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Characterizing the kinetics of lymphocytosis in patients with chronic lymphocytic leukemia treated with single-agent ibrutinib

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ABSTRACT

Increased absolute lymphocyte count (ALC) is a key feature of chronic lymphocytic leukemia (CLL) but is also observed during treatment with B-cell receptor pathway inhibitors including ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase. In patients with CLL treated with single-agent ibrutinib in two multicenter, open-label, randomized, phase 3 studies (RESONATE-2, NCT01722487; RESONATE, NCT01578707), lymphocytosis was observed in 77 of 136 (57%) patients treated in first-line and 133 of 195 (69%) relapsed/refractory patients. On treatment, lymphocytosis resolved in 95% of patients in the first-line and 94% in the relapsed/refractory setting. The median duration of lymphocytosis was 12 and 14 weeks in the first-line and relapsed/refractory settings, respectively. Lymphocytosis is a common and predictable pharmacodynamic effect of ibrutinib treatment, and in the absence of other signs of progression, does not represent disease progression. Lymphocytosis resolves in the majority of patients and does not require interruption or discontinuation of ibrutinib therapy.

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Introduction

Although increased absolute lymphocyte count (ALC) is a defining feature of chronic lymphocytic leukemia (CLL), it is recognized as a class effect of treatment with B-cell receptor pathway inhibitors [1,2]. Ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase, is approved in the United States for the treatment of CLL and small lymphocytic lymphoma (SLL) and allows for treatment without chemotherapy [3–6]. Lymphocytosis is observed during ibrutinib treatment and may reflect redistribution of CLL cells from lymphoid tissues to the peripheral blood [3–5]. It typically occurs early after treatment initiation, has a variable rate of rise, peaks within days or weeks, and is generally asymptomatic [3–5]. During the phase 1 study of ibrutinib, lymphocytosis was reversed during treatment interruption and recurred upon ibrutinib reinitiation [7]. Data from studies of patients treated with rituximab-containing ibrutinib-combination regimens demonstrated that these regimens might abrogate

lymphocytosis faster but did not significantly change progression-free survival (PFS) [6,8–10]. Ibrutinib inhibits B-cell receptor signaling, cell proliferation, survival, migration, and adhesion in vitro and in vivo [11,12]. The abrogation of cell proliferation occurs in patients immediately after drug administration. Associated cell death without tumor lysis syndrome has been observed [13]. Redistribution of CLL cells is more prominent in patients with mutated *IGHV* versus unmutated *IGHV* and in the relapsed/refractory versus first-line setting [13].

Concerns exist that treatment-related lymphocytosis might be interpreted as a sign of disease progression, prompting premature interruption or discontinuation of ibrutinib. However, in the absence of other clinical signs of progression, treatment-related lymphocytosis with ibrutinib does not represent disease progression or treatment failure [14]. To better understand the clinical profile of lymphocytosis associated with ibrutinib treatment in patients with CLL, this analysis

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characterized the kinetic profile of lymphocytosis in 2 phase 3 studies of ibrutinib, PCYC-1115 (RESONATE-2) and PCYC-1112 (RESONATE).

Materials and methods

We analyzed two multicenter, randomized, open-label phase 3 trials of single-agent ibrutinib in patients with CLL. RESONATE-2 (NCT01722487) evaluated ibrutinib versus chlorambucil in the first-line setting in patients with CLL who were ≥ 65 years old and required treatment for active disease [15]. RESONATE (NCT01578707) evaluated daily ibrutinib versus ofatumumab in the relapsed/refractory setting in patients with CLL or SLL [16]. Full details of study methodology have been previously described [15,16]. Patients in both studies who were randomized to the ibrutinib arm received ibrutinib 420 mg once daily until disease progression or unacceptable toxicity. Both studies were conducted according to the principles of the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. The institutional review board or independent ethics committee at each participating institution approved the studies. All patients provided written informed consent.

In both studies, lymphocytosis was defined as a $\geq 50\%$ increase in ALC compared with baseline and an absolute cell count $\geq 5 \times 10^9/L$. Resolution of lymphocytosis was defined as ALC decreasing to baseline level or lower or achieving a level of $< 5 \times 10^9/L$, whichever occurred first. Treatment-related lymphocytosis was not considered progressive disease in the absence of other signs of progression according to the clarification of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Guidelines [14]. Investigator-assessed overall response rate (ORR), including complete response (CR), CR with incomplete blood count recovery, nodular partial response, and partial response, was evaluated in patients with and without lymphocytosis and required confirmation with two consecutive assessments that were at least 56 days apart

and no use of blood supportive product and/or growth factor during this period. Investigator-assessed progression free survival (PFS) was also evaluated in patients with and without lymphocytosis. Both ORR and PFS were assessed according to the clarification of the iwCLL Guidelines [1,14].

Data were summarized using descriptive statistics, including medians for continuous variables and proportions for discrete variables. ORRs are reported with 95% confidence intervals (CI). PFS was analyzed using Kaplan–Meier estimates and are reported with 95% CI.

Results

Among patients in the RESONATE-2 and RESONATE trials who received ibrutinib and had baseline and at least 1 post-baseline ALC measurement, lymphocytosis was observed in 77 of 135 (57%) first-line patients, and 133 of 192 (69%) relapsed/refractory patients, respectively (Table 1). At the time of the primary analyses of these studies, the median follow-up was 18.4 months in the first-line setting (for RESONATE-2) and 9.6 months in the relapsed/refractory setting (for RESONATE).

Median baseline ALC was higher in the first-line setting ($51.2 \times 10^9/L$; range, 1.4–383.4) compared with the relapsed/refractory setting ($29.5 \times 10^9/L$; range, 0.1–467.7). ALC levels increased rapidly in many patients but decreased with continued ibrutinib treatment (Figure 1). The onset of lymphocytosis occurred during the first month of ibrutinib, with peak ALC levels occurring at a median of 5.7 weeks (range, 1.6–26.1) and 4.1 weeks (range, 0.9–16.1) in the first-line and relapsed/refractory settings, respectively. Median peak ALC level in patients with lymphocytosis in the first-line setting was $104.8 \times 10^9/L$ (range, 9.0–432.9), a onefold increase from baseline and in the relapsed/refractory setting was $96.6 \times 10^9/L$ (range, 5.3–631.4), a twofold increase from baseline. In both the first-line and relapsed/refractory settings, the magnitude of ALC increase was less prominent

Table 1. Summary of lymphocytosis in phase 3 studies of ibrutinib in CLL.

| | RESONATE-2 (PCYC-1115) | RESONATE (PCYC-1112) |
|--|------------------------|----------------------|
| Disease setting | First-line | Relapsed/refractory |
| Number of patients | 135 | 195 |
| <i>IGHV</i> mutation status, <i>n</i> (%) | | |
| Unmutated | 58 (43) | 98 (73) |
| Mutated | 40 (30) | 36 (27) |
| Polyclonal | 3 (2) | NA |
| Missing/no amplification | 34 (25) | 61 (31) |
| Median duration of follow-up at primary analyses, months | 18.4 | 9.6 |
| Patients with lymphocytosis, <i>n/N</i> * (%) | 77/135 (57) | 133/192 (69) |
| Median duration of lymphocytosis (range), weeks | 12 (0.1–78) | 14 (1–58) |
| Patients who resolved lymphocytosis, <i>n/N</i> † (%) | 73/77 (95) | 102/133 (77) |

*Number of patients who had baseline and any post-baseline ALC measurement.

†Number of patients who resolved lymphocytosis at time of primary analyses.

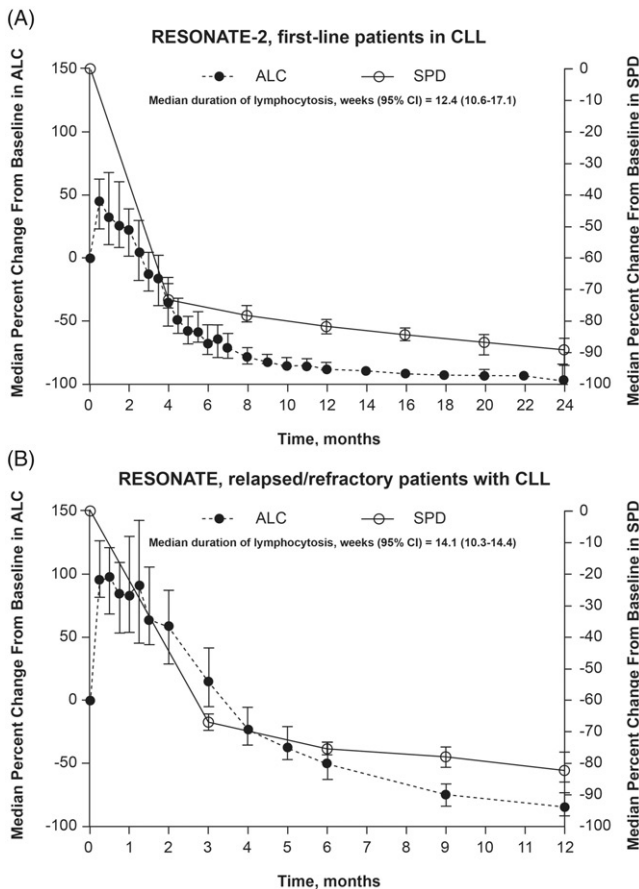


Figure 1. Median changes from baseline in ALC and lymph node sum of the product diameters (SPD) over time with ibrutinib treatment. Reduction in ALC and lymph node SPD from baseline are shown for patients with CLL treated in the first-line setting from RESONATE-2 (A) or patients with relapsed/refractory CLL from RESONATE (B). The baseline median SPD was higher in relapsed/refractory patients compared to first-line patients (5276 vs. 2907 mm²); however, percent reduction was similar at first assessment (66.9% reduction at 3 months and 73.2% reduction at 4 months for RESONATE and RESONATE-2, respectively), with further reduction over time. Lymphocytosis occurred concomitantly with a notable reduction in SPD.

among the unmutated *IGHV* subgroups compared with the mutated *IGHV* subgroups (Figure 2). For patients treated in the relapsed/refractory setting, the duration of lymphocytosis was also shorter for the unmutated *IGHV* relative to mutated *IGHV* subgroups, though this difference in duration was not observed in the first-line setting (Figure 2).

After a median follow-up of 18.4 months in the first-line setting and 9.6 months in the relapsed/refractory setting, lymphocytosis resolved in 95% of patients and 77% of patients, respectively, with a corresponding rapid reduction in lymphadenopathy (Figure 1). The median time to lymphocytosis resolution was 12 weeks in the

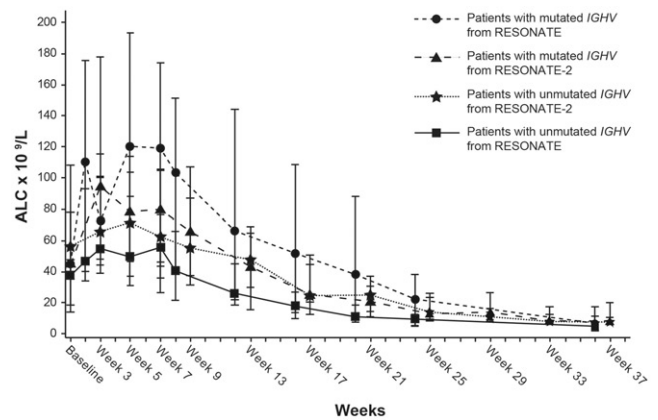


Figure 2. ALC over time by *IGHV* mutation status in RESONATE-2 and RESONATE.

first-line setting and 14 weeks in the relapsed/refractory setting (Table 1).

At the time of the primary analyses as noted above, almost all patients in the first-line setting experienced resolution of lymphocytosis, whereas more than 20% of patients in the relapsed/refractory setting did not experience resolution. With additional follow-up, the rate of resolution of lymphocytosis was increased in the relapsed/refractory setting. After a median follow-up of 56 months in RESONATE, 94% of patients in the relapsed/refractory setting experienced resolution of lymphocytosis; the median time to resolution of lymphocytosis remained the same as that of the primary analysis (Table 1).

Efficacy outcomes were similar in patients with and without lymphocytosis in both the first-line and relapsed/refractory settings as of the updated data with median follow-up of 49 months on RESONATE-2 and 56 months in RESONATE. In the first-line setting, the ORR was 92% (71/77; CR, 23%) in patients with lymphocytosis compared with 91% (53/58; CR, 24%) in patients without lymphocytosis. Similarly, in the relapsed/refractory setting, the ORR was 89% (119/133; CR, 8%) in patients with lymphocytosis and 83% (49/59; CR, 10%) in patients without lymphocytosis. Similar outcomes were also observed for PFS. In the first-line setting, the median PFS was not reached in either the patients with lymphocytosis or patients without lymphocytosis (hazard ratio 1.126; 95% CI, 0.551–2.300; Figure 3(A)). In the relapsed/refractory setting, the median PFS was 48 months (95% CI, 40.6–not estimable) in patients with lymphocytosis and 44 months (95% CI, 25.4–56.9) in patients without lymphocytosis (hazard ratio 0.752; 95% CI, 0.498–1.135; Figure 3(B)).

Persistent lymphocytosis, defined as lymphocytosis lasting >12 months, was uncommon in both the first-

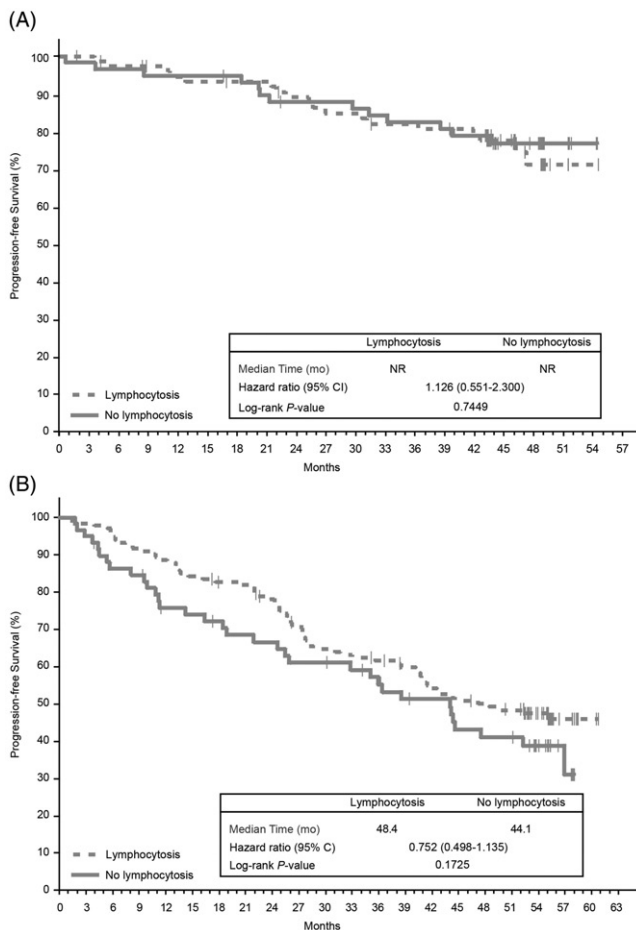


Figure 3. PFS outcomes by presence or absence of lymphocytosis in RESONATE-2 (A) and RESONATE (B).

Table 2. Peak absolute lymphocyte count (ALC) in all patients with CLL treated with ibrutinib at any time from RESONATE-2.

| Baseline ALC $\times 10^9/L$ | Post-baseline Peak ALC $\times 10^9/L$, n (%) | | | |
|------------------------------|--|------------|-------------|------------|
| | <50 | 50 to <100 | 100 to <400 | ≥ 400 |
| <50 (n = 66) | 33 (50) | 20 (30) | 13 (20) | 0 (0) |
| 50 to <100 (n = 26) | 2 (8) | 10 (38) | 14 (54) | 0 (0) |
| ≥ 100 (n = 43) | 4 (9) | 1 (2) | 37 (86) | 1 (2) |
| Total (n = 135) | 39 (29) | 31 (23) | 64 (47) | 1 (1) |

line and relapsed/refractory settings. Only 2 (1%) patients in the first-line setting and 15 (8%) patients in the relapsed/refractory setting experienced persistent lymphocytosis. In general, hyperleukocytosis (ALC $\geq 400 \times 10^9/L$) was uncommon in patients treated with ibrutinib and primarily occurred in patients with high ALC at baseline. A total of 1 of 135 (1%) patients in the first-line setting and 6 of 192 (3%) patients in the relapsed/refractory setting experienced hyperleukocytosis, respectively, and nearly all of these patients had baseline ALC $\geq 100 \times 10^9/L$ (Tables 2 and 3).

Table 3. Peak absolute lymphocyte count (ALC) in all patients treated with ibrutinib at any time from RESONATE.

| Baseline ALC $\times 10^9/L$ | Post-baseline Peak ALC $\times 10^9/L$, n (%) | | | |
|------------------------------|--|------------|-------------|------------|
| | <50 | 50 to <100 | 100 to <400 | ≥ 400 |
| <50 (n = 66) | 69 (58) | 25 (21) | 24 (20) | 1 (1) |
| 50 to <100 (n = 26) | 2 (6) | 10 (28) | 24 (67) | 0 (0) |
| ≥ 100 (n = 37) | 1 (3) | 1 (3) | 30 (81) | 5 (14) |
| Total (n = 192) | 72 (38) | 36 (19) | 78 (41) | 6 (3) |

Discussion

An increase in ALC is a hallmark pathological feature of CLL and has also been observed in patients receiving treatment with B-cell receptor pathway inhibitors including ibrutinib. Of note, treatment-related lymphocytosis in the absence of other signs of progression does not represent disease progression. To further characterize the kinetic profile of ibrutinib-related lymphocytosis, this report describes the clinical profile of lymphocytosis in patients with CLL receiving ibrutinib in the first-line (RESONATE-2) and relapsed/refractory (RESONATE) settings. The kinetics of lymphocytosis observed in these studies were similar to what has been previously described [3–5]. Although median baseline ALC was higher in the first-line setting than relapsed/refractory setting, the rapid rise in ALC level was followed by a continuous decrease over time in both treatment settings; moreover, lymphocytosis eventually resolved in almost all patients in both the first-line setting and relapsed/refractory setting. The pattern of lymphocytosis observed among patients with unmutated and mutated *IGHV* status was also consistent with previous reports [4,17,18]. Unmutated *IGHV* was associated with a less pronounced increase in ALC and more rapid resolution of lymphocytosis compared with mutated *IGHV*.

Lymphocytosis is an expected and predictable pharmacodynamic effect of ibrutinib treatment in patients with CLL. While not all patients who respond experience lymphocytosis, 92% of ibrutinib-treated patients with a partial response with lymphocytosis demonstrated improved response over time in a CLL clinical study [17]. Several studies have shown that prolonged (at 12 months) lymphocytosis in ibrutinib-treated patients is not associated with inferior efficacy or long-term survival outcomes [3,4,17]. A previous report characterizing the molecular and biochemical features of persistent lymphocytes before and after ibrutinib treatment showed absence of proliferation (based on ki-67 staining), and no evidence of increasing clonal aberrations (based on κ and λ expression and *IGHV* sequencing) or epigenetic alteration of ZAP-70 (based on ZAP-70 methylation status). Thus, lymphocytes from patients with persistent lymphocytosis are not actively proliferating, suggesting that these

patients do not represent a population likely to progress [3].

In the current analysis, efficacy outcomes, assessed by ORR and median PFS, were similar in patients with and without lymphocytosis regardless of whether patients were receiving ibrutinib in the first-line or relapsed/refractory setting. Slightly higher rates and longer durations of lymphocytosis may be expected during treatment in the relapsed/refractory setting compared with the first-line setting. This is suggested by the observation that in the relapsed/refractory setting, the proportion of patients with resolution of lymphocytosis increased from 77% at the time of primary analysis (median follow-up 9.6 months) to 94% with longer follow-up (median 56 months).

Ibrutinib treatment should not be interrupted or discontinued for lymphocytosis, and patients should be treated until confirmed disease progression or until the patient is unable to tolerate therapy [6]. Although uncommon, hyperleukocytosis ($ALC \geq 400 \times 10^9/L$) was seen in a few patients treated with ibrutinib in our analysis, and primarily occurred in the relapsed/refractory setting in patients with high ALC at baseline. Leukostasis has rarely been reported with ibrutinib treatment; isolated cases have occurred in the setting of disease progression or transformation. $ALC \geq 400 \times 10^9/L$ may confer increased risk of leukostasis; in such cases, temporary withholding of ibrutinib can be considered, and patients should be closely monitored [6].

Combination therapy with ibrutinib and rituximab has been shown to mitigate lymphocytosis in patients with CLL [6,8,10]. In a phase 2 study, 3/40 (8%) patients with high-risk CLL who received combination therapy with ibrutinib and rituximab experienced persistent lymphocytosis after 6 months of treatment [8]. In the phase 3 HELIOS study, 289 patients with relapsed/refractory CLL or SLL were treated with ibrutinib in combination with bendamustine and rituximab (BR) [6,9]. When ibrutinib was administered in combination with BR, lymphocytosis occurred in 7% of patients [6]. Ibrutinib in combination with rituximab has demonstrated faster resolution of lymphocytosis and increased rates of minimal residual disease negativity compared with single-agent ibrutinib, at 2 years of follow-up this combination was not shown to significantly increase PFS [10]. While this combination may be considered for some patients, single-agent ibrutinib remains the standard of care [10].

Lymphocytosis is a common pharmacodynamic effect of ibrutinib treatment. In order to guide patient expectations, it is important for physicians managing patients with CLL to understand the expected clinical

profile of lymphocytosis and that the occurrence of lymphocytosis does not alter the long-term benefit frequently achieved with ibrutinib therapy.

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