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Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial

Running title: Front-line ibrutinib in trial ineligible patients

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A**bstract**

Ibrutinib demonstrated superior response rates and survival for treatment-naïve chronic lymphocytic leukemia (CLL) patients in a pivotal study that excluded patients younger than 65 (<65) and/or with chromosome 17p13 deletion (del(17p13)). We examined outcomes and toxicities of CLL patients who would have been excluded from the pivotal study, specifically <65 and/or those with del(17p13). This multicenter, retrospective cohort study examined CLL patients treated with front-line ibrutinib at 20 community and academic centers, categorizing them based on key inclusion criteria for the RESONATE-2 trial: <65 vs. ≥65 and present vs. absent del(17p13). Of 391 included patients, 57% would have been excluded from the pivotal study. Forty-one percent of our cohort was <65, and 30% had del(17p13). Patients <65 were more likely to start 420 mg of ibrutinib daily; those who started at reduced doses had inferior PFS. The most common adverse events were arthralgias, fatigue, rash, bruising, and diarrhea. Twenty-four percent discontinued ibrutinib at 13.8 months median follow-up; toxicity was the most common reason for discontinuation, though progression and/or transformation accounted for a larger proportion of discontinuations in <65 and those with del(17p13). Response rates were similar for <65 and those with del(17p13). However, patients with del(17p13) had inferior PFS and OS. Ibrutinib in the front-line setting has extended beyond the population in which it was initially studied and approved. This study highlights and compares important differences in ibrutinib

dosing, treatment interruptions, toxicities, reasons for discontinuation, and survival outcomes in two important patient populations not studied in RESONATE-2.

Introduction

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor that is approved for all lines of therapy in patients with chronic lymphocytic leukemia (CLL).[1] The approval for front-line treatment-naïve CLL patients was based on the RESONATE-2 trial, which randomized patients to ibrutinib versus chlorambucil in treatment-naïve patients. In this study, ibrutinib demonstrated superior overall response rate (ORR) of 86%, estimated 24-month progression free survival (PFS, HR 0.16; P<0.001) of 90%, and estimated 24-month overall survival (OS, HR 0.16; P=0.001) of 98% at a median follow-up of 18.4 months.[2] However, this study only included patients age 65 years or older (≥65) with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and excluded patients with del(17p13). Whether the results of this trial are generalizable to younger patients who might be otherwise candidates for chemoimmunotherapy or to those with del(17p13) remains unknown. Outcomes and toxicities of ibrutinib-treated patients who would not have met the RESONATE-2 entry criteria are not known, though these data could impact clinical practice, treatment decision making, and the process of informed consent. Therefore, we analyzed 391 CLL patients who were treated with front-line ibrutinib, focusing on subsets that would not have been eligible for the RESONATE-2 trial. We studied the impact of age and/or del(17p13) status on outcomes and toxicities of ibrutinib. To our knowledge, this cohort represents the largest series of CLL patients treated with ibrutinib in the front-line setting.

Methods

We conducted a multicenter, retrospective cohort study of CLL patients treated with ibrutinib in the front-line setting at 20 community and academic cancer centers. The study was approved by the institutional review board of each participating institution. Medical chart review

of CLL patients was performed to identify all CLL patients at each institution treated with ibrutinib in the front-line setting. Investigators utilized chart review, electronic medical records, and related databases to obtain required information.

Patients were categorized based on key inclusion criteria for the RESONATE-2 trial: younger than 65 years of age at time of starting ibrutinib (<65) vs. ≥65 and chromosome del(17p13) present vs. del(17p13) absent. In addition, patients were stratified based on the presence or absence of *TP53* mutation in those who had this testing available, though this was not an exclusion in RESONATE-2 and not specifically tested or reported, and the presence or absence of somatic hypermutation of the B-cell receptor (*IGHV* mutated vs. unmutated).

The primary endpoint was PFS stratified by age at ibrutinib initiation and del(17p13) status (both categorical variables). PFS was defined as time from ibrutinib initiation to progression or death from any cause as per the Kaplan Meier method.[3] Patients were otherwise censored at the time of last follow-up. Secondary endpoints included ORR, complete remission (CR), OS, toxicity profile, reasons for discontinuation, and subsequent therapies following discontinuation. OS was defined as time from initiation of ibrutinib to death. The International Workshop on Chronic Lymphocytic Leukemia (iwCLL, 2008) criteria were used to define response and progression of disease. Select AEs were assessed using the Common Terminology Criteria for Adverse Events (CTCAE).[4, 5]

Reasons for ibrutinib discontinuation were categorized as follows: toxicity, progressive disease (PD), Richter's transformation (RT) to either diffuse large B cell lymphoma (DLBCL) or Hodgkin Lymphoma, planned cellular therapy (allogeneic hematopoietic stem cell transplantation

or chimeric antigen receptor genetically modified T-cell therapy), secondary malignancies, physician or patient decisions, financial constraints, and non-CLL related causes.

Comparisons of survival outcomes data were made using the long rank (LR) test. Cox regression analyses were used to estimate hazard ratios in univariate and multivariate analyses. [6, 7] [6,7] [6,7] [6,7] [6,7] [6,7] [6,7] All other comparison analyses were descriptive. All tests were two-sided at the 5% level. Statistical analyses were performed using STATA 10.1 (Stata Statistical Software: Release 10. 2007; StataCorp LP, College Station, TX)**.**

Results

Patient population

This analysis identified 391 CLL patients treated with front-line ibrutinib. Supplemental Table 1 lists participating centers. Baseline patient characteristics were compared with data available in RESONATE-2 (Table 1). Of note, 160 patients (41%) were <65 and 110 patients (30%) had del(17p13) at the start of ibrutinib; these patients would not have been eligible for RESONATE-2 based on published entry criteria. Eight additional patients had *TP53* mutations without del(17p13); notably, *TP53* mutational status was not available in RESONATE-2 data. Moreover, we identified 24 ibrutinib-treated patients who might be considered ideal candidates for chemoimmunotherapy combinations such as fludarabine, cyclophosphamide, and rituximab (FCR) based on their age and molecular / genetic profile (<65, *IGHV* mutated, without del(17p13), without *TP53* mutation).

Ibrutinib dosing and dose adjustments

Median starting dose of ibrutinib was 420 mg daily for the entire cohort. Older patients (≥65) were more frequently started at a dose below 420 mg daily compared to patients <65 (11.3% vs. 2.5%, p=.01). In addition, older patients were more likely to have a dose reduction before achieving a stable ibrutinib dose (19.9% vs. 13.1%, p=.01) (Table 2). No differences in starting dose or dose alterations were noted between patients with or without del(17p13). All patients in RESONATE-2 initiated treatment at 420 mg daily, but data on dose adjustments in RESONATE-2 were not available for comparison.

Impact of dose alterations

We identified 30 patients (7.6% of entire cohort) who initiated treatment at doses below 420 mg (140 mg daily n= 14 and 280 mg daily n=16). Reasons for lower starting dose and concomitant medications were not captured. For the reduced dose cohort, the median age was 76 years (range 47-96) vs. 67 years (range 36-96) in the standard dose cohort. Patients who received reduced doses had similar proportion of del(17p13) (27% vs 30%) and complex karyotype (21% vs 24%). In the reduced dose cohort, the 12-month PFS was inferior to standard dose (71% vs. 93%; HR 3.3, 95% CI [1.5-7.0], p=.003). Eighty-six (22%, 86/391) patients had a dose interruption ≥ 8 days (median duration = 14 days). The 12-month PFS was not impacted by dose interruption (90% if ≥ 8 days vs. 96% if <8 days, HR 1.48, 95% CI [0.48-4.6], p=0.49).

Adverse events (AEs) and ibrutinib discontinuation profile

AEs occurring during the study period are shown in Table 3. Of note, we did not include a cutoff of 15% as was done in RESONATE-2. As such, all AEs are reported (all grades and grade ≥ 3) to capture rare events not previously described in the front-line setting. Arthralgia, fatigue, rash, bruising, and diarrhea were the five most common AEs occurring in 21.2%, 18.7%,

17.9%, 17.9%, and 17.4% of the entire cohort, respectively. Grade ≥ 3 events were rare, and none occurred in > 5% of patients. The most clinically relevant AEs (atrial fibrillation, bleeding, and infection) are detailed in Table 3.

Table 4 describes the discontinuation rate and reasons for discontinuation in all patients and subgroups compared to the pivotal trial. With a median follow up of 13.8 months (vs. 18.2 months in RESONATE-2), ibrutinib discontinuation rate was 24%. For patients <65, discontinuation rate was 23%. For patients with del(17p13), discontinuation rate was 33%. The median time to ibrutinib discontinuation was 6.5 months for the entire cohort. When stratified by age, median time to ibrutinib discontinuation was longer for patients <65 (11.5 months) than for those ≥65 (4 months, p=.06). Toxicity was the most common reason for discontinuation in all groups. To date, 26 of 56 patients who discontinued ibrutinib for toxicity have been treated with a subsequent line of therapy. For these patients (n=26), the median time off ibrutinib prior to next therapy was 2 months (0.1-20 months). However, CLL progression and/or transformation accounted for a larger proportion of discontinuations in patients <65 and those with del(17p13). All 9 RT events occurred in patients with del(17p13). Median time to discontinuation stratified by reason for stopping therapy were 3.7 months for toxicity, 12 months for RT, and 22 months for CLL progression.

Response rates and survival outcomes

Supplemental Table 2 shows rates of response for all patients and subsets. Response rates were similar in all groups. ORR for the entire cohort was 81.8%, while it was 85.3% in patients <65, and 82.3% in patients with del(17p13). The ORR for patients with both del(17p13) and *TP53* mutation (n=34) was 91%. At a median follow up of 13.8 months, the median PFS

(Supplemental Figure 1A) and OS for the entire cohort have not been reached. At 1 year, PFS and OS were 92% and 95% respectively, and 80.6% of patients were alive and remained on iburtinib at 1 year (Supplemental Figure 1B). Patients with del(17p13) had both an inferior PFS (87% at 1 year, HR 1.9, p=.04) and OS (89% at 1 year, HR 3.9, p=.001) compared to those without del(17p13) (Figure 1A, 1B). PFS and OS were similar for patients when stratified by age (Figure 1C, 1D). PFS was not significantly different for patients with complex karyotype and del(17p13) compared to patients with del(17p13) without complex karyotype (Supplemental Figure 1C). No progression events or deaths were noted in patients <65, *TP53* wild type, *IGHV* mutated (Figure 1E). PFS did not differ for patients when stratified by del(11q) status or *IGHV* status (Supplemental Figure 1D, 1E).

Post-ibrutinib therapies

At the time of this analysis, 55 patients have been treated with a subsequent therapy following ibrutinib discontinuation. The most common therapy classes selected following ibrutinib discontinuation with ORR include anti-CD20 monoclonal antibody (n=18, ORR 58%), venetoclax (n=10, ORR 89%), chemoimmunotherapy combinations (n=9, ORR 50%), and alternative kinase inhibitor (n=7, ORR 40%). Table 5 describes treatment choice following ibrutinib discontinuation for patients <65 and those with del(17p13). Additionally, treatment choices stratified by reason for ibrutinib discontinuation (toxicity, CLL progression, and RT) are described in Supplemental Table 3.

Of the 39 patients who have discontinued ibrutinib and not received subsequent therapy, 9 died without receiving an additional line of therapy. Reasons for discontinuation included CLL progression in 5 of the 9 patients, Richter's transformation in 2 of 9 patients, toxicity in 1 of the 9

patients, and death not secondary to disease progression or toxicity in 1 of 9 patients. Of the 9 patients who discontinued ibrutinib and died without receiving a subsequent therapy, the median time to ibrutinib discontinuation was 3 months and the median time to death was 4 months.

Discussion

We report on this large series of CLL patients treated with ibrutinib in first-line setting, which represents the CLL patients treated with front-line ibrutinib in clinical practice. This analysis demonstrates that ibrutinib was frequently used in patients who were not studied in RESONATE-2, specifically those <65 and/or with del(17p13). Our study highlights both similarities and important differences in outcomes between patients included and excluded from clinical trials. This report also gives the first published insight into practice patterns during and following ibrutinib administration in the front-line setting. These observations have important implications for clinical practice as they provide data for the informed consent process in patients considering ibrutinib who would have been excluded in the landmark front-line trial.

Although RESONATE-2 did not include patients with del(17p13) and patients <65,[2] two published smaller series included such patients. CYC-1102 examined ibrutinib monotherapy in 31 CLL/SLL treatment naïve patients, age 65-84, with and without del(17p13). Five year outcomes have been reported but were not stratified by genetic profile.[8] In a combined analysis of front-line and relapsed/refractory patients treated on two separate studies, the presence of del(17p13), patient age, and *IGHV* status did not impact the proportion of patients achieving CR.[9] NCT01500733, a study of ibrutinib that included 35 treatment naïve patients with *TP53* aberration (del(17p13) and/or *TP53* mutation), showed an estimated 5-year PFS and OS of 74.4%

(95% CI [60.2-92.1]) and 85.3% (95% CI [74.2-98.1]). Outcomes were not further stratified by patient age in the cohort with *TP53* aberration.[10]

We report data on 110 patients with del(17p13), representing the largest reported experience with front-line ibrutinib for these patients. While ORRs were consistent with those reported in the RESONATE-2 study, patients with del(17p13) had inferior PFS and OS compared to their counterparts without del(17p13) when treated with ibrutinib in the front-line setting. A trend toward inferior prognosis, without statistical significance, was observed in patients with complex karyotype and del(17p13) as compared to patients with del(17p13) without a complex karyotype. In addition, while rates of progression due to CLL in the entire cohort were comparable to the RESONATE-2 report, there was a strikingly higher rate of RT, entirely in patients with del(17p13). These data suggest that patients with del(17p13) have the highest need for front-line clinical trials of novel combinations to potentially overcome this adverse prognostic factor.

These findings demonstrate the increasing use of ibrutinib in patients <65. Efficacy and toxicity data for ibrutinib in younger, treatment naïve patients are lacking but crucial as we discuss various front-line options, including ibrutinib, chemoimmunotherapy combinations, and participation in clinical trials. In addition, these data are important as we evaluate cost, as well as duration and sequencing of therapies. Our analysis indicates that younger patients have similar response rates and survival outcomes to their older counterparts. This is in keeping with the observation that PFS did not differ when older treatment naïve patients with CLL treated with ibrutinib on RESONATE-2 were stratified by age (age 65-74 years vs. age ≥ 75 years).*[11]*

A group of patients in our cohort were excellent candidates for chemoimmunotherapy. These 24 patients would have been FCR-ideal based on their young age, *TP53* status, and mutated *IGHV*.[12, 13] No progression or death events were observed in these patients, suggesting that FCR-ideal patients have excellent outcomes when treated with ibrutinib. Ongoing prospective studies comparing ibrutinib to FCR or BR have not yet been reported (NCT02048813, NCT01886872).

We provide the first non-trial series in which AEs were graded per CTCAE criteria for ibrutinib and include data on all toxicities regardless of rarity. Interestingly, 30 patients were initiated on lower than recommended doses of ibrutinib, predominately in patients ≥65. While dose reduction at the time of drug initiation, presumably to mitigate toxicity, was associated with inferior PFS (71% versus 93% for those maintaining 420 mg per day at 12-months), dose interruption of ≥ 8 days did not appear to affect PFS. Outcomes appear optimized when starting with the standard dose and interrupting only as needed per the FDA label. Dose interruption of ibrutinib appears to be a relatively common practice with 42% of patients having at least one interruption and 17% requiring sustained dose reduction following interruption. In contrast to a prior report of clinical trial patients with relapsed/refractory disease, dose interruption of ≥ 8 days does not appear to affect survival outcomes.[14] A higher percentage of patients in our analysis discontinued therapy due to toxicity than in the RESONATE-2 study, likely reflecting the increased availability of alternative effective biologic therapies and possibly more comorbidity in this patient population.[2]

We also provide information about selection of second line therapy following front-line ibrutinib with rates of response. While the numbers are small and follow up is too premature to

present survival outcomes, these data provide insight into the evolving treatment landscape of CLL.

This study has several limitations. While we included data from community practices, most patients were treated in academic centers, and this distribution could introduce selection bias. Data were collected retrospectively and are subject to differences in clinical experience, practice style, charting detail, and inconsistencies in chart review. As expected, the extent of missing data varied with each covariate. To address this, we included absolute numbers and percentages to highlight any data that was not reported for individual data points. Some prognostic information was missing; *IGHV* mutational analysis was collected in only slightly more than half of the patients included. This omission reflects lack of testing and emphasizes the importance of fully characterizing prognosis in CLL, as it could have implications for choice of front-line therapy.[15] Although iwCLL response criteria and CTCAE criteria for AEs were suggested to standardize data across centers, central review of toxicities, responses, and outcomes were outside the scope of this study. Indications for treatment were based on treating physicians' discretion and were not specified. The discrepancy in rate of clinical CR in our series compared to clinical trial CR rates may reflect the infrequency of confirmatory bone marrow biopsies as part of response assessment. This testing is not mandated by the iwCLL guidelines and is often omitted in clinical practice as a component of the response assessment. It is possible many of the reported clinical CRs would have been PRs had a bone marrow biopsy been performed. Similar discrepancies in response assessment are also observed in clinical trials. For example, a recent clinical trial of venetoclax and rituximab treated patients (vs. bendamustine and rituximab) had a significant discrepancy in CR rate between central and investigator assessments.[16] Finally, we

highlight a higher than expected incidence of RT in patients with del(17p13). This is consistent with the significant number of discontinuations in the RESONATE-17 trial due to RT. In our series, all RT events occurred in patients with del(17p13).[17] Additionally, due to limitations in resources we did not confirm if confirmatory biopsy was performed, and central review of biopsy results were outside of the scope of this study

Despite these limitations, this report details a large, multicenter clinical experience of front-line ibrutinib in the treatment of CLL. Fifty-seven percent of this cohort would have been excluded from RESONATE-2, and therefore, these data inform clinical practice for these patients. Our data highlight the substantial use of ibrutinib in patients with poor risk disease and suggest inferior incomes, including higher than expected rates of RT, for del(17p13) patients. We highlight practice patterns regarding dose reductions and interruptions. These data suggest that outcomes are improved when ibrutinib is initiated at the recommended therapeutic dose and demonstrate the importance of maintaining the dose during therapy. Finally, we provide insight into selection of subsequent therapy after first line ibrutinib, a key area of active clinical investigation. As novel agents are increasingly used to manage CLL, insight into outcomes and toxicities for groups lacking robust clinical trial data will allow for more informed decision making as we optimize our approach to CLL.

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