.1–62.3%) remained on ibrutinib therapy in the cohort with concomitant PPI, similar to the cohort with no concomitant PPI (53.7%, 95% CI: 42.1–68.5%).

Discussion

This study demonstrates that in real-world clinical practice in Australia, more than half of patients with R/R CLL treated with ibrutinib use prescription PPIs concurrently. This likely underestimates the total number of patients using PPIs, as some PPIs, albeit of lower strength, are also available as 'over-the-counter' (OTC) medications in pharmacies. As the solubility of ibrutinib is pH dependent, theoretically, PPI co-administration may decrease ibrutinib exposure and reduce its efficacy.[2] However, a PK study showed that the ibrutinib AUC, which is a more relevant measure of exposure, was only marginally affected by concomitant use with omeprazole, suggesting that ibrutinib co-administration with a PPI is unlikely to have a clinically relevant effect.[11] From our study, it is further evident that concomitant use of ibrutinib and PPIs does not seem to affect duration on CLL treatment in the real world, indicating co-administration of ibrutinib with PPIs does not affect treatment persistence.

We note several limitations associated with this analysis. While there is the possibility that some OTC PPI use has not been captured, it is likely the proportion of patients taking OTC PPI is small, given the majority of people aged 75 years or over have access to a pension or concession card, which makes the cost of prescription PPI under PBS less expensive compared to OTC PPI.[16] In addition, as PPI use was recorded only within 90 days prior to and including the index date, some patients in the ibrutinib without PPI cohort may have commenced on a PPI after the index date. As a result of a limited number of variables captured in the PBS data set, we

Table 1 Patient characteristics

Variable	Category	Ibrutinib regimen with concomitant PPI ($N = 103$)	Ibrutinib regimen without concomitant PPI ($N = 90$)
Age (years)	Median (Min–Max)	75 (46–97)	72 (30–94)
Age: categories	Age 18–60 years	13 (12.6%)	15 (16.7%)
	Age 61–70 years	25 (24.3%)	22 (24.4%)
	Age 71–80 years	38 (36.9%)	33 (36.7%)
	Age 80+ years	27 (26.2%)	20 (22.2%)
Time since first CLL drug administration to first ibrutinib prescription	Mean (years)	4.2	4
	SD (years)	3.9	3.3
	Median (years)	3	4
	Min–Max (years)	0–15	0–15
Time since first CLL drug by category	0–3 years	55 (53.4%)	43 (47.8%)
	3–6 years	20 (19.4%)	29 (32.2%)
	6–9 years	14 (13.6%)	12 (13.3%)
	9+ years	14 (13.6%)	6 (6.7%)
Sex	Male	68 (66.0%)	57 (63.3%)
	Female	35 (34.0%)	33 (36.7%)
Number of patients by line of therapy	Second line	61 (59.2%)	42 (46.7%)
	3+ lines of therapy	42 (40.8%)	48 (53.3%)

CLL, chronic lymphocytic leukaemia; PPI, proton pump inhibitor; SD, standard deviation.

were unable to undertake a broader adjusted analysis or assess the impact of other potential factors on treatment duration, such as high-risk genetics, comorbidities, prognostic factors and reasons for discontinuation. Some patients in our dataset would have previously accessed ibrutinib through the named patient programme or clinical trials, which may underestimate the duration of ibrutinib treatment.

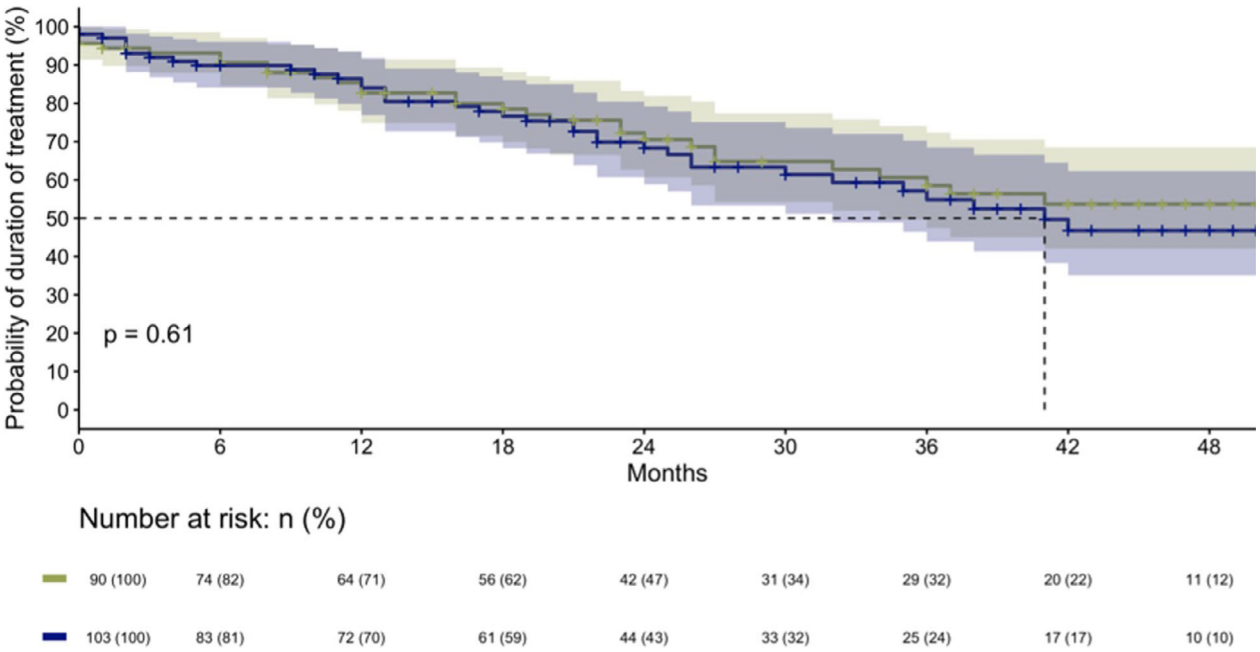

Figure 1 Treatment persistence for ibrutinib in cohorts with and without concomitant PPI (unadjusted analysis). PPI, proton pump inhibitor. (▬) Ibrutinib regimen without PPI; (▬) Ibrutinib regimen with PPI.

A separate analysis showed that more than half of CLL patients use PPIs concurrently with their CLL treatment,[7] the finding that concomitant use does not appear to impact treatment duration is reassuring for clinicians. With treatment persistence potentially being indicative of ibrutinib's continued effectiveness and tolerability in a real-world setting, ibrutinib appears unaffected by concomitant administration of PPIs. However, the impact of high gastric pH on drug absorption may vary across different BTK inhibitors and at this point in time, the data are not sufficiently mature for other BTK inhibitors to conduct similar real-world analyses. Therefore, clinicians should be vigilant for the potential for drug–drug interactions in patients with CLL treated with BTK inhibitors and concurrent PPI usage and refer to the respective product information for guidance.

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