Journal of clinical and experimental hematopathology
Vol. 59 No.4, 179-186, 2019

Original Article

Phase I study of ibrutinib in Japanese patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma

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This phase I study evaluated the safety and efficacy of single-agent ibrutinib in Japanese patients with treatment-naïve chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (aged 20-69 years and ineligible for chemotherapy using fludarabine or cyclophosphamide, or aged ≥70 years). Eight patients received oral ibrutinib 420 mg once daily until progressive disease or unacceptable toxicity. The primary endpoint was safety; secondary endpoints included the overall response rate (ORR). At the time of final analysis (August 22, 2018), eight patients (all with CLL; median age, 68.5 years) had received ibrutinib for a median of 32.2 months (range, 10.4-35.9); all patients had discontinued study treatment, with 50.0% of patients switching to marketing-approved ibrutinib as subsequent anticancer therapy. All patients had ≥1 adverse event (AE); the most common AEs included a decreased platelet count, upper respiratory tract infection, increased lymphocyte count, diarrhea, nasopharyngitis, peripheral edema and rash. Four patients (50.0%) had a total of eight grade ≥3 AEs, most commonly lung infection and decreased neutrophil count. Eight serious AEs were reported in four patients (50.0%); these included a case of muscle hemorrhage (grade 3), decreased neutrophil count (grade 4) that led to dose reduction and one case of fatal cardiac arrest. The ORR was 87.5% (7/8 patients [exact 95% confidence interval 47.3-99.7]). One patient had a complete response, six had a partial response and one had a partial response with lymphocytosis. Ibrutinib had an acceptable safety profile and high ORR in Japanese patients with treatment-naïve CLL.

Keywords: Chronic lymphocytic leukemia, covalent Bruton's tyrosine kinase inhibitor, ibrutinib, Japanese patients, small lymphocytic lymphoma

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of clonal B-lymphocytes in the bone marrow, peripheral blood and lymphoid tissues.[1,2] Small lymphocytic lymphoma (SLL) is a different manifestation of the same disease.[3] Although CLL is a common form of adult leukemia in Western countries,[4,5] the annual incidence of CLL is low in Japanese populations, being less than 0.5/100,000 person-years.[6-8] However, it is increasing in Japan, potentially due to the interaction of genetic predisposition with environmental factors such as the Westernization of lifestyle.[9]

Conventional treatment options for patients with CLL/SLL include chemoimmunotherapy that combines a CD20 antibody (rituximab, obinutuzumab or ofatumumab) with chemotherapy (fludarabine/cyclophosphamide or chlorambucil), but this limits patient outcomes due to poor survival following relapse.[10-13] Ibrutinib is a first-in-class, once-daily oral Bruton's tyrosine kinase inhibitor that blocks the signaling pathway required for the growth and maturation of malignant B-lymphocytes.[14] Importantly, ibrutinib provides an alternative treatment to chemotherapy, and is approved in the United States and many other countries for the treatment of both previously treated and treatment-naïve patients with CLL/SLL, including those with chromosome 17p13.1 deletion.[15,16] In phase III CLL/SLL trials (conducted outside of Japan), ibrutinib demonstrated efficacy and acceptable

Received: June 13, 2019. Revised: August 31, 2019. Accepted: September 23, 2019. Online Published: December 22, 2019
DOI:10.3960/jslrt.19023

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tolerability in both previously treated and treatment-naïve patients.[17-19] In older (≥65 years) treatment-naïve patients with CLL/SLL, ibrutinib (median duration, 18.4 months) provided a high overall response rate (ORR) of 86.0% versus 35.0% with chlorambucil, and the median progression-free survival (PFS) was not reached versus 18.9 months with chlorambucil.[18] In patients with relapsed/refractory CLL/SLL at risk of a poor outcome, including those with chromosome 17p13.1 deletion, ibrutinib (median duration, 9.4 months) provided an ORR of 42.6% versus 4.1% with ofatumumab, and the median PFS was not reached versus 8.1 months with ofatumumab.[17] There were no unexpected safety signals in these phase III trials, and most patients continued treatment at the completion of the trials.[17,18]

In Japan, ibrutinib was approved in March 2016 for the treatment of patients with relapsed/refractory CLL/SLL.[20] In a phase I dose-escalation study, ibrutinib at 420 or 560 mg (median duration, 13.5 months) was tolerable and had an acceptable safety profile in 15 Japanese patients with relapsed/refractory mature B-cell malignancies, including 11 with CLL/SLL.[21]

However, for patients with treatment-naïve CLL/SLL, treatment options in Japan are limited compared with many Western countries,[22] and access is generally restricted to chemotherapies such as fludarabine or cyclophosphamide. Therefore, this study aimed to confirm the safety and efficacy of single-agent ibrutinib, administered once daily, in Japanese patients with treatment-naïve CLL/SLL. This study led to the approval of ibrutinib in Japan for patients with treatment-naïve CLL/SLL.[23]

MATERIALS AND METHODS

Study design and patients

This was a phase I, multicenter, open-label study conducted at five sites in Japan (LEU1001; NCT02556892) and sponsored by Janssen Pharmaceutical KK. The study protocol and amendments were reviewed by an institutional review board at each hospital, and the study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

The Japanese patients enrolled had treatment-naïve CLL/SLL that met the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. Eligible patients had active disease meeting ≥1 of the iwCLL criteria for requiring treatment, and were either aged 20 to 69 years and ineligible for chemotherapy with fludarabine or cyclophosphamide, or aged ≥70 years. Patients with CLL were required to have measurable nodal disease by computed tomography (CT), defined as ≥1 lymph node >1.5 cm at the longest diameter at a site that had not been previously irradiated. Patients with SLL were required to have ≥1 measurable site of disease per the Revised Response Criteria for Malignant Lymphoma (i.e. >1.5 cm in the long axis regardless of the short axis measurement, or >1.0 cm in the short axis regardless of the long axis measurement, and clearly measurable in two perpendicular dimensions).[24] All eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

Exclusion criteria included known involvement of the central nervous system (CNS) by lymphoma or leukemia, history of Richter's transformation or prolymphocytic leukemia, uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura (within 4 weeks before study drug initiation), active cardiovascular disease, or history of myocardial infarction, unstable angina, acute coronary syndrome, stroke or intracranial hemorrhage (within 6 months before study drug initiation). Patients were also excluded if they had uncontrolled active systemic fungal, bacterial, viral or other infection, or required intravenous antibiotics, or if they were taking corticosteroids at dosages equivalent to >20 mg/day of prednisolone (within 1 week before study drug initiation).

Treatment

Patients received oral ibrutinib at 420 mg (three capsules) once daily. Ibrutinib treatment started on day 1 of cycle 1, with each cycle lasting 28 days. Treatment continued until signs of progressive disease or unacceptable toxicity. The study was terminated due to the approval of ibrutinib for treatment-naïve CLL/SLL in Japan.

Endpoints

The primary endpoint was safety, including adverse events (AEs): incidence, severity, type and those leading to treatment discontinuation or dose modification. An AE of special interest was major hemorrhage, defined as hemorrhagic AE of grade ≥3, serious bleeding (any grade) or CNS hemorrhage/hematoma (any grade). Other safety outcomes were clinically significant changes in clinical laboratory tests, electrocardiogram findings, vital sign measurements, ECOG performance status and physical examinations, including focused ocular questions. Efficacy assessments included ORR (complete response [CR] + partial response [PR]), time to response, PFS and overall survival (OS).

Evaluations

AEs were reported until 30 days after the last dose of ibrutinib or the start of subsequent anti-CLL/SLL therapy, whichever occurred first. AE severity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03. An AE was considered associated with study drug use if the relationship was classified as possible, probable or very likely (as opposed to not related or doubtful).

Baseline disease assessment was performed before treatment (within 30 days before the study drug was administered) and a response assessment was performed during treatment, on day 1 of cycle 3 and every odd-numbered cycle thereafter. Responses were evaluated per the guidelines for the diagnosis and treatment of CLL,[25] or for patients with

SLL, the International Working Group Revised Response Criteria for Malignant Lymphoma.[24] Assessments included CT of the area between the base of the skull and mid-thigh, and if needed, positron emission tomography.

Statistical analysis

Initially, six patients were planned to be enrolled in the safety evaluation due to the practical feasibility of recruiting eligible patients in Japan. After the safety of ibrutinib was confirmed in the first six patients, two additional patients were planned to be enrolled to further evaluate ibrutinib efficacy in Japanese patients with treatment-naïve CLL/SLL.

The safety population was defined as all enrolled patients who received ≥1 dose of the study drug, and was used for baseline, demographics, exposure and safety analyses. The efficacy-evaluable population was defined as all enrolled patients who received ≥1 dose of the study drug and who had a measurable lesion at baseline and ≥1 satisfactory post-baseline disease assessment.

RESULTS

Patients and treatment

Eight patients were enrolled, all of whom received ibrutinib and had post-baseline disease assessments; they were, therefore, included in the safety and efficacy-evaluable populations. Baseline demographics, and patient and disease characteristics are shown in Table 1. The median age was 68.5 years (range, 51-70), and there were six (75.0%) men and two (25.0%) women. All eight (100.0%) patients had CLL; none had SLL. Three (37.5%) patients had Rai stage IV disease. According to Binet staging, four (50.0%) patients had stage B and four (50.0%) had stage C disease.

The median duration of ibrutinib treatment at the final analysis was 32.2 months (range, 10.4-35.9). The median relative dose intensity was 98.5% (range, 60.2-100.0). In five of the eight (62.5%) patients, the relative dose intensity was ≥90%; one patient had a relative dose intensity of 60.2% primarily because their ibrutinib dose was reduced on two occasions due to AEs (from 420 mg to 280 mg due to muscle hemorrhage, and subsequently, from 280 mg to 140 mg due to a decreased neutrophil count). At the final analysis, study treatment was discontinued in all patients; 50.0% of patients switched to marketing-approved ibrutinib as subsequent anticancer therapy.

Safety

The reported AEs are summarized in Table 2. All eight patients reported ≥1 AE. The most common were decreased platelet count (n = 6, 75.0%), upper respiratory tract infection and increased lymphocyte count (four patients [50.0%] each), and diarrhea, nasopharyngitis, rash and peripheral edema (all n = 3; 37.5%). Grade ≥3 AEs developed in four (50.0%) patients. The most frequent grade ≥3 AEs were lung infection and decreased neutrophil count (n = 2; 25.0% each). Other grade ≥3 AEs included cardiac arrest, cellulitis, femoral neck fracture, hypertension, increased aspartate aminotransferase, muscle hemorrhage, worsening of Parkinson's disease, pneumonia, tibia fracture and hypokalemia (all n = 1; 12.5% each). All grade ≥3 AEs were resolved by the cutoff date, except one case each of hypertension, cardiac arrest

Table 1. Baseline demographics, and patient and disease characteristics

Characteristic	All patients (N = 8)
Age, years	
Mean (SD)	65.8 (6.7)
Median (range)	68.5 (51-70)
Male, n (%)	6 (75.0)
Weight, kg	
Mean (SD)	59.9 (9.7)
Median (range)	57.4 (46.9-77.0)
Duration of disease, months	
Mean (SD)	59.4 (40.4)
Median (range)	63.8 (5.8-130.0)
ECOG, n (%)	
0	6 (75.0)
1	2 (25.0)
Histological type, n (%)	
CLL	8 (100.0)
SLL	0
Rai stage, n (%)	
0	0
I	1 (12.5)
II	3 (37.5)
III	1 (12.5)
IV	3 (37.5)
Binet stage, n (%)	
A	0
B	4 (50.0)
C	4 (50.0)
Tumor bulk, n (%)[a]	
<5 cm	4 (50.0)
≥5 cm	4 (50.0)
<10 cm	7 (87.5)
≥10 cm	1 (12.5)
Tumor burden, cm^2[b]	
Mean (SD)	56.2 (76.9)
Median (range)	34.4 (3.8-236.3)
B symptom, n (%)	
Yes	2 (25.0)
No	6 (75.0)
Extranodal site, n (%)[c]	
Yes	7 (87.5)
No	1 (12.5)

[a] Tumor bulk was calculated using the largest diameter among measurable lesions.
[b] Tumor burden was defined as the sum of the product of two bi-dimensional measurements of all measurable lesions.
[c] Extranodal site was defined as any measurable or assessable extranodal lesions, except for in the spleen.
CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; SLL, small lymphocytic lymphoma.

(fatal) and Parkinson's disease.

Eight serious AEs (SAEs) were reported in four (50.0%) patients: cardiac arrest, cellulitis, femoral neck fracture, lung infection, muscle hemorrhage, decreased neutrophil count, pneumonia and tibia fracture. The first patient, a 70-year-old male, had fatal cardiac arrest 332 days after the start of ibrutinib treatment. Treatment was therefore discontinued due to death. The patient had no previous history of cardiovascular or cerebrovascular disease and no family history of cardiac arrest. On CT of the head and torso, no evidence of intracranial hemorrhage was detected, and no causes of unconsciousness or cardiac arrest were identified. Autopsy excluded myocardial infarction as the cause of death. There were no findings that directly indicated the cause of death in the organs of the chest or abdomen. Craniotomy was not performed as part of the autopsy. Events involving the CNS or arrhythmia in the heart were speculated as the cause of death. The cardiac arrest SAE was considered to have doubtful causality with the study drug, as there was no clinical basis to assess causality. In the second patient, cellulitis (considered unrelated to the study drug) led to the interruption of ibrutinib treatment for 14 days, after which treatment with ibrutinib at 420 mg was resumed. The femoral neck fracture in this patient (also considered unrelated to the study drug) led to the interruption of ibrutinib for bipolar hip arthroplasty and was resolved after 21 days; the patient restarted ibrutinib after recovery of the femoral neck fracture. The subsequent tibia fracture (considered unrelated to the study drug) led to the interruption of ibrutinib for an open reduction and internal fixation procedure. In the third patient, the lung infection SAE (considered possibly related to the study drug) did not lead to the interruption of ibrutinib treatment. The decreased neutrophil count (considered possibly related to the study drug) led to dose reduction. The muscle hemorrhage (considered very likely related to the study drug) led to the interruption of ibrutinib treatment for 13 days, after which, ibrutinib was resumed at a reduced dose of 280 mg; during this event, the patient did not take concomitant antiplatelet, anticoagulant or CYP3A4 inhibitor drugs. Their platelet count was also grade 0 during this event. In the fourth patient, the pneumonia SAE (considered probably related to study drug) led to the interruption of ibrutinib treatment for 18 days, after which ibrutinib at 420 mg was resumed. Except for the single patient with the cardiac arrest SAE, all SAEs were resolved by the end of the study.

Table 2. Summary of AEs

	All grades, n (%)	Grade ≥3, n (%)
Overview		
Any AE	8 (100.0)	4 (50.0)
Drug-related	8 (100.0)	3 (37.5)
Serious	4 (50.0)	4 (50.0)
Drug-related, serious	2 (25.0)	2 (25.0)
Leading to dose reduction	1 (12.5)	1 (12.5)
Leading to discontinuation of the study drug	1 (12.5)	1 (12.5)
Leading to death	1 (12.5)	1 (12.5)
AEs reported in ≥20% patients		
Gastrointestinal disorders	6 (75.0)	0
Diarrhea	3 (37.5)	0
Constipation	2 (25.0)	0
Gastritis	2 (25.0)	0
Stomatitis	2 (25.0)	0
Infections and infestations	6 (75.0)	3 (37.5)
Upper respiratory tract infection	4 (50.0)	0
Nasopharyngitis	3 (37.5)	0
Cellulitis	2 (25.0)	1 (12.5)
Lung infection	2 (25.0)	2 (25.0)
Pneumonia	2 (25.0)	1 (12.5)
Investigations	6 (75.0)	2 (25.0)
Decreased platelet count	6 (75.0)	0
Increased lymphocyte count	4 (50.0)	0
Decreased neutrophil count	2 (25.0)	2 (25.0)
Skin and subcutaneous tissue disorders	6 (75.0)	0
Rash	3 (37.5)	0
General disorders and administration site conditions	4 (50.0)	0
Peripheral edema	3 (37.5)	0
Malaise	2 (25.0)	0
Blood and lymphatic system disorders	3 (37.5)	0
Anemia	2 (25.0)	0
Musculoskeletal and connective tissue disorders	3 (37.5)	1 (12.5)
Arthralgia	2 (25.0)	0
Myalgia	2 (25.0)	0
Vascular disorders	3 (37.5)	1 (12.5)
Hypertension	2 (25.0)	1 (12.5)
Injury, poisoning and procedural complications	2 (25.0)	1 (12.5)
Contusion	2 (25.0)	0
Fall	2 (25.0)	0
Psychiatric disorders	2 (25.0)	0
Insomnia	2 (25.0)	0

AE, adverse event.

Hemorrhagic events were reported in five (62.5%) patients; these were grade 1 to 2, except for the study drug-related muscle hemorrhage SAE described above. There were no reports of CNS hemorrhage/hematoma. Cardiac events were reported in three (37.5%) patients; these events included fatal cardiac arrest, atrial fibrillation (grade 2) and palpitations (grade 2).

Efficacy

The response and survival findings are summarized in Table 3. The ORR with ibrutinib treatment was 87.5% (7/8 patients; exact 95% confidence interval 47.3-99.7), which demonstrated the efficacy of ibrutinib. One (12.5%) patient had CR, six (75.0%) patients had PR and one (12.5%) patient had PR with lymphocytosis. None of the patients had stable disease or progressive disease. For the seven patients who responded, the median time to initial response was 5.4 months (range, 1.9-20.2).

A waterfall chart showing the maximum reduction from

baseline in the sum of the product of the diameters (SPD) of measurable lesions in each patient is presented in Figure 1. All eight patients had a maximum reduction of ≥50.0% from baseline in the SPD of measurable lesions.

Table 3. Summary of response and survival parameters

Parameter	All evaluable patients (N = 8)
ORR (CR or PR)	
n (%)	7 (87.5)
95% CI	47.3-99.7
ORR with PRL (CR, PR or PRL)	
n (%)	8 (100)
95% CI	63.1-100.0
Best objective response, n (%)	
CR	1 (12.5)
PR	6 (75.0)
PRL	1 (12.5)
Stable disease	0
Progressive disease	0
Time to response,[a] months	
Median (range)	5.4 (1.9-20.2)
95% CI	1.9-5.6
PFS, months	
Progressed or died, n (%)	1 (12.5)
Censored, n (%)	7 (87.5)
Median (range)	NE (10.9-35.0+)
95% CI	10.87-NE
OS, months	
Died, n (%)	1 (12.5)
Censored, n (%)	7 (87.5)
Median (range)	NE (10.9-35.9+)
95% CI	10.87-NE

+, censored observation.
[a] Time to response in the seven responders (CR or PR).
CI, confidence interval; CR, complete response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRL, partial response with lymphocytosis.

The median PFS and OS were not reached at the time of the final analysis (Table 3). The Kaplan-Meier point estimates of both the PFS and OS rates at 12 and 24 months were 87.5%.

DISCUSSION

Treatment options for patients with treatment-naïve CLL/SLL in Japan are limited.[22] Some CLL treatments (e.g. chlorambucil, obinutuzumab) are not approved or indicated in Japan as of July 2019.[23,26] Those that are available include fludarabine, cyclophosphamide, rituximab and bendamustine. However, currently available drugs are associated with high rates of toxicity and low efficacy in patients with high-risk markers.[10-12] In March 2016, ibrutinib, an oral Bruton's tyrosine kinase inhibitor, was approved in Japan for the treatment of relapsed/refractory CLL/SLL.[20] The availability of ibrutinib helps to address an unmet therapeutic need for most of the CLL population who require treatment, including patients who are elderly and/or frail, those with high-risk markers associated with a reduced benefit from chemoimmunotherapy and those with relapsed disease after chemoimmunotherapy. Furthermore, in recent studies, ibrutinib alone or combined with an anti-CD20 antibody had a superior profile to chemoimmunotherapy.[27-29]

The present phase I study was conducted to assess the safety and efficacy of single-agent ibrutinib at 420 mg in eight Japanese patients with treatment-naïve CLL. The study demonstrated that ibrutinib treatment for a median duration of 32.2 months (range, 10.4-35.9) had an acceptable safety profile and high ORR in this patient population.

Ibrutinib treatment was generally well tolerated and no new safety signals were identified. One patient developed fatal cardiac arrest. Cardiac events, including cardiac arrhythmias and ventricular tachyarrhythmias, have previously been reported among patients with CLL treated by ibrutinib.[30-33] Grade 4 or 5 cardiac arrest has been reported in four phase III CLL/SLL trials conducted outside of Japan: one grade 4 and one grade 5 event in the HELIOS study (287

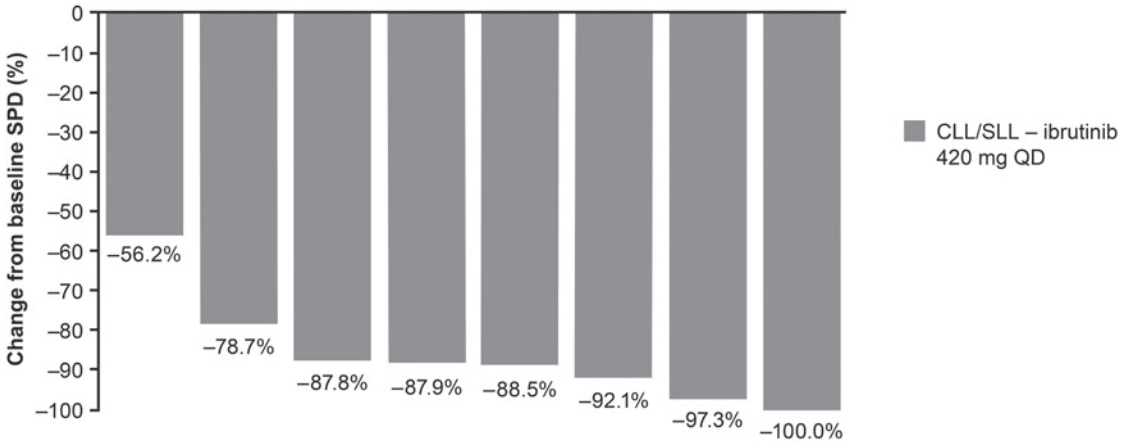

Fig. 1. Waterfall chart for the maximum reduction from baseline in the SPD of measurable lesions (N = 8 patients). CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; SPD, sum of the products of the diameters; QD, once daily.

patients treated with ibrutinib),[34] one grade 5 event in the iLLUMINATE study (113 patients),[29] one grade 4 event in the A041202 study (364 patients)[28] and one grade 4 event in the ECOG 1912 study (352 patients).[27] In the current study, most AEs reported were assessed as grade 1 or 2, whereas all grade ≥3 AEs resolved by the end of the study, except for one case each of cardiac arrest, hypertension and worsening of Parkinson's disease. Furthermore, the observed lymphocytosis in 50.0% of patients is a well-known transient phenomenon of B-cell receptor-targeted agents and is generally not perceived as a toxic effect.[35] Only two SAEs led to dose reduction (grade 3 muscle hemorrhage and grade 4 decreased neutrophil count). Regarding disease response, ibrutinib provided a high ORR of 87.5%, suggesting its efficacy. The median PFS and OS had not been reached by the end of the study.

These findings are largely consistent with those previously reported for single-agent ibrutinib in non-Japanese treatment-naïve patients. For example, in the phase III RESONATE-2 trial, ibrutinib demonstrated efficacy and acceptable tolerability in treatment-naïve patients with CLL/SLL,[18] leading to the approval of ibrutinib for this population in the United States and many other countries.[15,16] A total of 269 patients with CLL/SLL (aged ≥65 years) were randomized to initial treatment with either ibrutinib or chlorambucil for a median follow-up of 18.4 months.[18] Reported AE rates in the ibrutinib group included atrial fibrillation (all grades, 6.0%), hypertension (grade 3, 4.0%) and major bleeding (4.0%). Three patients in the ibrutinib group died: one from *Klebsiella* infection and two from unknown causes.[18] Ibrutinib provided a high ORR of 86% (vs 35.0% with chlorambucil). The median PFS was not reached with ibrutinib (vs 18.9 months with chlorambucil), and the relative risk of progression or death was 84.0% lower with ibrutinib (P<0.001). Three patients in the ibrutinib treatment group died during the study (vs 17 in the chlorambucil group). Patients with disease progression in RESONATE-2 were permitted to cross over to the other treatment regimen.[18] Subsequently, an updated analysis (median follow-up, 28.6 months) revealed that 41.0% of patients initially assigned to chlorambucil had crossed over to ibrutinib treatment, whereas 79.0% of patients assigned to ibrutinib continued on that regimen. In the updated analysis, ibrutinib provided an ORR of 92.0% (vs 36.0% with chlorambucil).

The findings of the present study are also consistent with those previously reported for ibrutinib in Japanese patients with relapsed/refractory disease. In a phase I dose-escalation study (the first clinical trial of ibrutinib in Japan), ibrutinib at 420 or 560 mg for a median duration of 13.5 months was tolerable and had an acceptable safety profile in 15 Japanese patients with relapsed/refractory mature B-cell malignancies, including CLL/SLL.[21] Based on efficacy analysis, ibrutinib provided a high ORR of 73.3%.

The longest follow-up data reported for ibrutinib treatment to date are from a phase Ib/II study that assessed single-agent ibrutinib in treatment-naïve symptomatic older patients (≥65 years) and relapsed/refractory patients with CLL/SLL.[37-39] During a 3-year follow-up period, ibrutinib led to sustained responses, with an ORR of 89.0%, and manageable toxicity.[39] A recent 5-year follow-up study reported sustained single-agent efficacy and tolerability of ibrutinib in both the treatment-naïve and relapsed/refractory patients.[40] The ORR remained at 89.0%, and CR rates improved over time. Furthermore, it was effective in patients with high-risk genetic features. In treatment-naïve CLL patients, the 5-year PFS rate was 92.0% (median not reached). Long-term ibrutinib had an acceptable safety profile with no new safety signals.

Although patients with SLL were not enrolled in the present study, it should be noted that CLL and SLL are essentially the same disease, differing only by disease manifestation at the time of diagnosis (CLL, peripheral blood; SLL, lymph nodes).[3] All eight patients with CLL included in this study had lymphadenopathy characteristic of SLL because they each had at least one enlarged lymph node measuring >1.5 cm at its longest diameter. Furthermore, all eight patients exhibited a maximum reduction of ≥50.0% in the SPD of measurable lesions from baseline, which meets the PR criteria of the International Working Group Revised Response Criteria for Malignant Lymphoma. This suggests that ibrutinib is effective in patients with SLL as well as those with CLL.

Although the long duration of ibrutinib treatment in the current study (median, 32.2 months) provides a valuable dataset for evaluating the safety and efficacy of ibrutinib in Japanese patients, the trial was limited by its small sample population size (N = 8); therefore, further studies are needed to confirm the findings in a large cohort of Japanese patients.

In conclusion, this phase I study demonstrated ibrutinib treatment at 420 mg/day to have an acceptable safety profile and high ORR in Japanese patients with treatment-naïve CLL, supporting the use of ibrutinib in this patient population.

ACKNOWLEDGMENTS

This study was funded by Janssen Pharmaceutical KK. We thank the patients who participated in this trial and their families. Writing assistance was provided by Safeer Mughal, PhD, and Ian Phillips, PhD, of Parexel, and was funded by Janssen Global Services.

The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

CONFLICTS OF INTEREST

HS has received honoraria from AbbVie, AstraZeneca, Celgene, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Fujimoto, Janssen, Kyowa Hakko Kirin, Mundipharma, Nippon Shinyaku, Novartis, Ono, Otsuka, Sanofi and Takeda;

and research funds from Astellas, Celgene, Chugai, Dainippon Sumitomo, Eisai, Fujimoto, Janssen, Kyowa Hakko Kirin, Mundipharma, Nippon Shinyaku, Ono, Otsuka, Shionogi, Taiho, Takeda and Teijin. **TT** has received honoraria from Bristol-Myers Squibb, Celgene, Chugai, Kyowa Hakko Kirin, Merck Sharp & Dohme Corp, Novartis, Pfizer and Takeda; and research funds from Astellas, Chugai, CMIC Holdings Fuji, IQVIA, Janssen, Kyowa Hakko Kirin, Nippon Shinyaku, Novartis, PPD-SNBL, Sanofi Shionogi, Sumitomo Dainippon SymBio and Takeda. **IC** has nothing to declare. **KH** has received personal fees from Celgene, Chugai, Daiichi Sankyo, Kyowa Hakko Kirin, Meiji Seika, Ono and Takeda; and grants from Eisai. **NS** has received grants from A2 Healthcare, Astellas, Dainippon Sumitomo, Janssen, Merck Sharp & Dohme Corp, Otsuka, Pfizer and PPD-SNBL. **NY** is an employee of Janssen Pharmaceutical KK.

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