Multicenter retrospective analysis of patients with chronic lymphocytic leukemia in Korea

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Background
Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia in Western countries but is rare in the East Asian countries. Due to its rarity and the lack of feasible novel agents and laboratory prognostic tools, there are limited data on the clinical outcomes of this disease in Asia. To clarify the current treatment status, we performed a multicenter retrospective analysis of patients with CLL in Korea.

Methods
The medical records of 192 eligible patients between 2008 and 2019 were reviewed for clinical characteristics, treatment courses, and outcomes. The first-line treatment regimens of the patients included in this analysis were as follows: fludarabine/cyclophosphamide/rituximab (FCR) (N=117, 52.7%), obinutuzumab plus chlorambucil (GC) (N=30, 13.5%), and chlorambucil monotherapy (N=24, 10.8%).

Results
The median progression-free survival (PFS) was 55.6 months, and the average 2-year PFS rate was 80.3%. PFS was not significantly different between the patients receiving FCR and those receiving GC; however, chlorambucil treatment was associated with significantly inferior PFS ($P<0.001$). The median overall survival was 136.3 months, and the average 5- and 10-year OS rates were 82.0% and 57.4%, respectively.

Conclusion
This is one of the largest studies involving Korean patients with CLL. Although the patients had been treated with less favored treatment regimens, the outcomes were not different from those reported in Western studies.

Key Words   Chronic lymphocytic leukemia, Outcomes, Asia

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a neoplasm composed of monomorphic small mature B cells that co-express CD5 and CD23. In Western countries, it is the most common type of adult leukemia [1]. In 2019, it was estimated that 20,720 people would be diagnosed with CLL in the United States and 3,930 would die from the disease [2]. The clinical course of the disease is extremely heterogeneous, as some patients with favorable factors may not require treatment, whereas those with unfavorable risk factors may need treatment immediately [3, 4]. Although the overall survival (OS) of CLL patients has improved over the past several decades owing to the introduction of novel agents [5, 6], these agents are costly and not readily available in real-world settings.

The incidence of CLL in Asia is approximately 20-fold lower than that in Western countries [7]. Moreover, people of Asian descent in Western countries present a lower incidence of CLL, suggesting that genetic factors play a bigger role than environmental factors in the development of CLL [8, 9]. In Korea, there were 157 cases of CLL in 2012, with an age-standardized rate of 0.2 [10]. Although its incidence is slowly increasing, CLL is considered a very rare disease that does not attract the attention of physicians. Consequently, the prognosis of CLL patients in Asia seems to be less favorable, probably due to the more aggressive biological features in Asian patients or the limited attention in healthcare settings [11, 12]. Furthermore, the lack of feasible novel agents and laboratory prognostic tools may contribute to poor prognosis. We performed a nationwide, multicenter, retrospective analysis in Korea to clarify the current treatment status of CLL patients.

MATERIALS AND METHODS

Patients

This retrospective study included CLL patients treated with alkylating agents, purine analogs, or anti-CD20 monoclonal antibodies at 18 tertiary institutions in Korea. Their medical records were reviewed for clinical characteristics, treatment courses, and outcomes.

Patients who were treated for CLL between 2008 and 2019 were included in the analysis. The inclusion criteria were as follows: 1) patients with a primary diagnosis of CLL according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria [13]; 2) patients who had received therapy for CLL; and 3) availability of reliable medical records for the analysis. The patients' medical records regarding age, sex, Rai staging, Binet staging, Eastern Cooperative Oncology Group performance status (ECOG-PS), treatment regimens, cytogenetics, and laboratory findings including complete blood count and creatinine clearance (CCr) rate were examined.

Analysis

Progression-free survival (PFS) was calculated from the date of treatment initiation for CLL to the date of progression or death, while OS was calculated from the date of treatment initiation to the date of death by any cause. Both PFS and OS were calculated using the Kaplan–Meier method, and subgroup comparisons were performed using the log-rank test. Responses were assessed using the iwCLL criteria [13]

Table 1. Clinical and molecular features during first-line treatment (N=192).

	N (%)
Age (median, range)	63 (34–87)
≤65 yr	117 (60.9)
≥66 yr	75 (39.1)
Sex	
Male	115 (59.9)
Female	77 (40.1)
ECOG-PS	
0–1	179 (93.2)
2–4	13 (6.8)
Rai stage	
0	1 (0.5)
I	46 (24.0)
II	46 (24.0)
III	50 (26.0)
IV	49 (25.5)
Binet stage	
A	22 (11.5)
B	76 (39.6)
C	94 (49.0)
Creatinine clearance (N=174)	
~69 mL/min	42 (24.1)
70 mL/min	132 (75.9)
Largest tumor diameter	
≤5 cm	180 (93.7)
>5 cm	12 (6.3)
FISH for del(11q) (N=51)	
Normal	43 (84.3)
Abnormal	8 (15.7)
FISH for del(13q) (N=42)	
Normal	24 (57.1)
Abnormal	18 (42.9)
FISH for del(17p) (N=46)	
Normal	39 (84.8)
Abnormal	7 (15.2)
TP53 mutation analysis (N=66)	
Mutated	10 (15.2)
Wild-type	56 (84.8)
FISH for del(17p) & *TP53* mutation analysis (N=26)	
Wild-type	21 (80.8)
Del(17p)	1 (3.8)
Mutated *TP53*	1 (3.8)
Del(17p) & mutated *TP53*	3 (11.5)
IgHV mutation analysis (N=10)	
Mutated	0 (0.0)
Wild-type	10 (100.0)

Abbreviations: del, deletion; ECOG-PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; *IgHV*, immunoglobulin heavy chain gene.

and compared using Pearson's λ^2 tests. For all statistical analyses, P-values <0.05 were considered statistically significant; the analyses were performed using IBM Statistical Product and Service Solutions Statistics for Windows, version 21.0 (IBM Corp, Armonk, NY, USA).

All procedures performed in this study were in accordance with the ethical standards of the institutional committee. The Institutional Review Boards of the respective centers approved the study protocol.

RESULTS

Patient characteristics and features at diagnosis

From 2008 to 2019, 192 patients were eligible for the analysis, and all patients were Asian. The median age at diagnosis was 62 years (range, 34–86), and 115 patients (59.9%) were male. The distribution of the patients according to the Rai stages at diagnosis was as follows: 0, 14 (7.3%); I, 55 (28.6%); II, 49 (25.5%); III, 36 (18.8%); and IV, 38 (19.8%). The distribution of the patients according to the Binet stages at diagnosis was as follows: A, 45 (23.4%); B,

80 (41.7%); and C, 67 (34.9%).

Treatment was initiated after a median observation period of 1.1 months (range, 0.0–135.8), when the patients' median age was 63 years (range, 34–87). The distribution of the patients according to the Rai stages during treatment was as follows: 0, 1 (0.5%); I, 46 (24.0%); II, 46 (24.0%); III, 50 (26.0%); and IV, 49 (25.5%). The distribution of the patients according to the Binet stages during treatment was as follows: A, 22 (11.5%); B, 76 (39.6%); and C, 94 (49.0%). The ECOG-PS of most patients was 0–1 (N=179, 93.2%), and the median CCr rate was 81.9 mL/min. Bulky disease characterized by lymph node(s) >5 cm in dimension was observed in 12 patients (6.3%), and B symptoms were present in 52 patients (27.1%). Molecular analyses were not performed for all cases. Fluorescence in situ hybridization (FISH) for 17p deletion (del) was performed in 46 cases (23.9%), of which 7 (15.2%) tested positive. *TP53* mutation analysis was performed in 66 cases (34.4%), of which 10 (15.2%) tested positive. Both FISH for del(17p) and *TP53* mutation analysis were performed in only 26 cases, and 21 cases tested negative for both. Immunoglobulin heavy chain (*IgHV*) gene mutation analysis was performed in only 10 cases, and no
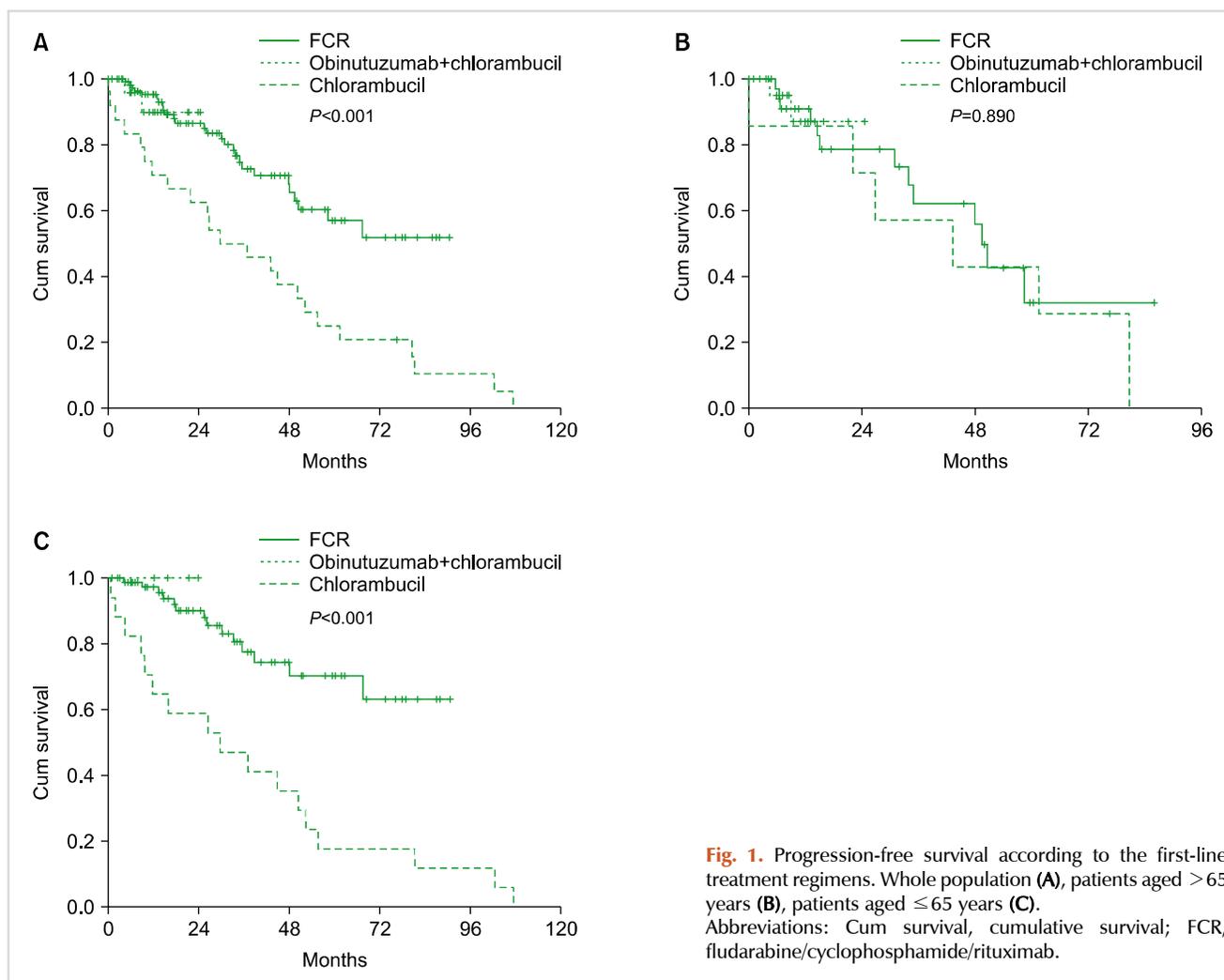

Fig. 1. Progression-free survival according to the first-line treatment regimens. Whole population **(A)**, patients aged >65 years **(B)**, patients aged ≤65 years **(C)**.
Abbreviations: Cum survival, cumulative survival; FCR, fludarabine/cyclophosphamide/rituximab.

mutation was detected in them. The clinical and molecular features of the patients are summarized in Table 1.

First-line treatment and outcomes

The fludarabine, cyclophosphamide, and rituximab (FCR) regimen was the most commonly used (N=117, 60.9%), followed by obinutuzumab plus chlorambucil (GC) (N=30, 15.6%). Other regimens included chlorambucil alone (N=24, 12.5%), fludarabine and cyclophosphamide (N=12), other fludarabine-based combinations (N=4), rituximab + bendamustine (N=4), and ibrutinib (N=1). The baseline characteristics of the patients according to the three major regimens (FCR, GC, and chlorambucil alone) are provided in Supplementary Table 1. The median PFS was 55.6 months [95% confidence interval (CI), 40.4–70.8], and the mean± standard deviation (SD) 2-year PFS rate was 80.3±3.4%. Complete response was achieved in 105 patients (54.7%) and partial response in 51 patients (26.6%), resulting in an overall response rate of 81.3%. There was no difference in the PFS between patients treated with FCR and those with GC (P=0.279). However, patients treated with chlorambucil alone showed a significantly shorter PFS than those treated with FCR or with GC (P=0.001). The mean±SD 2-year PFS rates of the patients treated with FCR, GC, and chlorambucil were 86.6±3.7%, 89.8±6.9%, and 62.5±9.9%, respectively (Fig. 1A).

None of the age cut-off values, including 60, 65, and 70 years, could discriminate PFS (data not shown). However, analysis of the PFS for each regimen according to age showed interesting results. Among patients aged ≥66 years, there

Table 2. Progression-free survival following first-line treatment according to clinical and molecular features.

	N	Median PFS (95% CI)	P
Del(17p)			0.043
Present	7	9.0 (5.1–12.9)	
Absent	39	52.3 (32.5–72.1)	
TP53 mutation			0.005
Mutated	10	12.8 (3.9–21.5)	
Wild type	56	44.9 (29.8–60.0)	
Del(13q)			0.133
Present	18	49.5 (45.9–53.1)	
Absent	24	30.1 (11.7–48.5)	
Del(11q)			0.053
Present	8	29.8 (2.0–57.6)	
Absent	43	49.5 (31.2–67.8)	
Age			0.258
≤65 yr	117	67.5 (37.6–97.4)	
≥66 yr	75	50.5 (34.8–66.2)	
Binet stage			0.156
A	22	47.9 (14.7–81.1)	
B	76	55.6 (28.1–83.1)	
C	94	58.4 (31.1–85.7)	
Rai stage			0.876
0	1	NA	
I	46	61.5 (46.6–76.4)	
II	46	47.9 (32.3–63.5)	
III	50	Not reached	
IV	49	58.4 (39.6–77.2)	
Treatment regimen			0.001
FCR	117	Not reached	
Obinutuzumab+Cbl	30	Not reached	
Cbl	24	29.8 (9.8–49.8)	
Patients aged ≤65 yr			<0.001
FCR	82	Not reached	
Obinutuzumab+Cbl	5	21.4 (NE)	
Cbl	17	29.8 (1.3–58.3)	
Patients aged ≥66 yr			0.890
FCR	35	49.5 (45.1–53.9)	
Obinutuzumab+Cbl	25	Not reached	
Cbl	7	43.2 (0.9–85.5)	

Abbreviations: Cbl, chlorambucil; CI, confidence interval; Del, deletion; FCR, fludarabine/cyclophosphamide/rituximab; NA, not applicable; PFS, progression-free survival.

was no significant difference in the mean±SD 2-year PFS rates between the three regimens: 78.6±7.9% for the FCR arm, 87.1±8.8% for the GC arm, and 71.4±17.1% for the chlorambucil arm (P=0.890) (Fig. 1B). In contrast, a marked difference was observed in the PFS among the patients aged ≤65 years (Fig. 1C). In this age group, the mean±SD 2-year PFS rate of the patients treated with FCR was 90.1±3.9%, which was superior to that of patients treated with GC (50.0±35.4%) or with chlorambucil (58.8±11.9%) (P<0.001) (Table 2).

Second-line treatment and outcomes

In total, 57 patients received second-line treatment at a median age of 64 years (range, 44–86). Ibrutinib was the most frequently used second-line treatment regimen (N=24, 42.1%), followed by FCR (N=16, 28.1%). Other regimens included fludarabine-based combinations (N=6, 10.5%), chlorambucil alone (N=3, 5.2%), and bendamustine with or without rituximab (N=3, 5.2%). The median PFS was

23.6 months (95% CI, 5.0–42.2), and neither treatment regimen nor age could discriminate PFS (data not shown). The median PFS of patients who received ibrutinib was 23.6 months (95% CI, 9.7–37.5), whereas that of patients who received FCR was 32.8 months (95% CI, 0.0–68.4). As only 10 patients were examined for del(17p) or *TP53* mutation, and only one patient tested positive for del(17p), their effects on PFS were not analyzed.

OS and prognostic factors

With a median follow-up duration of 80.3 months (95% CI, 73.42–87.18), the median OS was 136.3 months (95% CI, 100.1–172.5), and the mean±SD 5- and 10-year OS rates were 82.0±3.3% and 57.4±10.7%, respectively (Fig. 2A). Several clinical and cytogenetic features discriminated the OS. An age cut-off of 65 years could not discriminate OS; however, patients aged <60 years (median, 154.0 mo; 95% CI, 99.4–208.6) showed a significantly prolonged OS than that of patients aged ≥60 years (median, 104.2 mo; 95%
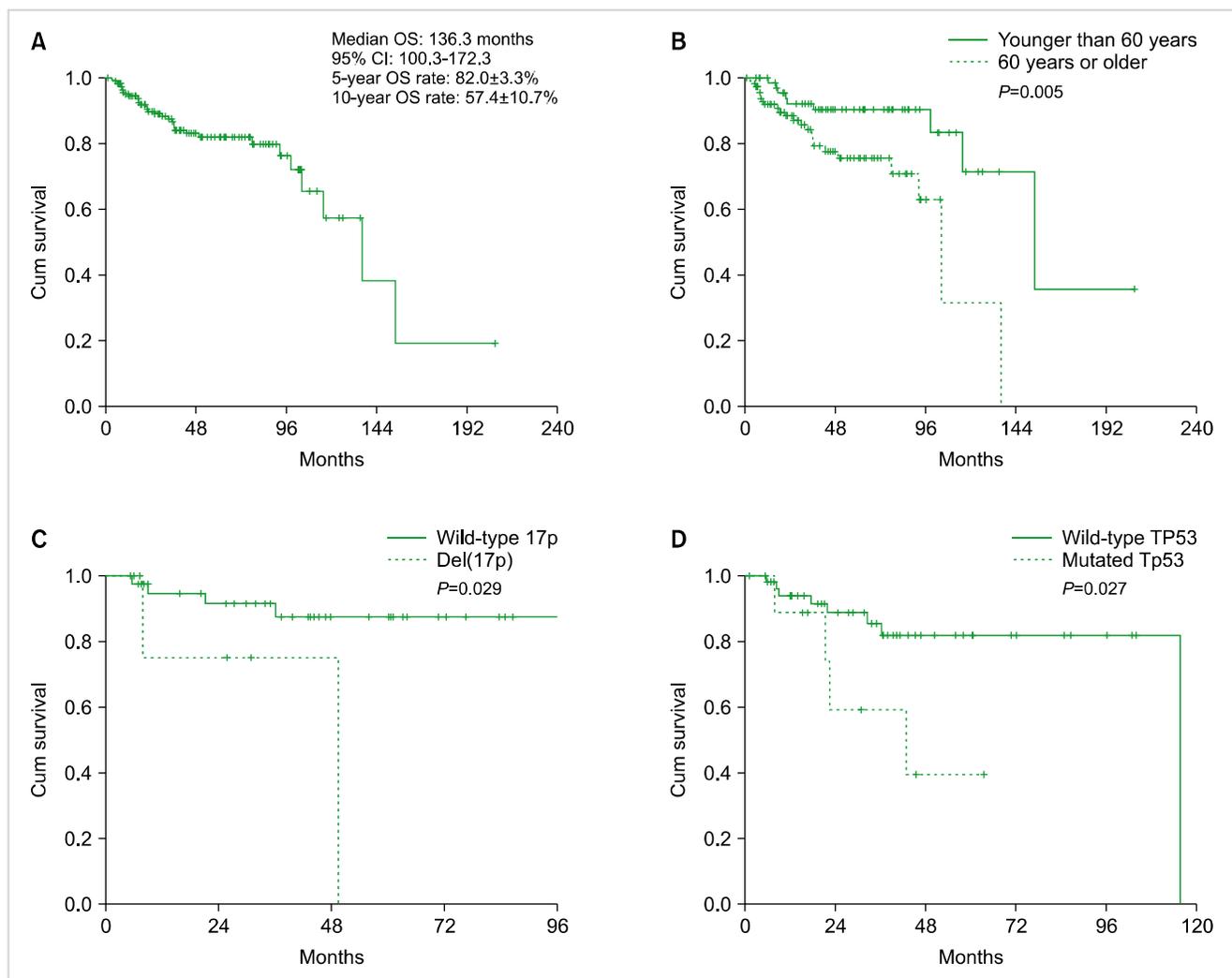

Fig. 2. Overall survival. Survival in the whole population (**A**), survival according to age (**B**), survival according to 17p deletion status (**C**) survival according to *TP53* mutation status (**D**).
Abbreviations: CI, confidence interval; Cum survival, cumulative survival; OS, overall survival.

CI, 87.6–120.8; *P*=0.005) (Fig. 2B). Neither the Rai stage nor the Binet stage could discriminate OS (data not shown). No significant difference was observed according to the first-line treatment regimen (mean±SD 5-year OS rate: FCR arm, 79.7±4.5%; GC arm, 73.6±12.4%; chlorambucil arm, 91.7±5.6%; *P*=0.549).

Although cytogenetic analyses were performed only in some cases, several abnormalities were found to affect the OS. Patients with del(17p) had worse OS rates than those with wild-type 17p (median OS, 49.5 mo vs. not reached; *P*=0.029) (Fig. 2C). Additionally, patients with *TP53* mutation had worse OS than that of patients with wild-type *TP53* (median OS, 42.8 mo vs. 115.8 mo; *P*=0.027) (Fig. 2D). There were no statistically significant differences in other cytogenetic abnormalities, including del(11q) and del(13q).

DISCUSSION

In this study, we analyzed 192 patients with CLL who were treated with alkylating agents, purine analogs, or anti-CD20 monoclonal antibodies. Treatment was initiated after a median observation period of 1.1 months (range, 0.0–135.8), and the median PFS and OS were 55.6 months (95% CI, 40.4–70.8) and 136.3 months (95% CI, 100.1–172.5), respectively. Age ≥60 years, del(17p), and *TP53* mutations adversely affected OS.

CLL is a heterogeneous disease with highly variable initial presentation, necessitating a wide range of initial management strategies including watchful waiting, chemoimmunotherapy, Bruton's tyrosine kinase (BTK) inhibitors treatment, and B-cell lymphoma-2 (BCL-2) inhibitors treatment. As the outcomes of these treatments depend on several prognostic factors, it is crucial to evaluate the clinical and molecular markers comprehensively to determine the treatment strategies. However, although CLL is the most common type of adult leukemia in Western countries, its incidence in Asia is extremely low (5%) as compared to that in Western countries [14, 15]. This could be largely attributed to the genetic discordance between Caucasians and Asians [16, 17]. Consequently, the natural course and prognostic factors of CLL that are well defined for Caucasian patients [3, 4, 18] are poorly defined for Asian patients.

Some studies have reported that the clinical and molecular features of Asian patients with CLL are different from those of the Western patients, including age, cytogenetics, and prognosis [9, 19]. Corroborating with these reports, the median age of our patients was 62 years (range, 34–86), which was much lower than that of the patients in Western studies [20, 21]. Despite the younger age at diagnosis, it has been reported that the disease progresses more aggressively in Asians [12, 22]. In this study, the mean±SD 5- and 10-year OS rates were 82.0±3.3% and 57.4±10.7%, respectively, which were not significantly inferior to those reported in Western studies. This could be partially explained by the similarity with the Western studies in the proportion of patients with advanced stages of CLL, such as Binet stage C or Rai stages III–IV [20, 21]. In terms of cytogenetics, it seems that the incidence of major cytogenetic abnormalities, including del(11q), del(13q), and del(17p), is similar between Caucasians and Asians [3]; however, *IgHV* mutation is more frequently found in Asians (~70%) [23, 24]. Although a limited number of patients in this study were examined for del(11q) (15.7%), del(13q) (42.9%), and del(17p) (15.2%), the proportion of cytogenetic abnormalities was similar to that in previous studies. The status of *IgHV* mutation, which is important in the management of CLL patients, was only assessed in 10 patients, and none of them had the mutation. This could be because tailored treatment according to the *IgHV* mutation status is not permitted in Korea.

CLL therapy has undergone considerable changes over the last few years, and combinations of BTK inhibitors, BCL-2 inhibitors, and anti-CD20 monoclonal antibodies are recommended as the first-line treatment [25]. In this study, most patients were treated with FCR or chlorambucil with or without obinutuzumab, which are considered less favorable therapies. The average 2-year PFS rate reported for the FCR arm and GC arm was significantly higher than that of the chlorambucil arm. However, among elderly patients (≥66 yr), there was no significant difference between the treatment arms. This finding is inconsistent with that of the CLL-11 trial in which elderly patients benefited from the combination treatment of obinutuzumab and chlorambucil [26]. One explanation for this is that del(17p) was more common in patients treated with GC than in those treated with chlorambucil alone (33% vs. 0.0%). As the current analysis began only 2 years after the approval of the treatment combination, the relatively short follow-up duration may have contributed to the biased results. Another interesting finding is that the differences in the PFS among the first-line treatment regimens did not lead to differences in the OS. This was also observed among patients who had received chlorambucil alone; the median OS of these patients was 136.3 months (95% CI, 98.7–173.9), which was similar to that of the other patients. Similarly, Chinese [27] and Indian [28] trials reported a median OS of over 100 months with first-line chlorambucil treatment, but the Western studies reported different findings. In the CLL-11 trial, the median OS for the chlorambucil arm was 58.5 months after long-term follow-up [29]. In the COMPLEMENT-1 trial, the median OS for the chlorambucil arm was 84.7 months [30]. Although baseline molecular features should be considered, these findings suggest that chlorambucil monotherapy may be a suitable first-line option for CLL patients, especially when resources are limited.

This study has several limitations. The data were retrospectively collected from multiple institutes. This could lead to inconsistent interpretations of the responses. Nevertheless, as we assessed both PFS and OS, the validity of the data may be regarded as acceptable, and it may reflect real-world clinical outcomes. Furthermore, the outcomes of the first-line and second-line treatment regimens were heterogeneous,

hindering the identification of an optimal treatment method for Asian patients with CLL. Although the data were collected from tertiary centers, analysis of various molecular markers was not performed. The disease may receive less attention from physicians due to its extremely low incidence, limited tailored treatment strategies, and novel first-line therapies.

In conclusion, this study analyzed the clinical and molecular features and treatment outcomes of 192 CLL patients in this study, and it is one of the largest nationwide studies in Korea to date. Although the patients had been treated with less favored agents, the outcomes were not different from those observed in Western studies. To determine the role of ethnicity in this "orphan" disease in Asia, further studies using novel agents are warranted.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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